Invasive mould infections in Indian ICUs – descriptive epidemiology, management and outcome (FISF study)

[FISF = Fungal Infection Study Forum, a non-profit making trust]
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Principal Investigator Contact Information
Name: Arunaloke Chakrabarti
Title: Professor and Head
Address 1   Department of Medical Microbiology
Address 2   Postgraduate Institute of Medical Education & Research
City, ST, Zip Chandigarh 160012, India
Phone/Fax: Phone: 91 172 2755155; Fax: 91 172 2744401
E-mail: arunaloke@hotmail.com

Introduction

Invasive fungal infections are important causes of morbidity and mortality in critically ill patients in ICUs. In recent Indian study over 27 ICUs, it was observed the frequency of candidemia at 6.51 cases/1000 ICU admission. Though Candida is commonest agent to cause invasive fungal infections, invasive mould infections is on the rise in ICU setting. ICU admission is considered as intermediate risk in causing invasive aspergillosis. Even clusters of mucormycosis have been reported in certain ICUs especially in patients with uncontrolled diabetes. Fusariosis and Scedosporiosis are emerging disease. However, there is no systematic study in Indian ICUs to know the prevalence of invasive mould infections, their risk factors, management and outcome. In the present study we aim to capture demographic, epidemiologic, clinical, treatment and outcome data on patients with IMIs from Indian ICUs. This would be a prospective observational study without any intervention in practiced protocol of any ICU.

Objectives

Primary objective

To determine the incidence and clinical determinants of Invasive mould infections (IMIs) in Indian ICUs.

Secondary objectives

To determine:
The incidence, demographics, and risk factors of IMIs in specific patient groups (medical – neutropenic, non-neutropenic; surgical; hematopoietic stem cell transplant, chronic liver disease, diabetics, chronic obstructive pulmonary disease)
The spectrum of agents causing IMIs
Antifungal resistance of mycelial fungi
Diagnostic methods practiced for IMIs
Treatment practice for IMIs
Outcomes in patients with IMIs

Background

Invasive mould infections are emerging causes of morbidity and mortality in ICU patients. This is attributed to prolonged ICU stay of critically ill patients with much co-morbidity. Modern medicine and multiple interventions make the patients susceptible to these prevalent moulds in the environment. In India the high frequency of IMIs in general has been attributed to environmental and host factors prevalent in this region. Additionally sub-optimal hospital care practice, frequent demolition and construction activities in the hospital make the patients susceptible to IMIs. There is no multicentric study available in India describing the epidemiology of IMIs in India. However, single center studies have reported distinct epidemiology of IMIs in India. High incidence, different spectrum and risk factors are possible unique features of IMIs in India.

Early diagnosis and optimal therapy improve the outcome of these patients. The conventional diagnosis including histopathology and culture has limitations. The tests are of low sensitivity and long turnaround time. The major challenge is collection of sample from deep tissue. Therefore majority of the patients in ICUs of India are managed empirically against invasive fungal diseases. The galactomannan test has improved the diagnosis of invasive aspergillosis. However, galactomannan test is not well standardized in non-neutropenic patients. Beta-glucan test is used for early diagnosis of invasive fungal infections other than mucormycosis. But the test is cumbersome for routine laboratories and expensive. Both tests are not available in majority of Institutions of India. PCR assay is not standardized and not performed routinely in any Institution.

Due these limitations in diagnosis, there is no uniform management protocol in ICUs of India. To develop optimal management protocol, we need to know the epidemiology, the right patient to treat, antifungal drug resistance, optimal drug and duration of therapy etc. The present study will provide descriptive epidemiology, present status of diagnosis and management practiced in India to treat IMIs in ICUs. This will help to find the suitable intervention strategies to improve outcome of IMIs in India.

Study summary

This descriptive observational prospective study will document the epidemiologic and clinical characteristics, as well as treatment and outcome data, of patients with IMIs in ICUs in India over one year.

Significance of the study

The prospective study will describe the epidemiology of IMIs in ICUs in India. The study will describe the incidence, risk factors, fungi causing IMIs and their susceptibility against antifungal agents, as well as the current strategies adopted by ICU physicians in the management of IMIs. It will also describe the outcome of IMIs. The study will help in planning future management strategies specific for IMIs in ICUs in India.

Methods

Study description: Prospective, multicenter study in ICUs in India.

Purpose: Determination of epidemiologic parameters, including risk factors, description of current management and outcome of patients with IMI will be

recorded prospectively. The study will help in understanding the epidemiology of IMI in ICUs and possible planning for future management strategies for IMI specific to India.

Risk: There is no risk to the patient from the study as it is only an observational study and no intervention is intended.

Site selection: 11 ICUs have been identified across the country where ICU physicians are well versed about invasive fungal infections and competent diagnostic mycology laboratory is available
A site feasibility survey was conducted. This ensured that participating sites fulfill the following inclusion criteria: a) maintains ICD coding and total number of discharges and deaths at the center; b) manages critically ill patients in ICU; c) has access to high-resolution CT (HRCT) scans; d) has a mycology laboratory that performs isolation and identification of fungi at least perform galactomannan test; and e) has histopathology facilities.

Study Period: January 1, 2016 to June 30, 2017. Case enrolment – April 1, 2016 to September 31, 2017. Analysis of data – October 1, 2017 to Dec 30, 2017

No. of patients: All consecutive patients with proven and probable IMI in ICUs at the study centers during the study period will be included.

Patient selection
All consecutive patients diagnosed for proven or probable IMIs in ICUs at the study sites will be included.

Inclusion criteria:
A patient must fulfill the definition for a case, as shown in the table below.

Criteria for Case

Proven	Any host irrespective of immunocompetent or immunosuppressed	Histopathology/cytology/direct microscopy demonstrating septate
Probable		Culture positive for mould from sterile sites
	Host satisfies host criteria of EORTC/MSG criteria	EORTC/MSG definition by De Pauw et al 2008
	Host with COPD	Definitions by Bulpa P, et al, 2007
	Host in ICU	Clinical algorithm by Blot SI, et al, 2012

Exclusion criteria: Patients with endemic mycoses (histoplasmosis, sporotrichosis, penicilliosis), yeast infections, and allergic fungal diseases like allergic bronchopulmonary aspergillosis will not be included. Infection limited to the skin only will also be excluded.

Conduct of the study

Investigators of the study: Arunaloke Chakrabarti is the coordinator of the study. Each site has a Principal Investigator – the site PI. Other investigators at the site are be co-investigators.

Other investigators:

Postgraduate Institute of Medical Education & Research, Chandigarh – PI – M R Shivaprakash, C0-PIs – L N Yaddanapudi, Ritesh Agarwal, Praveen Kumar, Jayshree M

Sri Ramchandra Medical University, Chennai – PI – Anupma Jyoti Kindo, Co-PIs - S. Arun kumar, MK Renuka, T. Dhansekar

Amri Hospital, Kolkata; PI – Subhash Todi, Co-PIs – Arpita Bhakta, Mahua Bhattacharyya

Tata Medical Centre, Kolkata; PI- Sanjay Bhattacharyya, Co-PI- Sudakshina Mullick, Jyotsna Goswami, Mammen Chandy, Gaurav Goel, Paromita Roy, Saugata Sen, Nandini Banerjee, Kasturi Sengupta,

Nijam Institute of Medical Sciences, Hyderabad; PI- Umabala P, Co-PI Ramachandran Gopinath, Paramjyothi GK, M.V.S.Subbalaxmi, Shantiveer G Uppin

Christian Medical College, Vellore; PI - Rajiv Karthik; Co-PI – Joy Michael, J.V. Peter

St John Medical College, Bengaluru; PI – Jayanthi Savio; Co-PI – Sriram Sampath, Priya Ramachandran, Poonam Panjwani

Sterling Hospital, Ahmedabad; PI – Atul Patel, Co PI- Mukesh Patel, Kamalesh Patel

Chirayu Medical College, Bhopal; PI – Pradip Bhattacharyya, Co-PI - Deepak Mendiratta

 Gangaram Hospital, Delhi, PI – Prakash Shastri, Co-PI -Ashok Anand, Chand Wattal, Jaswinder Oberoi.

Apollo Hospital, Chennai; PI – Ram Gopalakrishnan; Co-PI - Madhumita

Patient enrollment: The site PI (or one of the co-investigators) will review the patient's paper and electronic records to determine if the patient satisfies the inclusion criteria. Patients who fulfill the inclusion criteria will be included as a case.

Data collection: The demographic, clinical, treatment and outcome data will be captured. Investigators should complete CRF I an II and email the form to the study coordinator, Arunaloke Chakrabarti. Outcome will be measured on day of discharge/death/42 and 84 days (if no death) after the diagnosis of the IMI. The date of diagnosis of an IMI is the day on which the diagnosis is defined as proven or probable. For cases that were enrolled as probable but subsequently became proven, the date of diagnosis is the earlier date (means the date when probable diagnosis is made). In addition, each center will also obtain data from its relevant hospital authority on the total number of admission, discharges and deaths in ICUs for the period of April 1, 2016 to September 31, 2017. They will also provide the number of patients immunosuppressed or immunocompetent in ICUs during the study period.

Fungal isolates: All isolates from proven and probable IMIs will be sent to Mycology Reference Laboratory at PGIMER, Chandigarh for final identification and antifungal susceptibility testing.

Molecular identification: If required, the final identification at the coordinator's site will be done DNA sequencing. If the diagnosis of invasive mould infection is on histopathology only without culture, coordinator's site will attempt for identification of the fungus by molecular technique from biopsy sample or tissue section.

Patient management: The study will not interfere with patient management.

Statistics
The study will be analyzed using descriptive statistics. It is anticipated that the study will provide the following information:
Incidence of IMI among patients in ICUs during the study period in the participating centers
Relative frequency of each risk factor among IMI patients at the participating centers.
Six and 12 weeks survival of patients diagnosed with IMI.
Other data the study should be able to generate will be in accordance with the objectives.
Kaplan-Meier plots will be used to describe the survival of patients with IMI according to their underlying diagnosis.

Ethical considerations
Each site PI will be responsible for the 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 PIs must submit a copy of the approval from his/her IRB/EC to the study coordinator.

Benefits and risks to study participants
As this is an observational study, there are no risks to the study participants. No immediate benefit is expected to accrue to the individual patient. The study will improve the understanding of the epidemiology of IMI in ICUs of India; it will increase awareness of IMI among clinicians, and data from the study will contribute to the planning of management of IMIs in India.

Security and confidentiality
Once the patient is deemed eligible, a unique number will be assigned by site PI. The site PI at each center will maintain identification of the 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 only aggregate data of patients enrolled at other sites.

Publications
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 publication on its site's 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.

Sponsor
The study is conducted by Fungal Infection Study Forum (FISF).

Budget

Salary & benefits	Sanction Budget (Rs.)	Proposed Amendment
Description		
Clinical Research Follow	4,680,000	51,48,000
Study manager at coordinating centre	440,700	661,050
	51,20,700	58,09,050
Study Supplies		
Description		
Investigators meeting	650,000	650,000
Cost for data of 300 patients	6,82,500	6,82,500
Cost of identification of isolates per molecular identification from histopathology blocks	19,5000	19,5000
Cost of antifungal susceptibility testing	195,000	195,000
Travel to study manager in whole year	325,000	78,650
	20,47,500	18,01,150
Analysis & reports		
Description		
Statistical analysis	26,000	26,000
Printing	13,000	13,000
	39,000	39,000
Direct Costs	72,07,200	72,07,200
Indirect overhead rate %	7,20,720	5,92,720
One time fees		
Description		
EC fees	260,000	50,000
Data processing unit for the manager of the study – 1	104,000	104,000
	364,000	154,000
Total Budget	INR 82,91,920	INR 82,91,920

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