Multicenter observational study on epidemiology, treatment and outcome of Mucormycosis in India

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List of Abbreviations

L-AMB: Liposomal Amphotericin B
ABDC: Amphotericin B Deoxycholate
CI: Confidence Interval
OS: Overall survivalStudy Summary

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| Title | Multicenter observational study on epidemiology, treatment and outcome of Mucormycosis in India |
| Short Title | Description of epidemiology, treatment practice and outcome of mucomycosis in India |
| Protocol Number | FISF 001.3 |
| Phase | IV |
| Methodology | Observational study |
| Study Duration | 1 years |
| Study Center(s) | Multi-center. |
| Objectives | Primary:<br>- To describe the epidemiology, diagnosis, treatment practices and outcome of mucormycosis in India<br><br>Secondary:<br>Sites involved in mucormycosis<br>Underlying disease and risk factors for mucormycosis<br>Spectrum of agents causing mucormycosis<br>mode of diagnosis of mucormycosis |
| Number of Subjects | At least 300 |
| Diagnosis and Main Inclusion Criteria | Proven and probable cases of mucormycosis |
| Study Product, Dose, Route, Regimen | No study product will be used as it is only observational study |
| Duration of administration | not applicable |
| Reference therapy | Not applicable |

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| Statistical Methodology | Descriptive and quantitative statistics |

Study Purpose: To describe the epidemiology, diagnosis, treatment practices and outcome of mucormycosis
How the study would help? The findings from this study will provide evidence on epidemiology, outcomes associated with current management strategies for mucormycosis and inform the development of future optimal management strategies for patients with mucormycosis.
Critical issues & risk: There is no risk to the patients from this study as this is only observational study and no intervention is intended.

Introduction

Mucormycosis is a life threatening angio-invasive fungal infection generally occurring in immunocompromised individuals. In recent years the incidence has increased globally and alarmingly in India especially in patients with uncontrolled diabetes. Mucormycosis is associated with very high morbidity and mortality. Mortality can be reduced with increased awareness of the disease, and aggressive medical and surgical intervention. Among antifungal drugs, amphotericin B and its lipid preparations are used primary therapy and posaconazole as salvage therapy. Isavulconazole is a recent addition in the list of antimucor agents. This drug is approved by FDA in March 2015. However, this drug is not available in Indian market. Among amphotericin B and its lipid preparation, liposomal amphotericin B is recommended for treatment of mucormycosis due to its low toxicity and efficacy over other lipid preparations in animal models. Amphotericin B deoxycholate, though toxic, is commonly used in India to treat cases of mucormycosis due to cost constraints. Newer iron chelators like deferasirox was found to be efficacious in combination with liposomal amphotericin B compared to monotherapy in animal experiments. However, the only clinical trial DEFEAT study showed contrary result. The DEFEAT study was criticized due to the imbalance of the two arms of the study. Deferasirox has been used occasionally of-label in Indian patients. From Hinduja Hospital, Mumbai a study on seven patients reported better outcome when deferasirox was combined with amphotericin B. In animal experiments the combination of echinocandins and liposomal amphotericin B had demonstrated better outcome. However, no RCT is conducted yet to evaluate this combination. In India very few centers follow any guideline for managing patients with invasive mucormycosis. Moreover, it is not strongly recommended by any International center on optimum therapy - what drug, what duration, how to monitor therapy against mucormycosis. Though few case series of mucormycosis are published from India, multiple gaps in knowledge exist regarding epidemiology, diagnosis and management of the disease in this country. It is therefore proposed to conduct this multicentric observational study in India to evaluate epidemiology, mode of diagnosis, management practices and outcome in patients with mucormycosis.

Study Objectives
Primary:

- To describe the epidemiology, diagnosis, treatment practices and outcome of mucormycosis in India

Secondary:
Sites involved in mucormycosis
Underlying disease and risk factors for mucormycosis
Spectrum of agents causing mucormycosis
mode of diagnosis of mucormycosis

Methods: Observation chart review
Study Sites: We have assembled a network of health center across India called Mucormycosis Study Network (MSN), which consists of 17 centers across the country. Listed in Appendix 1.

Study design: We propose to conduct a single arm prospective observational study.

Inclusion criteria:
All consecutive patients regardless of age with a confirmed diagnosis mucormycosis through HPE & /or culture will be enrolled in this study.
All probable mucormycosis will also be included.

Working definition of Proven & Probable mucormycosis for our study
Proven: Presence of fungus in the tissue detected by direct microscopy (KOH, Calcoflor white) and Histopathological examination or from any aspiration /tissue from sterile site.
Probable mucormycosis: Clinical features of infection in organ-site with presence of mucorale in tissue (detected by direct microscopy and HPE) from non-sterile infected site.

Exclusion criteria:
Any subject without a confirmed diagnosis of mucormycosis.

Study procedures:
Post enrollment, all patients will receive treatment as per the discretion of treating physicians or local hospital protocol. Data on patients' clinical features, risk factors, laboratory and radiological findings will be collected on standardize case report forms (CRF).
Specifically, the extent of disease will be evaluated with appropriate radiological evaluation CT scan/ MRI (Brain, PNS, Thorax, abdomen etc.) Attempt will be made to collect follow up data till 6 months after diagnosis unless the patient lost in follow up or died before six months. All culture isolates will be sent to Mycology Reference Laboratory at PGIMER, Chandigarh for final identification and drug susceptibility testing. Blocks of histopathological specimen will be sent at reference mycology laboratory for patients with histopathological diagnosis of mucormycosis for DNA extraction and species identification.
Primary outcome
Overall survival at 45 & 90 days
Cure: defined as complete resolution of clinical, radiological and mycological

evidence
Improved: Resolution of clinical features, radiological regression

Secondary outcomes
1. Grade III and IV toxicities of antifungal agents

Data Collection
Data will collect using a standardized CRF. All collected data will be entered into a database prior to analysis. Broadly data will be collected on demography, clinical characteristics, diagnosis, treatment and outcome for each patient.

Patient characteristics: Demographics, Comorbidities (Diabetes, Solid organ Transplant, GVHD requiring steroids, Febrile neutropenia, prolong neutropenia + Steroid therapy, Voriconazole exposure, Immunocompetent patient, Nosocomial [Surgical site, wooden spatula, ECG lead etc], history of road traffic accidents, tsunami, hurricane, Patients receiving immunosuppressives for collagen diseases, Use of monoclonal antibodies for treatment of variety of medical conditions, Iron overload and desferioxamine therapy, Burns patients), Organ dysfunction, Bacterial super infections

Disease characteristics: Site of disease (pulmonary, PNS, Brain, skin and soft tissue, GI, Renal etc), number of lesions, species of mucormycosis
Treatment:
(1). Time to start antifungal drug after (a). Onset of disease i.e. first symptom (b). Diagnosis of mucormycosis
(2). Dose and duration of antifungal agent
(3). Time to Surgical Treatment after (a). Onset of disease i.e. first symptom (b). Diagnosis
(4). Type of Surgical treatment: Radical surgery, Debridement, Repeated debridement
Adjuvant treatment used e.g. Deferasirox, posaconazole
(5). Posaconazole maintenance after completion of ABDC

Outcomes:
Overall survival (OS): OS will be measured 2 ways: from onset of first symptoms as reported by patient and from day of admission to last follow-up.
Mortality
Related to mucormycosis, not related to Mucormycosis

Treatment Regimen:
The study will not interfere with management at any stage. Treating physician will determine all process of patient management including diagnosis and treatment. Information on antifungal agent used, dosage used and duration of treatment will be collected.
Information on surgical treatment will be collected i.e. time to surgical treatment after diagnosis, debridement, numbers and frequency of debridement, extensive surgical resection.
Adjuvant therapy used i.e. Deferasirox or Posaconazole.
Control of diabetes, reversal of metabolic parameters, management of immunosuppression will be noted.

Follow up data will also be collected similarly.

Patients will be assessed during hospitalization for drug compliance and toxicities. Adverse Event will be noted and graded according to standard grading system.
Prior and Concomitant Therapy
The details of any prior, concomitant or follow up therapy like deferasirox or Posaconazole will also be noted

Statistical Plan
Patient, disease and treatment characteristics will be summarized using descriptive statistics. Differences in the primary outcome of survival according to patient, disease and treatment characteristics will be assessed using a log-rank test and illustrated using the Kaplan-Meir analysis. Differences in OS will be summarized as hazard ratio along with 95% confidence intervals (CI). Differences in mortality and toxicities according to patient, disease and treatment characteristics will summarized as risk ratio along with 95% CI. All significance testing will be two sided and set at 5%.
Ethical Considerations: Each site PI will be responsible for clearance of study protocol by the respective Institutional review board(IRB)/Ethics Committee (EC). As this is observational study without any intervention, a waiver of patient consent will be requested. Site PI must submit a copy of the approval from his/her IRB/EC to the study coordinator.
Benefits and risks to the study participants: As this is an observational study, there is no risk related to the study to the participants. No immediate benefit is expected to occur to the individual patient. The study will improve the understanding of the epidemiology of Mucormycosis in India; this study will contribute valuable information to design treatment strategy to improve outcome of mucormycosis patients.
Security and Confidentiality:
Once the patient is deemed eligible, a unique number will be assigned. The site PI at each center will maintain identification of patient in accordance with each center's policies and procedures. The site PI will provide only the unique number when filling up the CRFs and transferring the data to the coordinator. Each site will be able to view the data of the patients it has enrolled, and the only aggregate data of the patients enrolled at other sites.
Funding: Expecting educational grant from Mylan India for this study
Conflict of Interest
Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by the study sponsor prior to participation in this study.
Subject Stipends or Payments
No stipend will be provided to study subjects
Publication Plan
Published in appropriate journal. In the event of publication, the order of authorship will be according to the number of cases enrolled in the study. All the co-investigators of this study will be cited in the appendix of each publication. The sponsor of the study will be acknowledged in each publication. None of the sites is permitted to make any publications on it's site data, based solely on the

parameters included in this study for the cases included in the present study. If there is any breach of this understanding, the data from that center will not be included in the final data analysis.

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Attachments
Study Procedures Flowchart/Table
CRF
Culture submission form

Appendix 1. List of participating centers

a) PGIMER, Chandigarh arunaloke@hotmail.com
b) Christian Medical College, Vellore, Joy Sarojini Michael MD FRCPath Professor Department of Microbiology Christian Medical College Vellore 632004 joymichael@cmcvellore.ac.in
c) Vardhman Mahaveer Medical College and Safdarjung Hospital, Delhi. Dr Malini R Capoor. rajeevmalini@rediffmail.com
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