# Fungal Infections In The Intensive Care Unit

**An Essay**

*Submitted for partial fulfillment of the Master Degree in*
**Intensive Care**

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بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ
ورَسُولُهُ والْمُؤْمِنُونَ

صدق الله العظيم

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*Ayat Ibrahim Mostafa El Maddah*

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# List of Abbreviations

| | | |
|---|---|---|
| 5FC | : | 5-fluorocytosine |
| ABCD | : | Amphotericin B colloidal dispersion |
| ABLC | : | Amphotericin B lipid complex |
| ADCC | : | Antibody-dependent cellular cytotoxicity |
| AIDS | : | Acquired immunodeficiency syndrome |
| APCs | : | Antigen-presenting cells |
| BHI | : | Brain heart infusion |
| BM | : | Bone marrow |
| BSIs | : | Blood stream infections |
| C-C | : | Carbon-carbon |
| CDC | : | Center for control diseases and prevention |
| CF | : | Cystic fibrosis |
| CGD | : | Chronic granulomatous disease |
| CMV | : | Cytomegalovirus |
| CNS | : | Central nervous system |
| COPD | : | Chronic obstructive pulmonary disease |
| CRBSI | : | Catheter-related blood stream infection |
| CrCI | : | Creatinine clearance |
| CRs | : | Complement receptors |
| CSF | : | Cerebrospinal fluid |
| CVCs | : | Central venous catheters |
| CYP | : | Cytochrome P450 |
| DAMB | : | Amphotericin B deoxycholate |
| DC | : | Dendritic cells |
| DMSO | : | Dimethyl sulfoxide |
| DNA | : | Deoxyribonucleic acid |
| ELC/CCL19 | : | Epstein-Barr II ligand chemokine |
| ELISA | : | Enzyme-linked immunesorbent assays |

# List of Abbreviations (Cont.)

| | | |
|---|---|---|
| FDA | : | Food and drug association |
| GI | : | Gastrointestinal |
| GVHD | : | Graft versus host disease |
| HCFs | : | Health care facilities |
| HCWs | : | Health care workers |
| HIV | : | Human immunodeficiency virus |
| HSCT | : | Hematopoietic stem cell transplantation |
| HSPs | : | Heat shock proteins |
| IA | : | Invasive aspergillosis |
| IC | : | Invasive candidiasis |
| ICRA | : | Infection Control Risk Assessment |
| ICU | : | Intensive care unit |
| IFI | : | Invasive fungal infection |
| IMA | : | Inhibitory mold agar |
| JAK | : | Janus kinase |
| KOH | : | Potassium hydroxide preparation |
| LAMB | : | Liposomal amphotericin B |
| MAP | : | Mitogen-activated protein |
| MBL | : | Mannose-binding lectin |
| MHC | : | Major histocompatibility compound |
| MRs | : | Mannose receptors |
| NADPH | : | Nicotinamide adenine dehydrogenase phosphate(reduced form) |
| NETs | : | Neutrophil extracellular traps |
| NKT | : | Natural killer T cell |
| NPV | : | Negative predictive value |
| PAMPs | : | Pathogen-associated molecular patterns |
| PAS | : | Periodic acid-schiff stain |
| PCP | : | Pneumocystitis pneumonia |

# List of Abbreviations (Cont.)

| | | |
|---|---|---|
| PCR | : | Polymerase chain reaction |
| PE | : | Protected environment |
| PMN | : | Polymorphonuclear |
| PPV | : | Positive predictive value |
| PRRs | : | Pathogen recognition receptors |
| ROS | : | Reactive oxygen species |
| SDA | : | Sabourand dextrose agar |
| SLC/CCL21 | : | Secondary lymphoid-tissue chemokine |
| SOT | : | Solid organ transplant |
| STAT | : | Signal transducers and activators of transcription |
| TARC/CCL17 | : | Thymus and activation regulated chemokine |
| TLRs | : | Toll-like receptors |
| TNF-α | : | Tumor necrosis factor –alpha |
| USA | : | United States of America |

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# Introduction

Over the past quarter of a century, invasive fungal infections have emerged as an important cause of morbidity and mortality among critically ill patients ***(Meersseman et al., 2004).***

Fungi are largely opportunists causing infection when host defenses are breached. The risk factors for invasive candidiasis such as central venous catheters, broad-spectrum antibiotics, corticosteroids, renal failure, and recent major surgery overlap with clinical characteristics of many critically ill patients ***(Hajjeh et al., 2004).***

This particular group of patients has recently been categorized into different risk classes: *high risk* (allergenic bone marrow-transplanted patients, neutropenic and hematological patients); *intermediate risk* (autologous bone marrow-transplanted patients, subjects suffering from malnutrition, under corticosteroid therapy, with diabetes or underlying pulmonary diseases) and *low risk* (patients suffering from cystic fibrosis and connective tissue disease) ***(Voss et al., 1997).***

The vast majority of nosocomial fungal infections are due to Candida species, and a substantial percentage occurs in the intensive care unit (ICU) ***(Hajjeh et al., 2004).*** Invasive aspergillosis (IA) and zygomycosis are far less common in the ICU, occurring predominantly in patients

with qualitative or quantitative neutrophil abnormalities . Cryptococcosis and histoplasmosis remain a major cause of systemic infection in patients with severe T-Iymphocyte dysfunction, as does Pneumocystis pneumonia. Many of these patients are admitted to the ICU ***(Vonberg and Gastmeier, 2006).***

Clinical diagnosis of fungal infections is problematic because clinical presentation is variable and non specific, e.g., fever that is unresponsive to antibiotics, leukocytosis, chorioretinitis, endophtalmitis and skin lesions. Invasive disease (deep candidiasis) may affect major organs, such as the kidneys, spleen, liver, lungs, eyes, brain, and heart. Organ involvement can lead to organ failure if infection is not treated quickly and effectively ***(Richardson and Arnock, 2003).***

Definitive diagnosis of fungal infection is based on demonstration of fungi in formed cultures as well as by serological tests such as antigen based tests ***(Lau et al., 2008).***

Antifungal drug usage can be divided into four strategies for prevention and treatment. These represent a continuum from prophylaxis (administration of drug to high-risk groups without evidence of disease), through empirical administration of antifungals (to neutropenic patients with persistent refractory fever), to pre- emptive (using clinical, radiological and laboratory markers to determine the

likelihood of disease), and finally to treatment of established fungal infection ***(Segal et al., 2007).***

The past few years have brought major advances to both the diagnosis and treatment of fungal infections. The development of newer therapeutic modalities to supplement existing treatment options includes a new class of antifungal agents, the echinocandins. Newer and improved agents of the azole class have emerged as available therapeutic options together with better delineation for the role of liposomal amphotericins ***(Herbrecht et al., 2002)***.

# Mycology and Epidemiology

**Fungi are *classified in three ways:***

1- Morphological classification.
2- Classification according to sexual spore reproduction.
3- Clinical classification.

None of these classifications is completely satisfactory to be used alone.

## I) Morphological classification.

The fungi seen in the clinical laboratory can easily be separated into yeasts and molds based on the macroscopic appearance of the colonies formed.

**Yeasts:**

The yeasts produce moist, creamy, opaque, or pasty colonies on culture media, e.g. Cryptococcus neoformans.

The yeasts are unicellular rounded or oval organisms that reproduce by budding; their microscopic morphological features usually appear similar for different genera. Identification of the yeasts requires not only recognition of certain microscopic features, but also the use of biochemical tests to provide a definitive species identification ***(Astoon et al., 1998).***

Less commonly, pneumonia could be due to other 'no-molds' fungal agents such as Candida spp., Cryptococcus spp., or Pneumocystis jirovecii ***(Pagano et al., 2005).***

## Molds:

Molds (filamentous fungi) produce fluffy, cottony, woolly, or powdery colonies. The definitive identification of the mold requires recognition of characteristic microscopic features of the organism e.g., dermatophytes.

The basic structural units of the molds are tube like projections known as hyphae. As the hyphae grow, they become intertwined to form a loose network called the mycelium, which penetrates the substrate from which it obtains the necessary nutrients for growth. The nutrient-absorbing and water-exchanging portion of the fungi is called the vegetative mycelium. The portion projecting above the substrate surface is known as the aerial mycelium; aerial mycelia often give rise to fruiting bodies from which the asexual spores are born. Recognition of certain types of vegetated hyphae is helpful in plating the organism into a certain group ***(linda et al., 2000).***

Most fungi form septate hyphae which are cross-walls perpendicular to the cell wall. Some species are non septate, they form hyphae as continuous cell. In both septate and non septate hyphae, multiple nuclei are present with free flow of cytoplasm along the hyphae or through pores in septa.

Morphology is more important in mold than yeast identification but even with yeast, morphology on a sporulation media such as corn meal agar is a key first step in identification process.

**Dimorphic fungi:**

Some of the slow-growing pathogenic fungi are dimorphic and produce either a mold form or a yeast form under certain circumstances depending on the temperature **.**

The yeast phase (parazitic) formed in host tissue, and at 37°C in culture and in nature (saprophytic), e.g. Histoplasma capsulatum. Serologic tests for antibodies and antigen detection are especially helpful in the diagnosis of histoplasmosis. Detection of Histoplasma capsulatum antigen in bronchoalveolar lavage fluid may be particularly helpful in patients with acute pulmonary histoplasmosis or disseminated disease with pulmonary involvement. Antifungal therapy is given to prevent reactivation of histoplasmosis during immunosuppressive therapy ***(linda et al., 2000).***

**Polymorphic fungi:**

Other organisms may also produce both yeasts and filaments but the two forms may exist together and their appearance is not necessarily determined by temperature. It is more appropriate to consider these fungi as polymorphic (pleomorphic), e.g., Malassezia furfur.

## II) Classification according to sexual spore reproduction

Fungi may reproduce **sexually** (meotic), **asexually** (mitosis) or by **both** means. Sexual reproduction is