

Epidemiology of Candidaemia: A Prospective Comparison between Invasive Candidiasis in Italy and All Over the World

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Introduction

Candida is an important cause of bloodstream infections (BSI), causing significant mortality and morbidity in health care settings [1]. Invasive candidiasis (IC) is a serious disease in hospitalized critically ill and immune-compromised patients [2]. The advances of the supportive therapies, of the complexity of surgical procedures, of the number of elderly people in our society and of the changes in patient demographic characteristics have progressively expanded the population at high risk for fungal diseases. Consequently, the prevalence of *Candida* infection has increased leading to a higher frequency of invasive candidiasis and candidaemia [3,4]. Bloodstream infections sustained by *Candida* species are a major cause of morbidity, hospital length of stay, cost of care and mortality in hospitalized patients, the latter ranking 20-30% of all nosocomial BSIs [5,6] or even more [7].

The epidemiology of candidaemia has been extensively investigated all over the world. The annual incidence of *Candida* BSI varies greatly by region based on epidemiological studies from Europe and USA (range from 3.0 to 26.2/100,000 inhabitants). Among the North-Europe countries, Norway, Finland and Sweden reported an incidence of 3/100,000 population whereas Denmark reported 8.6/100,000 population in a semi-national survey [8]. In the middle and southern parts of Europe population-based surveys, Switzerland, UK, Scotland, Italy and Spain reported 1.2-8.1/100,000 population [1,9]. Finally, in surveys conducted in Iowa, San Francisco, Atlanta and Connecticut (USA), rates of 6-14/100,000 population have been demonstrated [10] with the exception of the Baltimore area reporting 26.2/100,000 [11]. Then it can be deduced that the incidence of candidaemia varies in different geographical areas so that the study of the local data is crucial for an accurate knowledge of the epidemiological data and consequently for an adequate therapeutic approach [12].

Since early 90s, a trend for a steady enhancement of the incidence of candidaemia has been observed in Europe [13]. Accordingly, in Italy [2], it has been observed that the frequency with which *Candida* was cultured from BSI, increased over the time with a significant enhancement in the number of isolates from 2010 to 2012. This observation parallels to that of Bassetti et al. [7], who showed increased incidence of candidaemia from 2008 until 2010 in a study performed in a tertiary care hospital in northern Italy.

Risk factors for *Candida* BSI are well known and mainly include broad-spectrum antibiotic therapy, malignancy, total parenteral nutrition, presence of CVC (Central Venous Catheter), previous colonization by *Candida* spp, immunosuppressive treatment, neutropenia etc.

In Policlinico Umberto I°, Sapienza University of Rome, (Mascellino MT et al. 2015, submitted), *Candida albicans* was the most detected species (44%) whereas *non-albicans* strains altogether accounted for 56% being *Candida parapsilosis* the most frequent isolate (32%), followed by *Candida glabrata* (13%), *Candida tropicalis* (7%) and *Candida krusei* with other minor species such as *C. guilliermondii*, *C. lusitaniae* and *C. famata* (4%). *C. tropicalis* was significantly higher ($p=0.03$) in non-Intensive Care Unit patients whereas the opposite was true for *C. parapsilosis*. *C. albicans* showed a greater isolation rate in ICU (58%). In 2015, an isolation peak of *C. parapsilosis* (47%) has been observed overtaking the *C. albicans* detection rate (44%). Probably this is due to the fact that *C. parapsilosis* is reported to be able to attach to polymeric surfaces and generate a biofilm structure, protecting the organisms from the host defences and antifungal drugs, confirming the role of external devices as a leading risk factor for *Candida* infections [14].

All the strains tested were fully susceptible to echinocandins and amphotericin B. Decreased susceptibility to fluconazole was mainly seen with *C. glabrata* and *C. parapsilosis* (MIC 90 respectively 16 and 4 mcg/ml). Caspofungin and voriconazole resulted to be the most potent antimycotics with higher MICs of caspofungin for *C. parapsilosis*. All isolates were wild-type organisms and no acquired resistance was detected based on EUCAST breakpoints 2014 (<http://www.eucast.org>). Incidence of candidaemia per 10,000 admissions ranged from 6.8 to 12.4 over a 3- year period (2012-2014) (Mascellino et al., submitted 2015).

These findings agreed with those reported by other studies performed in Italy that showed similar ranking among the species isolated [1,7,15]. Unlike Italy, *C. glabrata* was the *non-albicans* species detected in USA with a higher frequency in BSI, being *C. parapsilosis* the third species isolated [11]. Therefore it seems as stated before, that the epidemiology of candidaemia varies in the different countries [5,16].

It was estimated that the relative frequency of IC and candidaemia was greater in patients hospitalized in Intensive Care Unit (ICU) considering also that the extensive use of indwelling central venous catheters could contribute to a higher incidence of candidaemia [14,16,17]. However other studies [1,8] have clearly demonstrated that these infections are not just confined to ICU, but rather they are widespread within the hospital with higher rates. The greater incidence of some pathology such as diabetes and other underlying medical conditions may account for a high impact in non-ICU patients. However the distinction between the species distribution and the susceptibility profiles detected in ICU from those in non-ICU environments, has been poorly studied (even among pediatric patients) especially at a local level [18-20], whereas high impact studies have been conducted at a global level [4,10].

In our hospital, a steady rise in the number of yeasts isolated from blood cultures was observed in ICU during 2014 as compared with 2012 (16.7% versus 40.9%, $p=0.002$) but always lower than the isolation rate in non ICU settings (more than 65%), with values quite similar to those of Bassetti et al. in northern Italy [7]. However, these rates were higher than those reported by Pfaller et al (55.5%), who conducted a worldwide study on the distribution and the resistance to antimycotics of *Candida* species in ICU and non-ICU wards through the Sentry Antimicrobial Surveillance Program [16]. The differences could reflect the local features, such as patient population characteristics, infection control strategies and specific antimicrobial practices [21] as compared with a large study which merged a vast quantity of data.

In conclusion, invasive fungal infections represent an increasing challenge both in ICU and in non-ICU clinical settings. The knowledge of the local epidemiology and of the susceptibility profiles are factors of paramount importance for the clinical management of these potentially lethal infectious diseases. The shift from *C. albicans* towards other species of *Candida* has been noticed all over the world in the last decades [22].

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