The ECMM/ISHAM Working Group on Zygomycosis

Global Registry

# STUDY PROTOCOL

## Table of Contents

## 1. Introduction

Although often described as a rare fungal infection, mucormycosis appears to be increasing in frequency [1]. This has been attributed to the growth of the number of severely immunocompromised patients, as well as to the rising prevalence of diabetes mellitus [1-3]. Differences in the epidemiology seem to exist depending on geography. In Europe and USA, the disease remains uncommon and is mostly seen in patients with hematological malignancies. In contrast, in Asia, especially in India, mucormycosis is more common, and cases occur mainly in patients with uncontrolled diabetes mellitus or trauma [3]. It mainly affects immunocompromised patients, such as those with haematological malignancies, recipients of haematopoietic stem cell or solid organ transplants, patients with diabetes mellitus, and infants with prematurity [4]. Mucormycosis may also affect immunocompetent patients with trauma or burns, or patients with elevated serum levels of iron under treatment with deferroxamine. Due to the relative rarity of the disease it is difficult to perform stringent epidemiological studies to estimate its exact incidence. Most of the available data stem from case series and pertain to haematological patients [5,6] or to patients who have undergone transplantation [7,8]. Taking into consideration the challenges related to epidemiology, treatment and outcome of mucormycosis, a Working Group on Zygomycosis was formed by the European Confederation of Medical Mycology (ECMM). The aim of the group was to analyze the clinical characteristics, microbiology, treatment practices and outcome of mucormycosis in Europe through a voluntary case registry. The results of the first 3 years (2005–2007) were published in 2011 [9]. In 2008 the Working Group became global, under the auspices of both ECMM and ISHAM (International Society for Human and Animal Mycology).

## 2. Objectives

The aim of this registry is to collect as many cases of mucormycosis as possible from all around the world, in order to better understand the various aspects of this rare disease.
Further aims of the group are:
1. To collect strains of mucormycetes for state-of-the-art molecular identification and long-term maintenance. Strains will thus have official accession-numbers which can be used in future publications.
2. To collect any available histology specimen for PCR. This will aid in the identification of fungi when no cultures are available, as well as for comparison with culture proven strains.

## 3. Study Period

Start of study: February 1, 2004.
First amendment of study: January 1, 2008.
End of study: not defined yet.

## 4. Inclusion – Exclusion Criteria

Inclusion Criteria

- The patient must have an invasive fungal infection due to agents of mucormycosis, diagnosed by direct microscopy, culture, histopathological or DNA evidence.
- The methods of diagnosis must be clearly stated.
- The case must not be older than 2008.

Exclusion Criteria

- If the data indicate that the positive culture represents colonization, the case is not eligible.

## 5. Case Report Form

The data pertaining to the case can be submitted either on-line or on a CRF form. The address of the on-line registry is www.zygomyco.net . The CRF form will be downloaded from the registry site and sent by e-mail to the study coordinators when completed.
In order to submit a case, a participant must register to the site, giving his name, country of origin and e-mail address.
All the parts of the form should be completed. The requested information includes:

Patient information
**Initials**: These are random letters or numbers chosen by the submitting participant.
**Country - City**: This is the country of residence of the patient, not of the submitting participant.
**Race**: Caucasian
**Patient code**: This is an automatic number, provided by the registry
**Age**: (Years:  Months:  ) Months are completed if the patient is an infant.
**Sex**: Female or Male
**Weight** (kg):
**Hospital/Ward:**
**Occupation:**
**Name of Physician**: This is either the name of the clinician treating the patient or of the mycologist making the laboratory diagnosis.

Clinical Data

**Date Zero**: This is the date when the diagnosis of mucormycosis was made or, alternatively, where the clinical signs and symptoms were attributed to mucormycosis.
**Underlying Disease at time of infection**: Enter yes or no. If yes, indicate which of the following are positive

• Malignancy: (If yes, write which malignancy)
• Transplantation:
• Diabetes mellitus:
• Renal Failure:
• Neutropenia:
• HIV infection:
• Low birth weight infant:
• Malnutrition:
• Autoimmune disease:
• Iron Overload:
• Other:

**Treatment BEFORE diagnosis of zygomycosis**:

These are the drugs given before the diagnosis of mucormycosis. If any antifungals were used, please insert the reason for using them. For example, this could be "empirical treatment for presumed aspergillosis" or "prophylaxis in transplantation" etc.

**Mode of transmission**

If the mode of transmission was not identified, don't forget to insert "Yes" next to "Unknown".

**Site of infection**

An infection is characterized as "localized" if it does not extend to adjacent organs. For example, if the site of infection is pulmonary and the infection extends to the pleura or the pericardium, then it is not localized.

If more than one organ is infected, and the organs are non-contiguous (e.g. lung and kidney) than the infection is "disseminated". In this case, only the site "disseminated" should be chosen and the involved organs should be mentioned next to it.

**Signs and symptoms of fungal infection**

Please insert a paragraph describing the clinical presentation of the infection.

<u>Diagnosis</u>

The methods of diagnosis MUST be completed, otherwise the case will not be included in the study. The results of the studies must be reported.

<u>Treatment of Zygomycosis</u>

Insert all available information. If the patient has received a polyene (conventional or liposomal amphotericin B) the dose should be written as mg/kg of body weight.

<u>Outcome</u>

- **Complete response**:
  complete resolution of attributable symptoms of signs of fungal infection, negative culture, PCR, significant imaging resolution (assuming positive at day zero).
- **Partial response:**
  Near complete resolution of attributable symptoms and signs of fungal infection,

negative culture or PCR, or significant improvement in imaging abnormalities, (assuming positive at day zero).

- **Clinical improvement:**
  definite clinical improvement (e.g. fever or headache resolution, improvement in cough, weight gain etc.) but with minor or no objective imaging or laboratory test improvement.
- **Stable**:
  minor clinical, imaging or laboratory improvement or deterioration, or no change (especially if course of therapy very short)
- **Deterioration or failure:**
  definite clinical, radiological or laboratory evidence of worsening of disease.

## 6. Laboratory Testing

If the participant wishes, he can send the isolated fungus to the laboratory of Dr. Cuenca-Estrella in Spain for molecular identification and susceptibility testing.
If an histology specimen is available, it can be sent to the same lab for PCR testing.

## 7. Budget

For every case submitted €100 will be given as compensation.
The cost for the tests done by Dr. Cuenca-Estrella and Dr. Ana-Alastruey Izquierdo will be covered by the Working Group budget.

## 8. Ethical Considerations and Data Privacy Protection

The study is non-interventional and, therefore, no informed consent is required according to the laws of most countries. There are no associated risks or 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. 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. The data submitted to the site are protected 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 according to European legislation. All data and results will be stored for at least 10 years after publication of results.
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. This procedure aims to ensure anonymous documentation of patient data. The microbiological analyses of isolates does not require informed consent of the patient, as there is no patient material involved.

## 9. Study coordinators – Contact information

- **George Petrikkos**, Convenor of the Working Group
  Acting Dean, School of Medicine
  Professor of Immunology, Medical Microbiology and Infectious Diseases
  e-mail: G.Petrikkos@euc.ac.cy , Web:http://www.euc.ac.cy
  Tel: 00357 22559532, mob: +357 99663060
  Emeritus Professor of Internal Medicine and Infectious Diseases
  National and Kapodistrian University of Athens
  e-mail: petrikos@hol.gr

- **Anna Skiada**, Study Coordinator
  1st Dpt. of Medicine, Laikon Hospital
  Agiou Thoma 18, Goudi 11527, Athens, Greece
  National and Kapodistrian University of Athens
  e-mail: askiada@yahoo.com
  Tel: +30 6944354279

- **Manuel Cuenca-Estrella**
  Subdirector General de Servicios Aplicados, Formación e Investigación
  Instituto de Salud Carlos III
  (*Deputy General Director of Institute of Health Carlos III*)
  Ctra. Majadahonda-Pozuelo Km2
  Majadahonda, Madrid 28220
  España/SPAIN
  Tfno/phone: +34 91 8223200
  e-mail: mcuenca-estrella@isciii.es

- **Ana Alastruey-Izquierdo**
  Mycology Reference Lab
  National Centre for Microbiology
  Instituto de Salud Carlos III
  Carretera de Majadahonda a Pozuelo Km. 2
  28220, Majadahonda, Madrid, Spain
  Email: anaalastruey@isciii.es
  Phone.: +34-918223784


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