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REVIEW

Nosocomial *Candida* infections: epidemiology of candidaemia

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Nosocomial *Candida* infections

The progress in medicine over the last two decades with introduction of new technologies and therapies, which has allowed the survival of more and more patients suffering from serious diseases, has brought about an increase in the number of hospitalised and immunocompromised subjects. These individuals are highly susceptible to nosocomial fungal infections, especially to candidosis. *Candida* spp. infections range from thrush to invasive diseases such as arthritis, osteomyelitis, endocarditis, endophthalmitis, meningitis, or fungaemia [1, 2].

Nosocomial candidosis may be exogenous or endogenous. Although the finding of *Candida* on superficial body sites cannot be considered evidence of infection, the adhesion and persistence of yeast on these surfaces is the first step in the development of candidosis. Disseminated candidosis is commonly associated with an inadequate immune response, sometimes with an abnormal production of IgA. This allows the invasion of the mucosal barriers, in proportion to the magnitude of colonisation [3-5].

Genotypical analyses carried out on colonising and infecting strains showed that strains causing infections often originate from a commensal population on the body surface and/or gastrointestinal tract of patients [3, 6]. This is supported by cases of candidaemia that occurred in patients in bone marrow transplant and haematology/oncology units, in positive-pressure or private rooms. In these situations, isolation, the proper employment of hygienic measures by the hospital personnel and the provision of specialized diets minimize the risk of cross-infection from patient to patient [2].

The exogenous acquisition of nosocomial candidosis is proved by several reported outbreaks. These cases seem to be associated with environmental factors, such as the presence of multiple doors into the rooms, the transportation of patients to different units or the contamination of liquid for infusion and biomaterials, but above all with the behaviour of the personnel [2, 3, 6, 7]. Studies carried out using different methods to verify the similarity among strains isolated from the hands of health care workers (HCWs) and strains colonising their patients demonstrated the role of personnel in the spread of infection; *C. parapsilosis* and *C. albicans* are the species most frequently isolated from the hands of HCWs [3, 8, 9].

The differentiation between endogenous and exogenous infections is important to determine suitable control measures to prevent further transmission of *Candida* [2].

Over the last 20 years there has been world-wide increase in mucocutaneous and invasive fungal infections [3]. The 115 hospitals participating in the National Nosocomial Infections Surveillance (NNIS) system reported between 1980 and 1990 an increase in the rate of nosocomial fungal infections from 2.0 to 3.8 per 1,000 discharges [10]. This trend was observed for all clinical manifestations including oropharyngeal infections, surgical site infections, and urinary tract infections, but especially for fungaemia, which rose from 5.4% of all nosocomial bloodstream infections (BSI) in 1980 to 9.9% in 1990 [2, 10]. In addition to the increase in the incidence of endemic nosocomial fungal infections, numerous nosocomial fungal outbreaks were reported [2, 4].

In the European Prevalence of Infection in Intensive Care (EPIC) study, carried out in 1992 on 1,417 intensive care units (ICUs) in 14 European countries, 17.1% were fungal infections. Fungi were the fifth most common cause of nosocomial infections after Enterobacteriaceae, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and coagulase-negative staphylococci [4, 12].

The majority of nosocomial fungal infections are reported to be caused by *Candida* spp. [2, 10]. *C. albicans* is the single most common species causing infections. The NNIS reported in 1990-1992 *C. albicans* as ranking seventh among the pathogens isolated from major infection sites (i.e., urinary tract, surgical site, bloodstream and lungs) [2, 13]. *C. albicans* accounted for 76% of 24,227 cases of candidosis reported in the NNIS hospitals in the period 1980-1990, with an increase in the proportion of nosocomial infections from 2% in 1980 to 5% in 1986-89; in the Netherlands it accounted for 73% of all *Candida* infections [3, 4, 14].

The second species most frequently associated to human infections is *C. glabrata* in the USA and Norway, and *C. parapsilosis* in Canada and South America [16-18].
C. albicans, *C. parapsilosis*, *C. tropicalis*, *C. glabrata* and *C. krusei* cause the most common clinical manifestations; at times other species such as *C. dubliniensis*, *C. guillermondii*, *C. kefyr*, *C. lipolytica*, *C. lusitaniae* and *C. rugosa* are involved.
The presence of *C. albicans* on mucosal surfaces may become the cause of chronic infections in individuals with insufficient or absent immune cell-mediated mechanisms. Critically ill and neutropenic patients are particularly at risk of developing invasive *C. albicans* infections, with fungaemia and the involvement of multiple organs.
C. tropicalis is isolated less frequently than *albicans* in the hospital setting, but it is an important cause of invasive candidosis, especially in leukemic patients [19].
Like *C. albicans*, *parapsilosis* is a commensal of several body sites. This species is often isolated from the blood of hospitalised patients, with various prevalence rates among different structures [19, 20]. Unlike *albicans* and *tropicalis*, *C. parapsilosis* in most cases originates from an environmental source: nosocomial infections caused by this species are frequently associated to the employment of a prosthesis or the application of invasive procedures. In several reports on the outbreaks of fungaemia, endophthalmitis and endocarditis caused by *C. parapsilosis*, the fluids for parenteral nutrition, intravascular devices, ophthalmic solutions and glove laceration during surgical procedures were shown to be involved [19, 21].
C. krusei can colonise the gastrointestinal, respiratory and urinary tracts and produce opportunistic invasive infections in neutropenic patients, particularly those with leukemia. A deterioration of the gastrointestinal mucosa subsequent to cytotoxic chemo- or radiotherapy is a risk factor for the development of *C. krusei* fungaemia. A high mortality is associated to this species for neutropenic patients [19, 22].
Candidaemia caused by *glabrata* have a higher complication rate than that caused by other non *albicans* species. The management of patients infected by *glabrata* or *krusei* is difficult due to their reduced susceptibility to azoles [19].

Nosocomial candidaemia

The invasive *Candida* spp. infections are candidaemia and disseminated or systemic candidosis. Systemic candidosis refers to the presence of yeast in non-adjacent, normally sterile sites, demonstrated by culture or histological analysis. The isolation of Candida from the blood of patients with clinical signs of infection is evidence of candidaemia, even though the clinical signs may be lacking in neutropenic patients or in subjects receiving steroids [1].
Candidaemia is widely studied, as it accounts for 10-20% of all candidosis and is the most common fungal bloodstream infection [1, 2, 7, 10, 15, 23].
Although the surveillance studies to date were not coordinated, the results contribute to delineating the epidemiology of candidaemia [24].
In the last two decades, the increasing number of immunocompromised patients has brought about a rise in the incidence of nosocomial candidosis, which was previously rare and limited to burn or severely traumatised patients [3, 10].
The origin of this problem is relatively recent: in a review of the aetiology of nosocomial BSI between 1935 and 1983, fungi (and *Candida* spp.) were reported only since 1953 as the cause of 3.8% of all BSI in Boston City Hospital [25, 26]. In the same hospital in 1972 *Candida* spp. were 4.2% of agents causative of sepsis [27].
In a study carried out from 1975 to 1977 in two US hospitals, *Candida* spp. were reported to be the third most common cause of BSI [28].
The NNIS system reported an increase in the rate of fungal BSI from 0.1 to 0.5 cases per 1,000 discharges between 1980 and 1990. Although the contribution of *Candida* spp. to this rise is not specified, 85.6% of all nosocomial fungal infections were caused by these yeasts [29].
Another analysis of NNIS data in 1986-1989 reported *Candida* spp. as accounting for 8% of infections and the fourth most common cause of sepsis, with *albicans* accounting for 5% [14].
Other studies confirmed the increase in invasive *Candida* spp. infections observed in 1980-1990: one of these, carried out on two US hospitals and on the National Hospital Discharge Survey (NHDS) data from 1980 to 1989, reported a rise in the rate of disseminated candidosis from 0.013 to 0.15 cases per 1,000 admissions. The Authors defined the phenomenon as "an epidemic of the 1980s" [29].
This trend however was not an isolated phenomenon, but was part of the global rise in bacteraemia and fungaemia in 1980-1990 [15, 25].
In contrast with the data referring to the 1980s, the incidence rate levelled off or in some cases decreased during the 1990s [1, 17, 30-34].
In accordance with what was reported by Schaberg in the previous decade, the NNIS system showed *Candida* spp. as the fourth most common cause in 14,000 cases of BSI; similar results were registered in 1995-1998 in 49 US non-NNIS hospitals, and in 1995-1996 in the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) program [8, 25, 35, 36]. A study carried out in a US hospital from 1989 to 2000 on 328 episodes of candidaemia showed a decrease in the incidence, with the highest values in 1993 and the lowest levels in 1997 [25, 32].
As for Europe, recent surveys carried out in different countries such as Finland, England, Holland, Spain, Ireland, Hungary, Switzerland, Sweden and the Lombardy region of Italy showed a lesser contribution of candidaemia to nosocomial BSI than that reported in the USA [30, 37-46].
Many of these studies were performed for the surveillance study on candidaemia promoted by the European Confederation of Medical Mycology (ECMM); the

overall incidence was 0.20-0.38 cases per 1,000 admissions [47].

On the whole, as outlined in Table I, the data collected show, with few exceptions, an elevation in the incidence in the early 1990s followed by a levelling off to lower values. Furthermore, the predominance of candidaemia in the USA compared to Europe is probably attributable to differences in health practices. It should be taken into account that the reduction reported in recent years may be related to the specific geographical areas or subpopulations examined. Indeed, this trend is not consistent with that registered in neonatal ICUs, in which the incidence of candidaemia increased implacably in the 1980s and still appears to be increasing [25, 48].

As for the role of the different species, *C. albicans* is the most common cause of invasive infections in a range which includes *glabrata*, *krusei*, *guillermondii*, *parapsilosis* and *tropicalis*, with different geographical distributions. In several trials carried out in USA from 1986 to 1989 and from 1995 to 1998, the percentage of candidaemia caused by non *albicans* species rose from 37.5% to 46.8% [14, 25, 35]. This was confirmed by studies carried out in USA from 1987 to 1992 and in Dutch hospitals from 1987 to 1995 [39, 49]. The decrease reported by Garbino et al. in the period 1989-2000 was attributed to a considerable reduction in *C. albicans* BSI but with no modification in those caused by non *albicans* species [25, 32].

In the last few years, other studies have shown an increase for non *albicans* BSI, especially for those caused by *C. glabrata* and *parapsilosis* [41, 45, 46, 50, 51]. The contribution of the different species varies with the type of patients and treatment. Oncologic patients with a solid tumour are more frequently infected by *glabrata*, which, instead, was rarely isolated in neonatal units. In these wards, on the contrary, *parapsilosis* predominates [25, 52, 53]. Non-*albicans* infections arise in general after chemotherapy for haematological malignancies rather than for solid tumours [25, 54].

Although in the last few years the contribution of non *albicans* species in the aetiology of candidaemia has increased, they have been responsible for a significant proportion of invasive fungal infections for many years. In the early trial on bacteraemia and fungaemia carried out in 1975-1977, they caused 66.7% of candidaemias, of which 33.3.% of *glabrata* alone, i.e. similar to the incidence of *albicans* BSI [28].

The progressive increase in the involvement of non *albicans* in invasive infections is correlated with a series of epidemiological factors. For example, it has been hypothesised that the increased use of fluconazole in therapeutic and prophylactic treatments in the 1990s favoured the emergence of *glabrata* and *krusei*, which are relatively resistant to this drug [25].

According to some Authors, all patients with candidaemia should be treated regardless of its source or duration, because of the frequency of hematogenous dissemination, its high mortality, and the difficulties in es-

Tab. I. Incidence of candidaemia: summary of reported studies.

Authors	Year of publication	Period	Type of population, country	Incidence				Proportion (%)	Rank
				Rate/1.000 admissions	Rate/1.000 discharges	Rate/1.000 patient days	Rate/10.000 CVC* days		
McGowan Jr JE [27]	1975	1935-1972	single hospital, USA	0-> 2.5				0-> 4.2	
Weinstein MP [28]	1983	1975-1977	two hospitals, USA	0.9				7.1	3
Beck-Sague C [10]	1993	1980-1990	NNIS hospitals, USA		0.1->0.5 (fungaemia)				
Schaberg DR [14]	1991	1986-1989	NNIS hospitals, USA					8	4
Fisher-Hoch SP [29]	1995	1980-1989	NHDS hospitals , USA	0.013-> 0.15					
Trick WE [92]	2002	1989-1999	1.116 NNIS ICUs, USA				9.6-> 3.7		
Garbino J [32]	2002	1989-2000	single hospital, USA			0.02-0.05			
NNIS [36]	1996	1986-1996	231 NNIS hospitals, USA					5	4
Edmond MB [35]	1999	1995-1998	49 hospitals, USA					7.6	4
Pfaller MA [8]	1998	1995-1996	50 SCOPE hospitals , USA					8	4
Lyytikainen O [37]	2002	1999-2000	four hospitals, Finland					4	8
NINSS [38]	2000	1997- 2000	NINSS hospitals, England					2	9
Voss A [39]	1996	1987-1995	five hospitals, Holland			0.32-> 0.74		3.2-5. 6	
Alonso-Valle H [40]	2003	1995-1999	single hospital, Spain	0.81				5.2	
McMullan R [41]	2002	1984-2000	single hospital, Ireland					2-2.5	
Doczi I [30]	2002	1996-2000	single hospital, Hungary	0.2-0.4				1.4-2.6	
Marchetti O [42]	2004	1991-2000	17 hospitals, Switzerland					2.9	7
Klingspor L [43]	2004	1998-1999	Sweden hospitals	0.32					
Tortorano AM [44]	2002	1997-1999	35 hospitals, Italy (Lombardy)	0.38					
Tortorano AM [47]	2004	1997-1999	106 ECMM hospitals, Europe	0.20-0.38					
Boo TW [46]	2005	1999-2003	single hospital, Ireland	0.48		0:07			
Peman J [45]	2005	1997-1999	19 hospitals, Spain	0.035					

* Central Venous Catheter

tablishing an accurate diagnosis. However, the treatment of candidaemia is difficult because therapy must be tailored for each individual, and consequently standard therapeutic recommendations cannot be made [3, 55, 56].
Therefore, patients which are exposed to high risk for development of *Candida* invasive infection should be identified so that proper prophylactic treatment can be applied [4]. Many of the studies in the literature have allowed the role of several factors in the pathogenesis of candidaemia to be determined. The main factors are reported below.

Previous colonisation

The spread of Candida from the abdominal cavity to other body sites was first demonstrated in the 1980s [4, 57].
Analyses of different patient populations have demonstrated the importance of a previous colonisation as a risk factor for candidaemia. In a study carried out on oncologic patients, candidaemia occurred in 32% of patients with multiple colonisation, in 1% of patients with colonisation at a single site, and in 0.5% of those not colonised with Candida [4, 58]. A subsequent study confirmed these data, with 22%, 5% and 0% respectively in the three groups of patients [59].
A prospective survey of 29 surgical patients colonised by *Candida* spp. showed a positive correlation between the entity of colonisation and the development of invasive infections [60]. This was confirmed by a study carried out on a group of low birth weight infants that correlated the density of colonisation, the presence of gastrointestinal symptoms and candidaemia [61].
A high concentration of *Candida* spp. in the stool of cancer patients was proven to be a risk factor for the development of candidaemia [62]. In addition, the presence of the yeast in specimens obtained from the peritoneal cavity is predictive of invasive infections [1, 17, 63, 64].
The differentiation between *Candida* spp. colonisation and an invasive infection in critically ill patients is still difficult. Microbiological surveillance may help in these cases, but the significance of positive cultures is often unclear [65, 66]. Many Authors suggest that in cases of clinical suspicion, the colonisation of more than two body sites may be sufficient to predict candidosis and begin antifungal therapy [1, 25, 57, 67].

The use of antibiotics

Since systemic candidosis is often the result of an excessive proliferation of yeast in the gastrointestinal tract and a subsequent penetration of the mucosa, which leads to the haematogenous dissemination, the use of antibiotics is a major risk factor for candidaemia because of the alteration they cause in the gastrointestinal flora [1, 25].
Many studies have shown the importance of the number of antibiotics and the duration of their employment [60, 68]. In a survey on candidaemia patients, 94% of them had been treated with antibiotics, and 61% with more than four different agents [55].
Different types of wide spectrum drugs may have a different role on the predisposition of patients to excessive *Candida* proliferation. Analyses carried out on the effects of antibiotics have demonstrated that the increase in the yeast population in the gastrointestinal tract is correlated to a decrease in the number of anaerobic bacteria isolated from the stools after treatment [25, 69].
Some evidence shows that therapy with cephalosporin, particularly cephtriaxone, may readily favour the proliferation of Candida compared to treatment with aminoglycosides or imipenem [70].

Neutropenia

Since neutrophils are essential components of the host defence against mycetes, neutropenia has been shown to be one of the major risk factors for invasive candidosis and the most important in cancer patients [3, 71-73]. Intensive treatment of patients with neoplasia leads to significant and prolonged neutropenia, which allows the development of infection. Moreover, injuries to the oropharyngeal mucosa caused by aggressive cytostatic drugs such as cytarabine facilitate yeast colonisation and subsequent invasion [68].

Intravascular devices

The care of critically ill patients often requires the use of intravascular devices. In US hospitals they are responsible for about two thirds of BSI and 35-80% of cases of candidaemia; particularly implicated is the central venous catheter (CVC) [1, 31, 74, 75].
An indwelling CVC may be a substrate for the formation of a biofilm that is relatively resistant to immune effector mechanisms and antifungal agents [25, 76].
In some studies parenteral nutrition has been associated with a significantly increased risk of candidaemia, especially during epidemics [65].
Finally, additional risk factors have been identified, such as certain surgical procedures, renal insufficiency, the use of steroids, the severity of an underlying disease and the length of stay in hospital. Many Authors suggest that the more numerous these factors are and the longer the exposure to them, the greater the risk will be [1, 68, 77].
A different prevalence of various factors may, in part, account for the geographical differences in the epidemiology of invasive Candida infections. At present, the information on the prevalence of specific clinical procedures is scanty and does not reveal the true impact of the different healthcare practices [25].
Candidaemia is the only severe form of candidosis for which the precise impact has been calculated. Globally, the crude mortality rate is over 50%, with variations that reflect the severity of underlying diseases [1, 78, 79]. In the 1980s, Miller and Wenzel suggested that the development of candidaemia predicted a fatal outcome [80]. This was confirmed by a subsequent study of 1,745 cases of BSI, in which candidaemia was associated with the highest mortality rate [81].
Different mortality rates were associated with different *Candida* species: the outcome of infections caused by

krusei or *glabrata* is worse than that of candidaemia due to species susceptible to triazole compounds. Instead, a lower mortality rate was associated to candidaemia caused by *parapsilosis*.
Among the risk factors considered for their possible role as predictors of a fatal outcome, an older age and the severity of an underlying illness have been associated with a worse outcome, while among the controllable parameters the absence of antifungal treatment, catheter removal and prolonged blood culture positivity have been identified as independent predictive factors of candidaemia.
The length of hospital stay of patients who survived candidaemia was about 30 days longer than that of non-infected subjects, with a consequent prolonging of care and increased costs [1, 3, 68].
Therefore, candidaemia is associated with high morbidity and mortality, and the significant employment of additional resources. All the technical and behavioural measures to prevent the occurrence and spread of candidosis may contribute to improving the safety of hospitalised subjects and the prognosis of critically ill patients.

Candidaemia in Intensive Care Units (ICUs)

ICU patients are exposed to a higher risk of nosocomial BSI than other hospitalised individuals. Clinical procedures that interfere with the host barriers against the entry of microorganisms or with the mechanisms of eliminating them add to the critical condition of these patients. These procedures include mechanical ventilation, the employment of intravascular catheters, parenteral nutrition and multiple transfusions [25].
Twenty years ago Wenzel et al. reported that 45% of nosocomial BSI occurred in ICU, despite the fact that these units accounted for only 5-10% of hospital beds [82].
More recently, a multicentre study carried out in France revealed that the risk of developing nosocomial BSI is 12 times higher for ICU patients than for patients in other wards [83].
Other surveys have shown an increasing trend for BSI in ICU. This is especially associated with the use of intravascular catheters and with low respiratory tract or intra-abdominal infections; the mortality rate is about 40% [19, 84, 85].
As for yeast invasive infections, Candida colonisation affects 50-86% of critically ill patients during a prolonged stay in ICU and exposes them to a higher risk for the development of deep infections [11, 60, 66, 68].
Surveys carried out in the 1980s reported Candida as the fourth most common pathogen isolated in US intensive care units [86]; in Europe, the EPIC study reported mycetes as the fifth most common cause of nosocomial infections in these wards [12].
The length of stay in an ICU has been shown to be a significant risk factor for the development of candidaemia [87].
NNIS data reported *Candida* spp. to be the fourth most common cause of BSI in these units in 1990-1999, a similar frequency to that registered for the hospital as a whole [88].
Fifty per cent of the cases of candidaemia that were registered by SENTRY Antifungal Surveillance Program in America in 1997 involved ICU patients [8].
Causing about 60% of cases, *C. albicans* is the most common species responsible for candidaemia, while other species are emerging as important pathogens [8, 89, 90].
Several studies have shown an increase in the number of non *albicans* BSI in ICU. A survey carried out in Holland in 1991-1994 reported an increase from 15 to 56% [39]. The surveys carried out separately in North and Latin America and in NNIS hospitals reported non *albicans* species to be responsible for 46% of cases of candidaemia [90, 92]. The data on the episodes of candidaemia occurring in 1,116 NNIS ICUs from 1989 to 1999 showed a steady decrease in the incidence, due to a reduction in the *C. albicans* infections, while no variations were found regarding non *albicans* infections [25, 92].
C. glabrata cases increased from 0.2 to 0.5 for CVC days, and this species replaced *tropicalis* as the second most common cause of candidaemia [92]. The striking increase in BSI caused by *C. glabrata* was probably due to the US Food and Drug Administration's approval of fluconazole in 1990.
In general, *C. albicans* strains isolated from blood are susceptible in vitro to amphotericine B and fluconazole, which allows their employment in prevention and therapy [91, 93, 94]. Therefore, the increasing use of fluconazole in clinical practice warrants a careful monitoring of fungal isolate susceptibility to prevent the spread of resistant strains and of the species distribution to evaluate the presence of those intrinsically resistant to azoles [93, 95, 96].
This monitoring should identify the onset of resistance to other drugs such as echinocandines, particularly caspofungin, which are frequently used for the treatment of invasive candidosis due to their proven efficacy and safety [97].

Conclusions

As stated, a survey of candidaemia is fundamental both for the prevention of resistance selection, through the analysis of species distribution and antifungal susceptibility, and for the control of infection transmission in hospitals by identifying the contagion chain. Laboratory analyses on the genotypical and phenotypical characteristics of the isolates provide data that may identify any risk practices and indicate the choice of therapy and suitable prevention measures.
In the last few years the surveillance of nosocomial candidaemia has been intensified: in the USA programs that integrate the NNIS activity have been set up, while in Europe the ECMM has implemented a prospective surveillance system that involves seven countries, including Italy.

However, as reported, the data available on the epidemiology of candidaemia are often discordant. This is certainly due to a different geographical distribution of the species, but also to a different influence of the risk factors associated to the clinical practices, to the local situations, and to the differences in the study design and data collection.

Therefore, an intensification and improvement in the surveillance programs, through the standardisation of protocols, is warranted to define more exhaustively the epidemiology of candidaemia.

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