Risk factors, Diagnosis and Management of invasive candidiasis and candidemia in adult intensive care unit patients

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LIST OF ABBREVIATION

Abb	
AmB	Amphoterecin B
APACHE	Acute Physiology and Chronic Health Evaluation
BAL	Bronchoalveolar lavage
BC	Blood culture
Bid	Twice daily
BSIs	Blood stream infections
CAGTA	C. albicans germ-tube antibodies
CBC	Complete blood cell count
Crcl	Creatinine clearance
CS	Candida score
CT	Computerized tomography
CVC	Central venous catheter
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
FC	Fluorocytosine
FDA	Food and Drug Administration
FISH	Fluorescent in situ hybridization
FLC	Fluconazole
GM	Galactomannan
GI	Gastrointestinal
IC	Invasive candidiasis
ICU	Intensive care unit
IDSA	Infectious disease society of america
IFD	Invasive fungal disease
ITC	Itraconazole.
IFI	Invasive fungal infection
IQR	Interquartile range

Abbreviation

IV	Intra venous
KTC	Ketoconazole
LOS	Length of stay
lip Am B	liposomal amphotericin B
Ld	Loading dose
MALDITOF-MS	Matrix-assisted laser desorption ionization time of flight mass-spectrometry
MICs	Minimum inhibitory concentrations
Ms	Modest activity
MV	Mechanical ventilation
NPV	Negative predictive value
NA	Not assessed
NAS	Non- albicans species
PCR	Polymerase chain reaction
PCT	Procalcitonin
PO	Per oral
PPV	Positive predictive value
Qid	Four times daily
R	Resistant
RC	Resistance depending on the concentration
S	Susceptible
SDd	Susceptible dependent on dose
SEN	Sensitivity
SICU	Surgical intensive care unit
SOAP	Sepsis Occurrence in Acutely Ill Patients
SPE	Spesifity

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Introduction

Candida is part of our normal microbial flora on mucosal surfaces, from where it may cause local infections like thrush in the oral cavity and candida vaginitis. However, in patients with various underlying diseases or host factors, candida may cause invasive candidiasis, most often as bloodstream infection (candidaemia) with or without secondary dissemination to the eyes, liver, spleen, bones, heart valves, central nervous system or as deep-seated candidiasis, such as peritonitis after gastrointestinal surgery. The overall mortality (within 30 day) associated with candidaemia is around 30–40% and depends on the severity of underlying disease, the candida species involved, and timing and choice of antifungal treatment ***(Hassan et al.,2009).***

In population-based studies, the most important patient groups associated with invasive candidiasis are the following:

1- Neonates especially if being low-birth weight or preterm babies.

2-Critically ill patients especially if having severe disease and a long term stay in ICU.

3- Patients undergoing abdominal surgery especially if complicated or repeated.

4-Patients with malignant disease or acute necrotizing pancreatitis.

5-Transplant recipients.

6-Burn patients especially if burns involve larger body surface area or full thickness area. ***(Vardakas et al., 2009).***

The severity of the underlying disease is an important factor for mortality after systemic infection, overall mortality is consistently higher in candidaemic ICU patients than other candidemic patient in general.

Invasive candidiasis manifests as either isolated candidaemia, invasive candidiasis without documented candidaemia or a combination of the two ***(Leroy et al., 2009).***

The treatment of invasive candidiasis and candidemia can be schematically described as prophylactic, pre-emptive, empiric or curative. Prophylactic treatment covers all the situations where the patient is not infected and lacks the signs and symptoms of infection. In pre-emptive treatment, based on evaluation of the patient's risk factors combined with positive surrogate markers of infection, the goal is to decrease candida-related mortality. Empiric therapy describes individuals with symptoms of infection with no obvious source who merit therapy based on clinical grounds. Finally, curative treatment focuses on a microbiologically documented pathogen ***(Parkins et al., 2007).***

Patient groups and risk factors

Invasive fungal infections are increased in patients admitted to intensive care units and are associated with high mortality rates. The majority of these life-threatening infections are caused by opportunisticpathogens that belong to the genus candida, and c. albicans represents the most common cause ***(Conciaet al., 2009).***

In the past, invasive fungal disease (IFD) was more commonly found in patients who were neutropenic, had received a solid organ transplant or had been treated with corticosteroids or cytotoxic agents ***(Kauffman., 2006).***

The incidence rate for invasive fungal infections has increased globally over the past 2 to 3 decades, especially in healthcare settings. Along with this trend, these infections occurred more often in the non neutropenic critically ill patients than in those patients who were neutropenic or had received organ transplantation in the past. Candida species comprised the majority of these pathogenic fungi ***(Arendrup et al., 2009)***

Before considering treatment issues, clinicians must appreciate the risk factors for fungal BSIs. Through understanding the issues and variables that heighten the potential for candidemia, one can focus on efforts not only at prevention but also on prompt diagnosis and treatment.Common risk factors predisposing to candidemia include candidal colonization, prior exposure to antibiotics, renal failure, presence of a central venous catheter (CVC), and need for total parenteral nutrition (TPN) ***(Blumberg et al., 2001).***

Certain hospitalized individuals are well known to be at risk for acquiring candidemia during hospitalization as a result of their underlyingmedical condition, including patients with hematologic malignancies or neutropenia, patients undergoing gastrointestinal surgery, premature infants, and elderly persons ***(Eggimann et al., 2003).***

Within these high-risk groups, additional risk factors have been recognized, and these specific exposures have not changed significantly during the past 2–3 decades. The presence of vascular catheters, exposure to broad-spectrum antimicrobial agents, renal failure, mucosal colonization with candidaspecies, prolonged ICU stay, and total parenteral nutrition are all recognized to increase the risk for nosocomial candidemia ***(Puzniak et al., 2004).***

TABLE1: Candidemia risk factors for hospitalized patients*(Ostrosky-Zeichner and Pappas, 2006).*

Risk factors	Possible role in infection
Antimicrobial agents	Promote fungal colonization
Adrenal corticosteroid	Immuno-suppression
Age	Immuno-suppression
Chemotherapy	Immuno-suppression Mucosal disruption
Malignancy	Immuno-suppression
Previous colonization	Translocation across mucosa
Gastric acid suppression	Colonization and translocation

Indwelling catheter	Direct vascular access
Central venous catheter	Contaminated product Pressure transducer
TPN	Direct vascular access Hyperglycemia Contamination of infusate
Neutropenia (_500/mm3)	Immuno-suppression
Surgery (gastrointestinal)	Route of infection Direct vascular access
Mechanical ventilation	Route of infection
Renal failure/hemodialysis	Route of infection Immuno-suppression
Malnutrition	Immuno-suppression
Hospital or intensive care unit stay	Exposure to pathogens Exposure to additional risk factors
Severity of disease.	Immuno-suppression Invasive procedures

Analysis of risk factors:

The risk factors examined varied between the studies. All the risk factors that were identified as statistically significant associated with IFD in one or more of the 10 studies that carried out a multivariable analysis. Candidate risk factors, in descending order are described below.

1. Surgery:

Seven studies examined the association between surgery and IFD. The type and timing of surgery varied across the studies, with two looking at abdominal surgery and the others looking at any surgical procedure. Five of the seven studies reported a significant association between surgery and invasive fungal diseases(IFD) on both univariable and multivariable analyses***(Chow et al., 2008)***.

Injury, trauma, and blood loss in surgical patients, whichresult in marked depression in cell-mediated immunity, may specifically be associated with high incidence of invasive fungal infection (IFI). However, some factorsotherthan underlying disease and characteristics of patients admitted to the ICU may also contribute to the high incidence. First, some of the patients werediagnosed as having IFI butwithoutbiopsy, whichmaylead to enrollment of patients with fungal colonization and overestimation of IFI in surgical patients with severe sepsis. Second, most of the enrolled patients with severe sepsis had been hospitalized in the surgical wards before their ICU admission and hence, they were more susceptible to nosocomial fungal infection ***(Volk ., 2002).***

2. **Total parenteral nutrition:**

Six of the twelve studies assessed total parenteral nutrition as a risk factor, and all found a significant association with IFD on univariable analysis ***(Chow et al., 2008).***

3. Fungal colonization:

Candida colonization should be addressed as a risk factor and not as an infection itself. This is particularly true when the colonization index (an index based on the number of positive sites/ cultured sites) increases ***(Piazza et al., 2004).***

Fungal colonisation has been associated with the development of invasive candidiasis IC. Yet, a small proportion(3%–25%) of colonized patients subsequently develop invasive disease***(Agvald-Ohman et al., 2008).***

Different risk factors for invasive candidiasis, including prior candida species colonization, could allow recognition of patients at highest risk. Such patients may be potential candidates for preemptive antifungal therapy***(Piarroux et al., 2004).***

Colonization was defined as the presence of candida species in non significant samples obtained from the oropharynx, stomach, urine, or tracheal aspirates. Colonization was considered unifocal when candida species were isolated from one focus and multifocal when candidaspecies were simultaneously isolated from various non contiguous foci, even if two different candidaspecies were isolated, oropharynx and stomach were considered one site (digestive focus).

Unifocal and multifocal colonization persistence was defined by at least two weekly consecutive sets of candida positive cultures (***León et al., 2006).***

Patients were classified into three groups as follows:

a. Neither colonized nor infected,
b. Unifocal or multifocal candida species colonization without proven infection,
c. Proven candidal infection ***(Leónet al., 2006).***

Candida colonization could be found in the respiratory samples obtained by broncho-alveolar lavage (BAL), endotracheal aspirate or protected specimen brushing in critically ill patients. Since patients with chronic lung pathology provide a suitable nidus for fungal colonization, screening such patients for fungal colonization of the respiratory tract would enable us to identify individuals requiring closer monitoring for the development of possible complications like acute invasive fungal infection or dissemination via hematogenous spreed ***(Delisle et al., 2011).***

4-Renal replacement therapy:

Seven studies examined renal replacement therapy as a risk factor for IFD, of which five found a significant association on univariable analysis***(Jordà-Marcos et al., 2007).***