The Incidence of Systemic Fungal Infection Associated With Central Venous Catheter at Neonatal Intensive Care Unit in Ain Shams Pediatric Hospital

Thesis

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By

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INTRODUCTION

Invasive fungal infections in infants and neonates, especially in neonatal Intensive Care Units (NICUs), are a problem in clinical treatment and are accompanied with a high mortality ***(Brissaud et al., 2011).***

Candida is the third most common cause of late onset sepsis in NICU patients and accounts for 9-13% of blood stream infections (BSI) in neonates ***(Oberoi et al., 2012).***

Although Candida albicans has historically been the most frequently isolated species, recently non-albicans Candida (NAC) have emerged as important opportunistic pathogen, notably Candida (C.) tropicalis, C. parapsilosis, C. krusei and C. glabrata ***(Goel et al., 2009).***

Clinical presentation of candidemia resembles sepsis syndrome and to establish a clinical diagnosis is difficult. Respiratory insufficiency, feeding intolerance, abdominal distention, temperature instability, lethargy, and decreased perfusion are the various clinical manifestations associated. Candida BSIs are associated with very high crude mortality of over 60%, while attributable mortality may be as high as 49% ***(Ariff et al., 2011).***

Central venous catheters (CVCs) are widely used in NICUs. They provide an intravenous route for the safe

administration of fluids and medications. The most common types of CVCs used in NICUs are umbilical venous catheters (UVC) and peripherally inserted central catheters (PICC) ***(Menon, 2003).***

Adverse events related to the use of CVC are infections, mechanical adverse events and thrombosis. According to the literature, mechanical adverse events occur in 5 to 19% of patients with a CVC, infectious adverse events in 5 to 26% and thrombosis in 2 to 26% ***(Hsu et al., 2010).***

The major risk factors for invasive candidiasis and candidemia are central venous catheters, use of broad spectrum antibiotic therapy and parenteral nutrition ***(sardana et al., 2012).***

Use of multiple invasive devices (catheters, endotracheal tubes) or surgery causes break in the skin and mucosal integrity, which predisposes these sites for colonization and infection by Candida ***(Zaoutis et al., 2010).***

Although the overall incidence of candidemia is decreasing from 0.92 to 0.2 infections per 1,000 central IV line days, treatment is still a challenge ***(Benjamin et al., 2006).***

AIM OF WORK

The aim of this study was to detect the incidence rate of systemic fungal infection associated with central venous catheters, assessing the risk factors of fungal infection and the effect of empirical antifungal treatment on the neonates at NICU of Ain Shams Pediatric Hospital.

Chapter 1

MEDICALLY IMPORTANT FUNGI

Fungi are neither plants nor animals and are placed in their own kingdom, though historically this was not always the case. Taxonomists initially placed fungi in the plant kingdom (Plantae) because, plants and fungi are both sessile (not free-moving) and have cell walls. However, fungi lack chlorophyll (and thus cannot make their own food via photosynthesis) and have walls made of chitin, not cellulose as seen in plants. Fungi are closely related to animals and bacteria and were once placed in the animal kingdom (Animalae), but fungi are not motile. Fungi proved to be unique life forms deserving their own kingdom ***(Wilson, 2000).***

- **Morphology**

Fungi are eukaryotic microorganisms that occur ubiquitously in nature. Only about 200 of the thousands of species have been identified as human pathogens and among these known pathogenic species fewer than a dozen are responsible for more than 90% of all human fungal infections ***(Marr et al., 2002).***

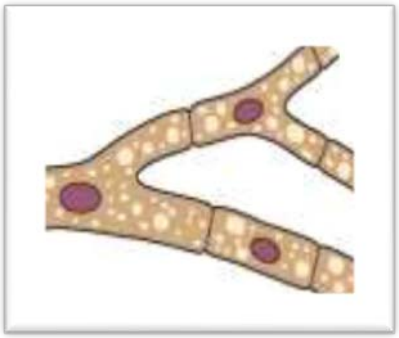
Fungi may be classified simply on the basis of morphology as either yeast or molds ***(Marr et al., 2002).***

1. **Yeasts:**

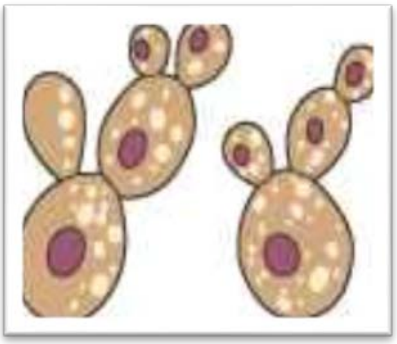
Yeasts are unicellular (oval or spherical cells ranging in diameter from 3-5 μm), budding cells, producing moist, creamy opaque or pasty colonies. They are multiple by the production of buds. Candida buds may be produced one from the other in a linear fashion without separation forming what is termed "pseudohyphae" ***(Nucci et al., 2013).***

2. **Molds**:

Molds are multicellular, filamentous forms of fungi consisting of thread like filaments termed hyphae that interweave to from a mat-like structure termed mycelium, producing fluffy, cottony, wooly or powdery colonies ***(Nucci et al., 2013).***



(A) Mold form, hypha.



(B) Yeast form, budding.

Figure (1): Basic morphological forms of fungi ***(Nucci et al., 2013)***.

- **Subcellular structure of fungi**

In most, fungal cells are larger than most bacteria. They possess all the cytoplasmic organelles indicated in figure (2) with the exception of chloroplasts, and consequently are not photosynthetic. The medically important structures of a fungus are capsule, cell wall and cytoplasmic membrane ***(Carter et al., 2004).***

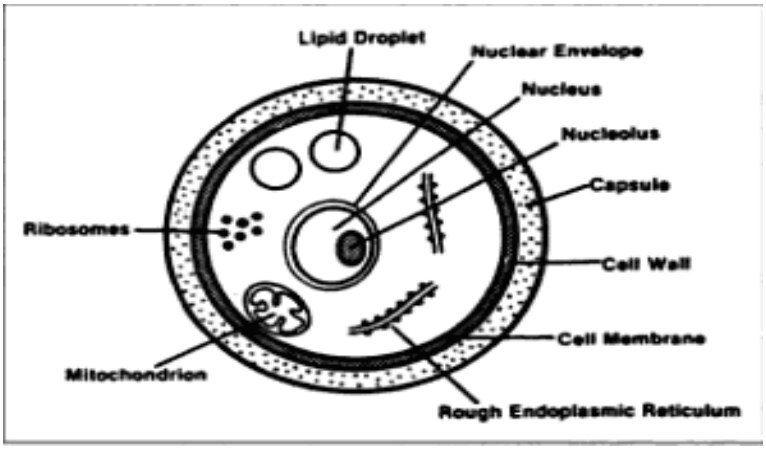


Figure (2): Schematic drawing of a yeast cell ***(Carter et al., 2004).***

The cell walls of fungi consist of nearly 90% carbohydrate and fungal membranes are rich in sterol types not found in other biological membranes (e.g., ergosterol) ***(Kaufman et al., 2014)***.

CANDIDA SPECIES

Candida (C.) is yeast and is a frequent colonizer of human skin and mucous membranes. Candida is a member of normal flora of skin, mouth, vagina, and intestine. It is found in the environment, particularly on leaves, flowers, water, and soil ***(P. Manzoni et al., 2011).***

A.Classification:

Candida is classified into C. albicans which is the most common opportunistic yeast and non-albicans candida ***(Posteraro et al., 2010).***

- **Candida albicans**

C. albicans is an asexual, diploid, dimorphic fungus that is widespread on humans and in their environment. We still don't understand why this common commensal sometimes becomes pathogenic, although impaired host defense mechanisms seem crucial. A variety of fungal virulence factors is being actively explored by researchers, but fungal adherence may be most important ***(Posteraro et al., 2010).***

- **Non-albicans Candidiasis**

Not all fungal infections are due to C. albicans, more than a third are due to other organisms such as C. Glabrata, C. Krusei, C. Parapsilosis, C. Tropicalis, C. Kefyr (previously named C. Pseudotropicalis), C.Dubliniensis and occasionally very resistant species like C. Lusitaniae ***(Eugene Leibovitz, 2012).***

B. Virulence factors of candida:

Most candida species are known to possess virulence factors. The ability to switch between different cell phenotypes, adhesion to inert and biological substrates, immunomodulation of host defense mechanisms and variability are also considered virulence factors ***(Murphy, 2000).***

1. Adhesion to mucosal cells:

C. albicans has the ability to adhere to mucosal cells, a feature that distinguishes it from most other candida species. The ability of yeast forms to adhere to the underlying epithelium is a critical step in the pathogenic process. It is achieved by combination of specific and non-specific mechanisms. Specific mechanisms involve the ability of the yeasts to recognize a variety of host cell receptors with cell surface adhesions. Nonspecific mechanisms include

electrostatic forces, aggregation and cell surface hydreopocicity ***(Wiener et al., 2002).***

2. Dimorphic transition:

The pathogenic potential of C. albicans is strongly associated with morphogenetic conversion from budding yeast to the filamentous growth form or hyphae ***(Rodrigues et al., 2001).***

This is based on the appearance of hyphae in invasive lesions. Hyphae of C. albicans may be able to elaborate an extracellular proteinase, which digests epithelial cells**.** C. albicans hyphae have the capacity to bind to a number of molecular structures found in human tissues. These include components of the extracellular matrix such as fibronectin, collagen, virtonectin, llaminin and complement C3 conversion products. This binding is mediated by mannoprotein and may influence its morphology and pathogenic behavior and there by tissue invasion and dissemination ***(Wiener et al., 2002).***

3. Proteinase production:

This proteinase probably facilitates invasion and may also play a role in adherence. The secreted aspartyl proteinases of C. albicans, C. tropicalis and C. parapsilosis may play an active role in the progression of oral candidiasis particularly with regard to the low PH microenvironments in the oral cavity, which are regularly replenished with dietary carbohydrates.

Protease's negative mutants of C. albicans are less pathogenic in experimental infections ***(Rodrigues et al., 2001).***

C. albicans produces higher levels of proteases and is more adherent to epithelial cells than non albicans strains ***(Rodrigues et al., 2001).***

4. Lipase production:

Various species of candida have been reported to have lipolytic activity by producing esterases. These enzymes mediate candida pathogenesis, by facilitation the hyphal invasion especially in disseminated candidiasis ***(Kamtarcioglu, 2001).***

5. Blastoconidia formation:

C. albicans produce budded cells known as blastoconidia. C. albicans blastoconidia have lower hydrophobicity than non-albicans strains ***(Rodrigues et al., 2001).***

6. Germ tube formation:

The germ tube formation by C. albicans is assumed to be an important virulence factor by promoting adherence to host cells and also for tissue invasion. Resistance to phagocytosis increases with increasing rate of germ tube formation and also with the length of the germ tubes ***(Jabra-Rizk et al., 2000).***

C. Epidemiology:

Candida infections are a major cause of septicemia in NICU. Most neonatal fungal infections are caused by C. albicans and C. parapsilosis, and in the last few years there has been an increase in cases caused by C. tropicalis. The sources of candidiasis are mostly endogenous, and many papers described such outbreaks ***(Leibovitiz et al., 2006).***

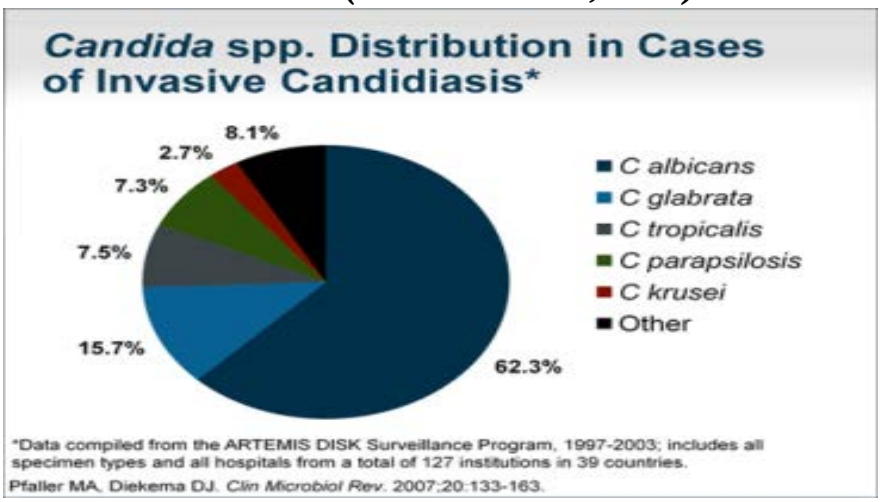


Figure (3): The distribution of candida spp.

It was reported that Candida was responsible for 9% of all episodes of late-onset (>3 days of life) bloodstream infections among infants. Candida infections are a significant cause of mortality (10-54%) and morbidity (25%) in the NICU. Acquired late onset systemic fungal infections occur in neonates who have risk factors ***(Leibovitiz et al., 2006).***

ASPERGILLUS SPECIES

A. Classification:

The aspergilli compose a group of rapidly growing; hyaline molds that commonly cause opportunistic infections in human. Of 700 aspergillus (A) species, only 19 species have been cited by ***Rinaldi, (1983)*** as causing human infection; of these only four species are recovered with frequency form hospitalized patients: A. fumigatus, A. flavus, A. niger and A. terreus ***(Pattron, 2006)***.

B. Virulence factors:

It is well documented that there is an increased risk of aspergillosis in individuals who are immunocompromised, thus it is difficult to assess whether specific fungal virulence factors play a role in the development of the disease ***(Summerbell RC, 2003).***

1. **Elastases**: A. fumigatus is known to produce two elastases, including a serum proteinase and a metallo-proteinas, which may act on elastin that compromises approximately 30% of the lung tissue. However, no definitive evidence has been shown that elastases are related to pulmonary infection ***(Summerbell RC, 2003).***

2. **Catalase**: it may be a virulence factor contributing to aspergillosis. The association of catalase production with aspergillosis is uncertain ***(Summerbell RC, 2003).***
3. **Aflatoxin**: is a toxin produced by A. flavus ***(Summerbell RC, 2003).***

C.Epidemiology and pathogenesis

Several species of aspergilli are among the most frequently encountered organisms in the clinical laboratory; some are pathogenic, whereas others are infrequently associated with infection or do not cause infection at all. The aspergilli are wide spread in the environment, where they colonize grain, leaves, soil and living plants. Conidia of the aspergilli are easily dispersed into the environment, and humans become infected by inhaling them. It is difficult to assess the significance of members of the genus Aspergillus in a clinical specimen. They are found frequently in cultures of respiratory secretion, skin scrapings, and other specimens ***(Summerbell RC, 2003).***

Aspergillus species is capable not only of causing disseminated infection, but also of causing a whole variety of other types of infection, including lung infection, pulmonary fungus ball, allergic bronchopulmonary Aspergillosis, external otomycosis, mycotic keratitis, onychomycosis, sinusitis, endocarditis and central nervous system infection ***(Nucci and Marr, 2005).***