

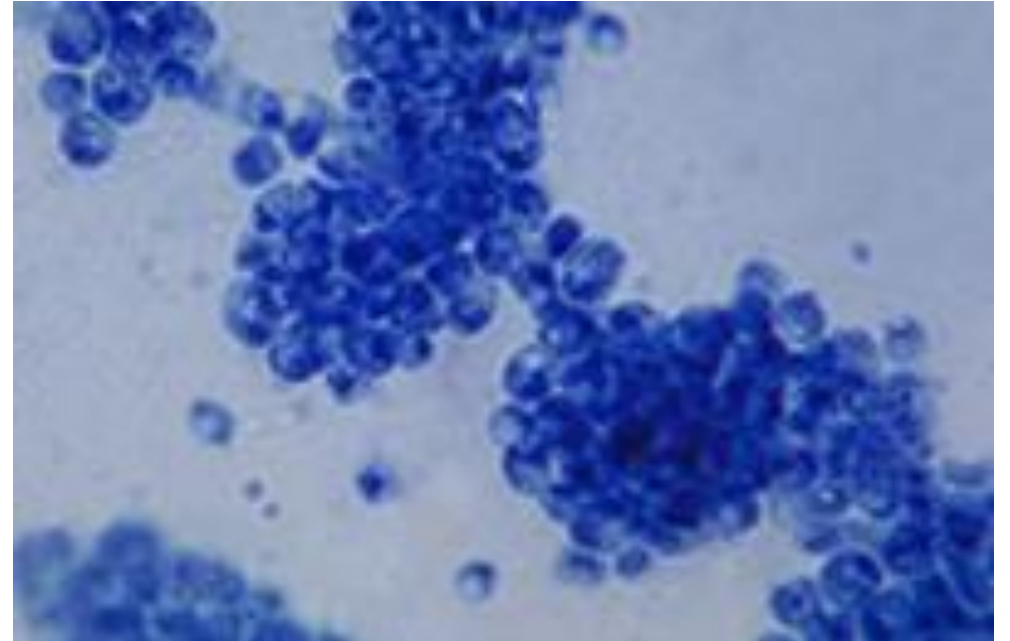
The Rise of Invasive Fungal Infection (IFI): Science Behind Invasion and Infection

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Introduction

- Fungi are Eukaryotes
- 1.5 million species
- Of which 300 species cause disease
- Dispersed via spores



Candida Fungus

<https://www.cdc.gov/fungal/diseases/candidiasis/index.html>

Fungal Nutrition

Fungi are heterotrophic: 3 different ways

- From dead decaying matter-Saprophytes
- Feed on living hosts by living in/ on other organisms-Parasites
- Causing disease in humans and other organisms-Pathogens

Opportunistic Fungi: What are they?

- Fungi are mostly saprophytes-evolved mechanisms gives them the ability to survive in mammalian hosts.
- They cause infections in people with poor defense mechanisms
- Many fungi are opportunists but are not pathogenic unless host is immunocompromised.

What are IFIs?

IFI-Invasive Fungal Infection

The definition was proposed by:

1. Invasive Fungal Infections Cooperative Group (IFICG)
2. European Organization for Research and Treatment of Cancer (EORTC)
3. Mycoses Study Group (MSG) of National Institute of Allergy and Infectious Diseases (NIAID)

- IFI's are opportunistic fungi
- Use the weakened immune system to invade
- Potentially cause diseases
- Invaded deep tissues and established itself resulting in prolonged illness.

IFI: Types of Fungi Involved in Infection

- Any part of the body can get affected
- Disease caused by fungi is called Mycosis
- The presence of fungal elements with mold or yeast in deep seated tissues can be described as Invasive Fungal Infection
- IFIs can be caused by any of the following:
 1. Yeasts:- e.g. Candida, Cryptococcus
 2. Molds:- e.g. Fusarium, Mucor, Aspergillus
 3. Dimorphic Fungi:- e.g. Histoplasma, Blastomyces

Risk Factors for IFIs

- Low neutrophils of <500 for more than 10 days
- Diabetes
- Cancer
- Bone marrow transplantation
- Invasive medical procedures/ major surgeries
- HIV/AIDS Infection
- Severe Burns
- Stem cell / organ transplants
- Therapy with corticosteroids, immunosuppressive agents
- Mal nutrition
- Prolonged >7 days stay in ICU

IFI Statistics

- Mortality rate often exceeds 50%
- Approximately 1.6 million people die, worldwide, every year
- Equivalent to the deaths caused by tuberculosis
- Difficult to diagnose
- Hard to treat

IFI: Transmission and Infection

Transmission:

- Inhalation of spores
- Percutaneous inoculation via skin trauma, needle or burn
- Penetration into mucosa by commensal organisms, such as candida
- Ingestion of a toxin in contaminated food/ drink

Infection:

- Can be mild, superficial or cutaneous or maybe life threatening
- Clinical manifestations-highly variable

Difference in Colonization and Invasion

Colonization:

- Fungi present in or on host
- Grows and multiplies
- Does not invade into tissues
- Does not cause damage

INVASION:

- Enter the host
- Resist host defense mechanism
- Damage the host

Fungal Infections - Classification

1. **Primary Infection** - Develop in Immunocompetent
2. **Opportunistic Infection** - Develop in Immunocompromised

Infections can be:

Local - Develops in both immunocompromised or immunocompetent

OR

Systemic - Attacks the low immune system by opportunistic fungi

Science Behind Invasion

To infect host and cause disease best studied in Candida and Cryptococcus

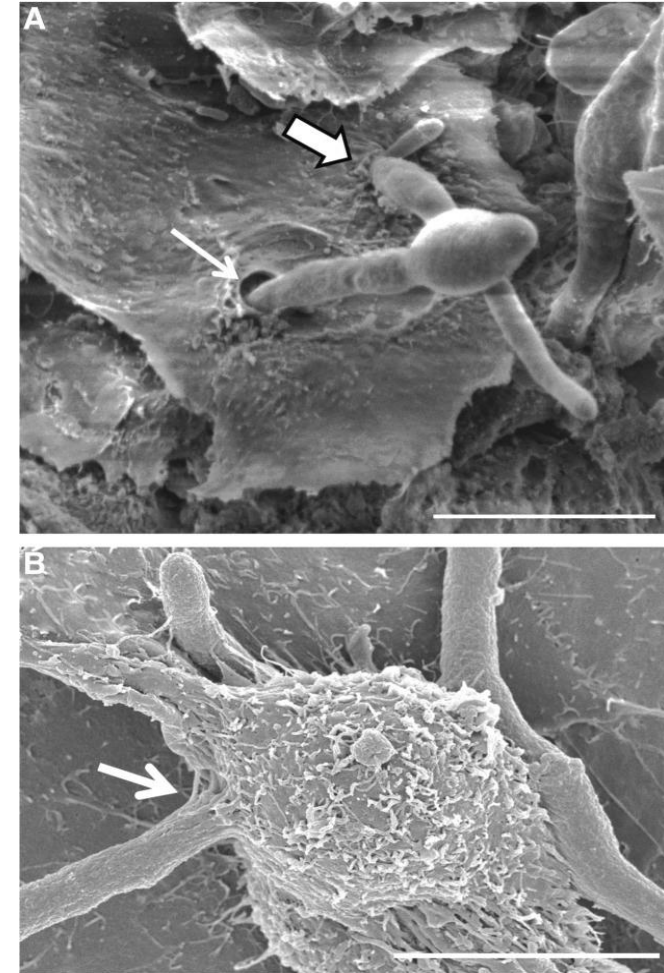
Host cell invasion is a two step process:

1. Adherence to non-phagocytic cell
2. Invasion then follows by 2 different mechanisms
 - a. Induced endocytosis
 - b. Active penetration
3. A third mechanism by Candida albicans called paracellular mechanism

Invasion

Invasion of epithelial cells by *C. albicans* and *Aspergillus fumigatus*. Scanning electron micrograph of (A) *C. albicans* invasion of the epithelial cells on the dorsum of the tongue of a cortisone acetate–treated mouse with oropharyngeal candidiasis.

Thick arrow indicates a hypha that is likely invading by induced endocytosis, which is characterized by ruffling of the epithelial cell plasma membrane at the site of invasion. Thin arrow indicates a hypha that is probably invading by active penetration. (Krause et al. 1969)



<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4292075/>

Diagnostic Testing

- Microscopy
- Cultures
- PCR
- Pathogen specific tests such as antigen/ antibody tests
- Histologic diagnosis

Other tests:

- Molecular
- Serological
- Antifungal susceptibility testing

Diagnosis of Fungal Infection

1. Knowing the causative fungus helps in the choice of antifungal drugs, dose and duration
2. At times additional or dual infections can be identified
3. Insight into the extent of infection required, for severity
4. Assessment to antifungal resistance
5. Blood and urine samples easy to take and assess while biopsies and respiratory samples pose challenges

IFI: Candidiasis

- Candida sp. is a commensal organism
- It's a yeast, inhabits gastrointestinal tract and skin without causing problems
- Infection and disease seen in poor immune systems
- Common hospital acquired
- Candidiasis of the esophagus common in HIV patients

Cryptococcus is a basidiomycete yeast

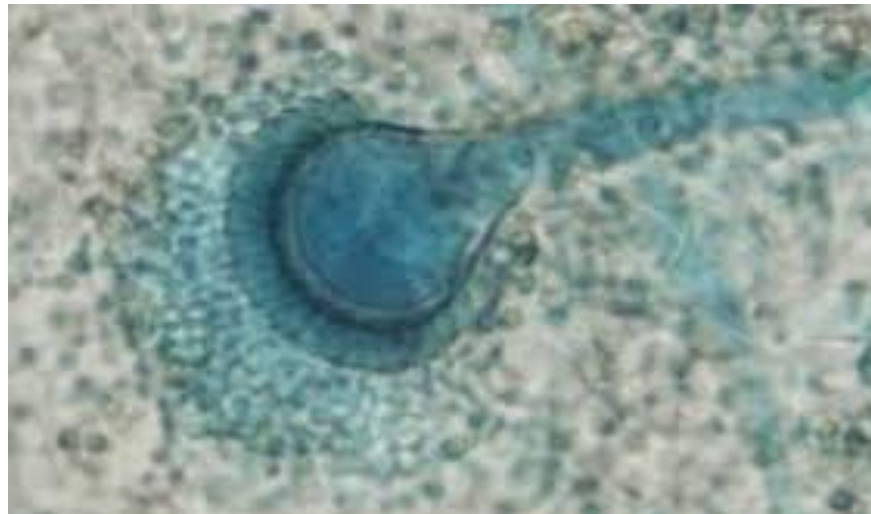
- Has thick polysaccharide capsule, evades the host
- Spreads through faecal matter of the host

IFI: Aspergillosis

- Causative organism *Aspergillus* sp.
- Common mold found outdoors and indoors
- Filamentous fungi, spores get aerosolized easily
- Entry by inhalation
- Sometimes through damaged skin
- Infection in lungs and nasal passages subsequently spread to other parts
- Tendency to infect open spaces like sinuses, extra auditory canals, pulmonary cavities

IFI: Aspergillosis (continued)

- A. fumigatus commonly causes pulmonary disease
- A. flavus also causes pulmonary infections



<http://www.falaboratories.com/lab-services/microbiology/library/aspergillus-fumigatus.asp>

IFI: Aspergillus sp. (continued)

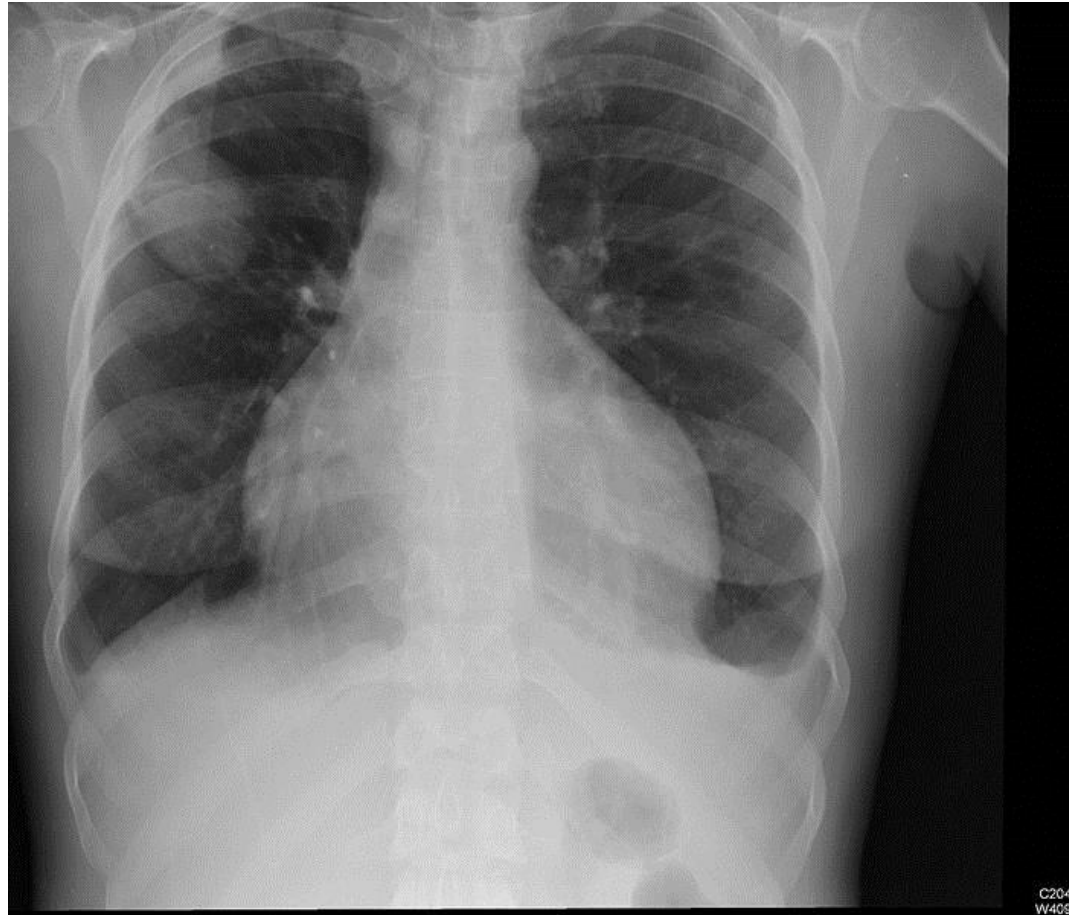
- Found in Lungs:
- It starts off as a spot called “lung nodule”

As tangled mass of hyphae with fibrin exudate and few inflammatory cells with fibrous tissue that is encapsulated and form Aspergilloma

- Found in eyes with trauma/ surgery

Causes Endophthalmitis

Aspergilloma-Fungal Ball



Source: https://www.researchgate.net/figure/Chest-radiography-showing-a-fungus-ball-with-an-air-crescent-in-the-right-upper-lobe_fig1_258029154

IFI: Zygomycetes

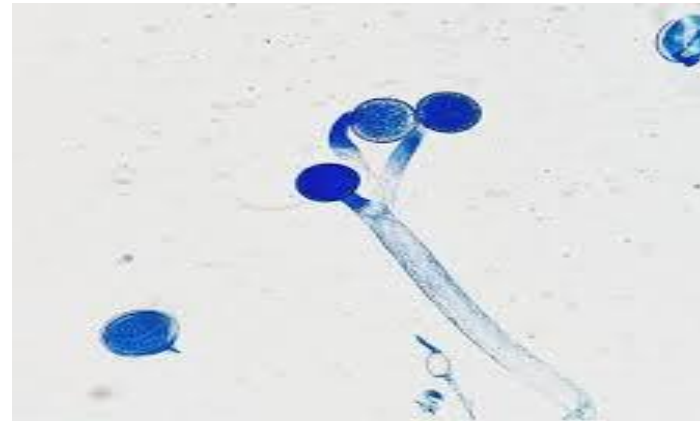
- Group of fungi found on decaying soil and organic matter such as leaves, wood and compost
- Mucor, Rhizopus (bread mold), Absidia, Syncephalstrum are some examples
- Characterized by very broad ribbon like hyphae that are branched
- Presence of asexual spore forming sporangiophores
- Commonly seen on air plates and surface samples
- Easily grows on most media.
- Plates covered within 3-5 days

IFI: Zygomycosis

- Zygomycete infections result in Zygomycosis
- Zygomycosis is the most lethal opportunistic fungal infection particularly in diabetic patients, patients receiving deferoxamine treatment and hematological malignancies
- Order, Mucorales cause majority of infections, infections are known as Mucormycoses
- Rhizopus, Mucor and Rhizomucor species account for upto 75% of Mucormycoses infections

IFI: Zygomycosis (continued)

- Lungs, rhino facial-cranial areas, skin are commonly affected
- Disease can take place via inhalation or by minor trauma of skin such as insect bites
- Can cause broad spectrum of infections in humans including superficial and disseminated



IFI: Blastomycoses

- Found in moist soil and dead decaying matter
- Relatively rare
- Causative organism Blastomyces
- Dimorphic fungi
- Occasionally seen on culture sample as a restrictive white colony and
Direct Microscopic Examination
- Lungs are affected and patients show little to no symptoms
- As the infection spreads, skin lesions on the face and neck appear

Blastomyces sp. - Dimorphic Fungi

Yeast form



Filamentous form



IFI: Fusariosis

- Fusariosis is caused by Fusarium species
- Fusarium found in soil, plant and plant debris
- Its relatively prevalent
- In humans can cause local and superficial infections
- Airways are the principal method of entry
- Entry through skin due to trauma
- Entry via mucosal membranes
- Can result in occurrence of sinusitis and/or pneumonia

IFI: Fusariosis (continued)

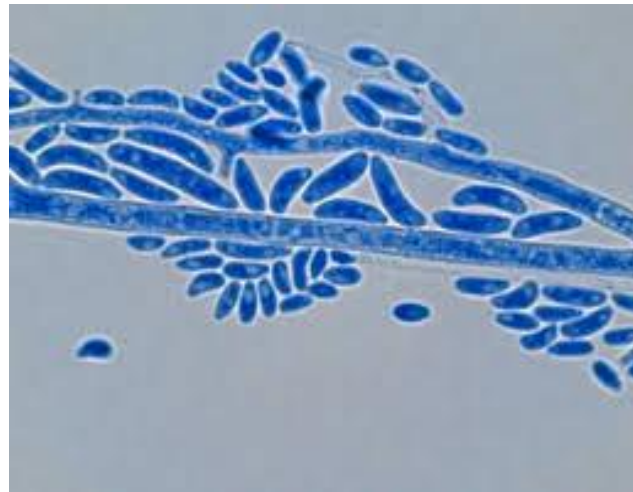
- Localized disease occurring mostly in immunocompetent
- Superficial infections include keratitis and onchomycosis
- Local invasive/ disseminated infections, the latter mostly in immunocompromised
- Causes allergic diseases such as sinusitis in immunocompetent
- Contaminated food ingestion can cause mycotoxicoses in human and animals due to toxin producing *Fusarium* sp.
- Its commonly seen in cultures. Common outdoor spores esp. in warm weather
- Indoors, common around bathtubs, shower heads, faucets

IFI: Fusarium

- Fusarium is characterized by the presence of macro and micro conidia
- It has the ability to produce mycotoxin
- *Fusarium solani* is considered a virulent species
- Immunocompetent host-can cause allergic sinusitis
- Immunocompromised host-sinusitis always invasive



Fusarium solani



Fusarium oxysporum

Standard Definitions for IFIs

1. European Organization for Research and Treatment of Cancer (EORTC)
2. National Institute of Allergy and Infectious Diseases (NIAID)
3. Mycoses Study Group (MSG)

In 2002 published standard definitions to establish a framework
“Proven” “Probable” and “Possible” invasive fungal infection used

Definitions for IFI

- Proven Invasive Fungal Infection

Fungus detected by histological analysis or culture taken from site of disease

- Probable and Possible Fungal Infections depended on:

1. Host factor, which pinpoints the risk of the patient
 2. Clinical sign
 3. Symptoms
- } Pertains to the diseases and the evidence from the culture and microscopic analysis and other relevant tests

This was used for strategy trials for formulation of clinical guidelines

Refining of Definitions

A little modification to include other groups of populations

- Criteria for Proven IFD (Invasive Fungal Disease)

Includes microscopic analysis, culture and blood culture from the site

- Criteria for Probable IFD

Host factors such as:

1. History of neutropenia
2. Receipts of stem cell transplant
3. Use of corticosteroids
4. Other treatments to be included

Clinical Criterion

- Respiratory tract fungal infection
- Lesions
- Ulcers, nodules in the airways
- Sino nasal infection

Mycological Criterion

- Mycological findings should be related to the symptoms
- This is evolving with time and technology

Diagnosis and Management

- Usage of biomarkers for detecting invasive mycosis
- Biomarkers reduces the invasive diagnostic procedures such as biopsy
- PCR techniques
- Histopathology and cultures
- Use of Electronic noses (E-noses) to detect VOC in patients
- Mandatory use of antifungal drugs initiated

IFIs- A Growing Global Problem

- IFIs uncommon in the early, 20th century
- Fungi have evolved and pose a major health problem that is reaching global proportions
- We know that increase in technology, new drugs, growing complicated health issues have resulted in IFIs on the rise

What can we do?

Conclusions

Its important:

- To regularly update predisposing factors of IFIs
- Prompt diagnosis
- Initiating early treatment and continue long term therapy, if needed
- Maintain treatment strategies for effectiveness
- Focus on control practices in hospitals
- Regular and frequent environmental screening of hospitals
- Effective disinfection strategies will reduce and curb incidents
- Increased awareness is important for being vigilant for timely and appropriate action

After all- “we all do better when we all do better”.

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Questions?

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