doi: 10.5123/S2176-62232016000200006

Evaluation of infections by *Candida* at a university hospital of Vale do Paraíba region, São Paulo State, Brazil: species distribution, colonization, risk factors and antifungal susceptibility

Avaliação de infecções por *Candida* em um hospital universitário da região do Vale do Paraíba, Estado de São Paulo, Brasil: distribuição de espécies, colonização, fatores de risco e suscetibilidade antifúngica

Evaluación de infecciones por *Candida* en un hospital universitario de la región del Vale do Paraíba, Estado de São Paulo, Brasil: distribución de especies, colonización, factores de riesgo y susceptibilidad antifúngica

Sonia Khouri
Universidade do Vale do Paraíba, São José dos Campos, São Paulo, Brasil

Luciana da Silva Ruiz
Seção de Ciências Biomédicas, Instituto Adolfo Lutz, Bauru, São Paulo, Brasil

Marcos Ereno Auler
Faculdade de Farmácia, Universidade do Paraná, Guarapuava, Paraná, Brasil

Bosco Christiano Maciel da Silva
Laboratório de Investigação Médica em Dermatologia e Imunodeficiências, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brasil

Virgínia Bodelão Richini Pereira
Seção de Ciências Biomédicas, Instituto Adolfo Lutz, Bauru, São Paulo, Brasil

Carina Domaneschi
Faculdade de Odontologia, Universidade de São Paulo, São Paulo, Brasil

Rosane Christine Hahn
Laboratório de Micologia, Faculdade de Medicina, Universidade Federal de Mato Grosso, Cuiabá, Brasil

Claudete Rodrigues Paula
Faculdade de Odontologia, Universidade de São Paulo, São Paulo, Brasil

ABSTRACT

The present research aimed to carry out an epidemiological study, recording the prevalence of *Candida* spp. causing infection, as well as the colonization, distribution of the different species in clinical specimens from different sectors of a university hospital, risk factors and their susceptibility to antifungal drugs. Over a one-year period, 100 samples of *Candida* from 67 patients were isolated and identified, which 74% were characterized as colonization and 26% as nosocomial infections. *C. albicans* was the most frequent (40%), followed by *C. tropicalis* (25%), *C. parapsilosis* (21%), *C. glabrata* (9%), *C. rugosa* (2%), *C. novergensis* (1%), *C. krusei* (1%) and *C. guilliermondii* (1%). Non-*albicans Candida* species represented 71.4% of the colonization cases and 52.1% of infection. *C. albicans* was the most common species found in secretions and blood, *C. parapsilosis* was the most isolated from venous catheter, while *C. tropicalis* and *C. glabrata* were the most frequently isolated species in probes. The hospital wards with the largest number of yeasts were the Intensive Care Units (45%). Renal failure and multiple traumas were the most frequent underlying diseases and the mainly risk factors for colonization or infection were antibiotic therapy and invasive procedures. Most of the samples showed high susceptibility to the antifungal agents studied. Epidemiological investigations of these agents in the hospital environment are very important, especially at the studied hospital, so that preventive measures may be taken against infections.

Keywords: *Candida*; Nosocomial Infections; *Candida albicans*; Antifungal Agents.

Correspondence / Correspondência / Correspondencia:
Sonia Khouri
Universidade do Vale do Paraíba
Av. Shishima Hifumi, 2911. Bairro: Urbanova
CEP: 12244-000 São José dos Campos-São Paulo-Brazil
Phone #: +55 (12) 3947-1000
E-mail: soniak@univap.br

INTRODUCTION

Fungal infections have been increased in recent years, and they are an important cause of mortality and morbidity in hospitalized patients[1,2]. This situation is mainly associated with the increasing number of immunocompromised patients, including patients of solid organ and bone marrow transplants, cancer and HIV patients, premature infants, the elderly and patients recovering from major surgeries[3,4,5]. Besides this, the rate of colonization in hospitalized individuals is considered higher than in general community. Clinical procedures, underlying disease and a longer hospital stay contribute to the rapid multiplication of colonizing agents that can cause infection[6,7]. The number of species of *Candida* yeast has increased over the last decades, and currently constitutes the predominant group of hospital-based fungal infections. *Candida* species are responsible for up to 78% of nosocomial fungal infections[8,9]. Although *C. albicans* is the main species isolated in patients with invasive fungal infections, non-*albicans Candida* species are becoming increasingly significant and the most important among them are: *C. tropicalis, C. parapsilosis, C. glabrata, C. guilliermondii, C. krusei,* and *C. kefir*[2,10]. Based on this information, this study aimed to identify and record the colonization and infection by *Candida* species in patients admitted to a general university hospital and mapped the distribution of the various clinical specimens in different sectors of the hospital, risk factors and the sensitivity of the isolates to antifungals.

MATERIALS AND METHODS

The study was conducted at the Hospital Universitário de Taubaté, Vale do Paraíba, São Paulo, Brazil. It is a large general university hospital, with 170 beds and receives patients mainly from the Brazilian public health system.

Clinical isolates from adults, children and neonates, who had been hospitalized for more than 72 h and with clinical suspicion of nosocomial infection, were included in this study. The classification whether as infection or colonization was carried out by the Infection Control Commission (Comissão de Controle de Infecção Hospitalar – CCIH) of the hospital, and was based on criteria defined by the Centers for Disease Control and Prevention and National Health Surveillance Agency (Agência Nacional de Vigilância Sanitária – Anvisa).

The yeasts were isolated from clinical specimens and medical equipment in different sectors of the hospital from February 2002 to February 2003, with the approval of the Ethics Committee of the hospital and Instituto de Ciências Biomédicas of the Universidade de São Paulo (number 702/CEP). Liquor, secretions (tracheal, wounds, maxillary, sputum, ear, oropharyngeal, abdominal, scrotal, anal, vaginal) catheter tip, vesical probe, blood, ascitic fluid, bronchial lavage, gastric lavage, intracaths, peritoneal fluid, pressure ulcers (bedsores) and bone fragments were all considered as clinical specimens for culture. The collection of the material for culture followed the recommendations prepared by the microbiology laboratory and CCIH.

Patient data related to age, gender, type of material to be analyzed, hospital sector, underlying disease, use of antifungal agents, corticosteroids, radiotherapy, chemotherapy and hospitalization time were recorded.

The yeasts were identified by their macroscopic, microscopic, reproductive and physiological characteristics according to the methods established by Kurtzman et al[11] and by sugar assimilation using the commercial API 20C kit (bioMérieux Vitek Inc. Hazelwood, Missouri, USA). Definitive yeast identification was carried out molecularly using the ribotyping technique and the Uni-f and Uni-r primers followed by sequencing and analysis with the SeqManTM II (DNA Star Inc.) program[12].

All yeasts isolates were evaluated against five antifungal agents (fluconazole, ketoconazole, itraconazole, voriconazole and amphotericin B), using the Etest® (bioMérieux, Solna, Sweden) method to establish the minimal inhibitory concentration (MIC). MIC interpretations follow the criteria established by M27A3 and M27S4E documents[13,14].

Regarding to the amphotericin B and ketoconazole antifungals, the breakpoints were not discussed. However, values greater than 2 μg/mL for amphotericin B may be resistant, as shown by some studies. No report was found to ketoconazole.

All tests used *C. albicans* (ATCC 90028), *C. parapsilosis* (ATCC 22019) and *C. krusei* (ATCC 6258) strains as quality controls.

RESULTS

During the study period, 954 clinical specimens and medical equipment were analyzed from 67 patients with clinical suspicion of nosocomial infection. One hundred positive cultures for *Candida* species were detected, which 74 were characterized as colonization cases and 26 as cases of nosocomial infection. In 43.4% of the infection cases, the patients died. Of all patients who developed these infections, 15 (65.2%) were previously colonized by the same yeasts.

A comprehensive sampling of patient data such as gender, underlying diseases and risk factors is shown in table 1. This table shows higher rates in females, as well as highlighting the cases of chronic renal failure, multiple trauma and underlying pathologies like neoplasia. The use of antibiotics and invasive procedures is shown as the major risk factors for both colonization and infection.

Of all isolates, the most frequent species was *C. albicans* (40%), whereas non-*albicans Candida* species were the most frequent in 71.5% of colonization cases and 52.2% of infection cases (Figure 1).

Tables 2 and 3 show that the majority of isolates for all species which occur from secretions and tip probes were predominantly cases of colonization. In addition, the table 3 shows that there was a predominance of *C. albicans* species in the secretions.

Table 1 – Data of 67 patients admitted to the Hospital Universitário de Taubaté, Vale do Paraíba, São Paulo, Brazil, according to gender, underlying disease and risk factors

Patient data	No. of cases (%)
Gender	
Female	40 (59.7)
Male	27 (40.3)
Underlying disease	
Chronic renal failure	20 (29.8)
Multi trauma	14 (20.9)
Neoplasia	12 (17.9)
Septic shock	10 (14.9)
Diabetes	8 (11.9)
Others	3 (4.4)
Risk factors	
Use of antibiotics	48 (71.6)
Invasive procedures	40 (59.7)
Immunodepression	18 (26.9)

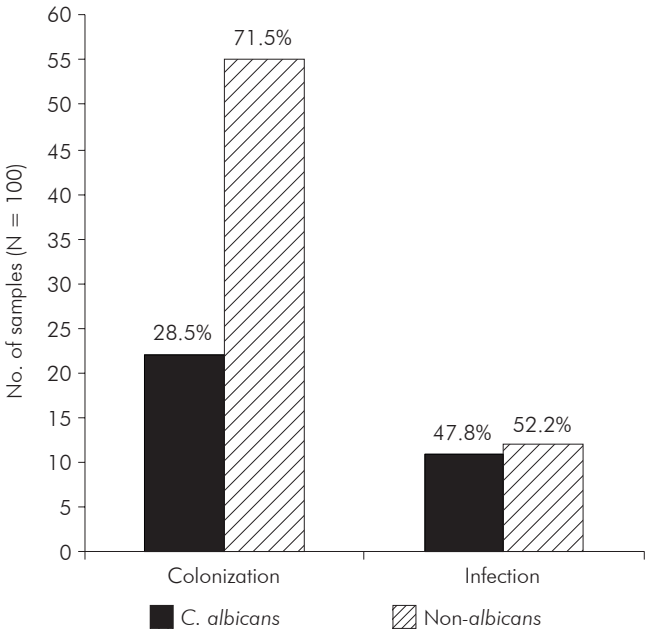

Figure 1 – Correlation of cases of nosocomial infection and colonization caused by *C. albicans* and non-*albicans* *Candida* species isolated from 67 patients admitted to the Hospital Universitário de Taubaté, Vale do Paraíba, São Paulo, Brazil

Table 2 – Occurrence and distribution of *Candida* species of hospital infection in clinical specimens and medical equipment in the Hospital Universitário de Taubaté, Vale do Paraíba, São Paulo, Brazil

Species	Clinical specimens and medical material										Total %
	Secretions		Probe tips		Blood		Venous catheter		Gastric lavage		
	N	%	N	%	N	%	N	%	N	%	
C. albicans	1	20.0	3	37.5	6	60.0	1	33.3	–	–	42.3
C. tropicalis	1	20.0	4	50.0	–	–	–	–	–	–	19.3
C. parapsilosis	–	–	1	12.5	4	40.0	2	66.7	–	–	26.9
C. glabrata	3	60.0	–	–	–	–	–	–	–	–	11.5
C. rugosa	–	–	–	–	–	–	–	–	–	–	–
C. novergensis	–	–	–	–	–	–	–	–	–	–	–
C. krusei	–	–	–	–	–	–	–	–	–	–	–
C. guilliermondii	–	–	–	–	–	–	–	–	–	–	–
Total	5	100.0	8	100.0	10	100.0	3	100.0	–	–	100.0

Conventional sign used: – Numeric data not equal to zero due to rounding.

Table 3 – Occurrence and distribution of *Candida* species of colonization in clinical specimens and medical equipment in the Hospital Universitário de Taubaté, Vale do Paraíba, São Paulo, Brazil

Species	Clinical specimens and medical material										Total %
	Secretions		Probe tips		Blood		Venous catheter		Gastric lavage		
	N	%	N	%	N	%	N	%	N	%	
C. albicans	19	42.2	6	31.6	–	–	2	33.4	2	100.0	39.1
C. tropicalis	11	24.4	8	42.1	–	–	1	16.6	–	–	27.0
C. parapsilosis	9	20.0	–	–	2	100.0	3	50.0	–	–	18.9
C. glabrata	2	4.4	4	21.0	–	–	–	–	–	–	8.1
C. rugosa	2	4.4	–	–	–	–	–	–	–	–	2.7
C. novergensis	–	–	1	5.3	–	–	–	–	–	–	1.4
C. krusei	1	2.2	–	–	–	–	–	–	–	–	1.4
C. guilliermondii	1	2.2	–	–	–	–	–	–	–	–	1.4
Total	45	100.0	19	100.0	2	100.0	6	100.0	2	100.0	100.0

Conventional sign used: – Numeric data not equal to zero due to rounding.

The hospital ward with the greatest number of *Candida* species isolations was the Intensive Care Unit (ICU), with 45% of isolates (Figure 2). In all hospital wards studied, the *Candida* species most frequently isolated was *C. albicans*.

Table 4 shows the main susceptibility data of *Candida* species to antifungal drugs. It was observed that all isolates of *C. albicans* were susceptible to the antifungals tested. However, non-*albicans* *Candida* species showed lower sensitivity indices.

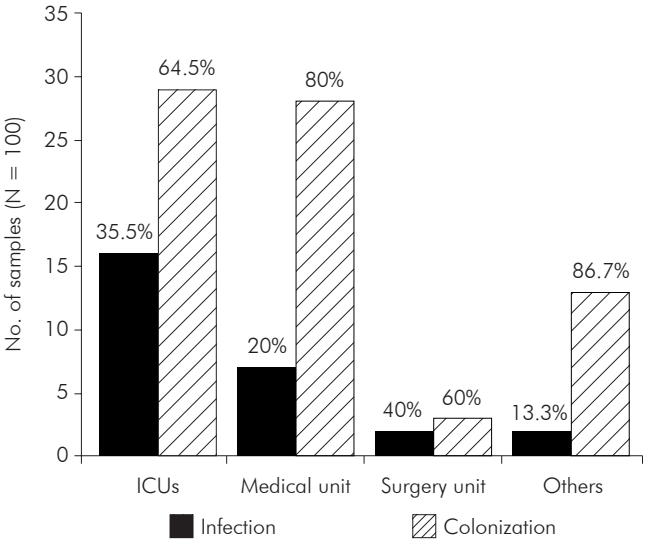

Figure 2 – Distribution of 100 *Candida* spp. samples isolated from different clinical specimens and medical equipment, according to the hospital service, Hospital Universitário de Taubaté, Vale do Paraíba, São Paulo, Brazil

DISCUSSION

Candida yeasts are important due to the high frequency of colonization and infection in humans. During the period of this study, 100 samples of *Candida* were isolated from different medical equipment and clinical specimens of 67 patients admitted to different sectors of the hospital. Of this total, 26% were cases of infection and 74% were cases of colonization. Our results were similar to those found in the literature, which indicate that colonization by *Candida* is present in 5-15% of hospitalized patients but can reach extremes of 50-86%[15].

Although exogenous nosocomial transmission by *Candida* has been reported, some studies showed that endogenous colonization is responsible for the large majority of severe candidiasis[16,17]. The colonization of multiple sites by *Candida* spp. is considered as a risk factor for the acquisition of invasive fungal infections in critically ill patients[15]. In this study, 65.2% of patients with acquired *Candida* infection had been previously colonized by this yeast. These data agree with other studies which reported that colonization by this fungus often precedes an invasive fungal infection[15,18] and also revealed that most candidiasis were acquired by endogenous microbiota.

Early diagnosis of invasive candidiasis is difficult, usually reported at the end of the course of infection. This may be in part responsible for its high crude and attributable mortality rates[19]. In this study, the mortality rate among patients with *Candida* infection was 43.4%, a value that lies within the mortality rate attributed to this yeast, which is between 40-50%[20], making this infection a major challenge for clinicians which work in tertiary hospitals in different countries.

Table 4 – *In vitro* susceptibility of *Candida* spp. samples isolated from clinical specimens and medical equipment against six antifungals using the commercial Etest® method

Species (no. of isolates)	Antifungal	MIC range (μg/mL)	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	Sensitivity (%)
C. albicans (40)	Amphotericin B	0.012 – 0.064	0.011	0.013	100
	Fluconazole	0.047 – 0.75	0.016	0.056	100
	Voriconazole	0.003 – 0.032	0.0015	0.016	100
	Itraconazole	0.006 – 0.94	0.0045	0.032	100
	Ketoconazole	0.004 – 0.25	0.0036	0.022	N/A
C. tropicalis (25)	Amphotericin B	0.023 – 4	0.09	1.75	92
	Fluconazole	0.094 – 3	0.25	1.2	94
	Voriconazole	0.006 – 0.12	0.009	0.001	100
	Itraconazole	0.047 – 8	0.18	1	72
	Ketoconazole	0.01 – 8	0.047	4	N/A
C. parapsilosis (21)	Amphotericin B	0.012 – 12	0.75	2	76
	Fluconazole	0.125 – 96	0.31	80	86
	Voriconazole	0.004 – 4	0.0047	0.094	95
	Itraconazole	0.002 – 16	0.025	16	76
	Ketoconazole	0.002 – 16	0.16	2	N/A
C. glabrata (9)	Amphotericin B	0.004 – 23	0.07	1	89
	Fluconazole	0.094 – 96	60	64	33
	Voriconazole	0.003 – 1	0.0035	1	N/A
	Itraconazole	0.006 – 1.5	0.77	1	33
	Ketoconazole	0.008 – 54	1.5	32	N/A

In general, *C. albicans* was the most frequently isolated species, followed by *C. tropicalis, C. parapsilosis* and *C. glabrata*. There are significant geographical variations in the pattern of the *Candida* spp. strains isolated. While North America is noted to have a prevalence of *C. glabrata*, in South America there is a predominance of *C. parapsilosis* and *C. tropicalis* among non-*albicans Candida* species[21]. These data agree with the present study in relation to the main species isolated.

Non-*albicans Candida* species were predominated with 71.4% and 52.1% of the colonization cases and infection respectively, as the results of previous studies performed in tertiary hospitals in Brazil[22,23,24,25].

There are few studies reporting the prevalence of *Candida* species related to candidiasis in different clinical samples. In the current study, *C. albicans* was the most frequently isolated species from blood and secretions, the latter being the source with the highest number of *Candida* spp. isolates. *C. parapsilosis* was the species most frequently found in venous catheter, confirming other studies that indicate that this species is the most important in candidemia[24,26]. *C. tropicalis* and *C. glabrata* were more common in the probe tips.

The ICUs were the hospital wards with the highest isolation of *Candida* spp. (45%). Invasive fungal infections, mainly cases of candidiasis, are very common in patients admitted to ICUs and are related to high mortality rates. Such patients, who are often critically ill, are more susceptible to colonization and hospital infection due to the severity of their condition and frequent invasive procedures[27].

Risk factors associated with invasive candidiasis have been well established and have not changed substantially over the last two decades in relation to these factors, which include the exposure to broad-spectrum antibiotics, chemotherapy catheter, parenteral nutrition, neutropenia, hemodialysis, surgery and renal failure[28]. In this study, it was found that the use of broad-spectrum antibiotics, invasive procedures and immunosuppression were the main risk factors associated with cases of infection and colonization by *Candida*.

In terms of drug susceptibility, all the samples of *C. albicans* found in this study were susceptible to the antifungal agents tested, which is consistent with the information that this species is naturally susceptible to antifungal drugs for systemic use, although cases of acquired resistance to azoles have been reported[29,30]. The other *Candida* species have shown resistance to some antifungal drugs such as itraconazole. The *C. glabrata* species showed the greatest resistance, since this species is intrinsically less sensitive. Thus, it is extremely important to make the correct identification of the species in combination with the tests of susceptibility to establish the appropriate antifungal therapy.

CONCLUSION

This study presented epidemiological data of *Candida* infections at a university hospital in São Paulo State, which are important because it will be possible to compare them with future epidemiological surveillance at hospitals in that State, as well as other regions of Brazil. The presence of *Candida* yeast is still a common complication among patients admitted to tertiary hospitals, showing the importance of epidemiological investigations of these agents in this environment, especially about the appropriate preventive measures against such infections can be adopted.

ACKNOWLEDGMENTS

We would like to thank Dr. Mariana da Silva Ruiz for help with the English review of the manuscript.

FINANCIAL SUPPORT

This work was supported by the São Paulo Research Foundation (FAPESP) and the National Counsel of Technological and Scientific Development (CNPq).

Avaliação de infecções por *Candida* em um hospital universitário da região do Vale do Paraíba, Estado de São Paulo, Brasil: distribuição de espécies, colonização, fatores de risco e suscetibilidade antifúngica

RESUMO

A presente pesquisa teve como objetivo realizar um estudo epidemiológico, registrando a prevalência de *Candida* spp. que causa infecção, assim como a colonização, distribuição de diferentes espécies em espécimes clínicos de diversos setores de um hospital universitário, fatores de risco e sua suscetibilidade às drogas antifúngicas. Acima de um período de um ano, 100 amostras de *Candida* de 67 pacientes foram isoladas e identificadas, as quais 74% foram caracterizadas como colonização e 26% como infecção nosocomial. *C. albicans* foi a mais frequente (40%), seguida de *C. tropicalis* (25%), *C. parapsilosis* (21%), *C. glabrata* (9%), *C. rugosa* (2%), *C. novergensis* (1%), *C. krusei* (1%) e *C. guilliermondii* (1%). As espécies *Candida* não *albicans* representaram 71,4% de casos de colonização e 52,1% de infecção. *C. albicans* foi a espécie mais comum encontrada nas secreções e no sangue. *C. parapsilosis* foi a mais isolada das amostras do cateter venoso, enquanto que *C. tropicalis* e *C. glabrata* foram as espécies mais frequentemente isoladas em sondas. As alas hospitalares com o maior número de leveduras foram as Unidades de Terapia Intensiva (45%). A falência renal e os múltiplos traumas foram as doenças de base mais frequentes e os principais fatores de risco para colonização ou infecção foram a terapia com antibióticos e procedimentos invasivos. A maioria das amostras mostrou alta suscetibilidade para os agentes antifúgicos estudados. Investigações epidemiológicas desses agentes no ambiente hospitalar são bastante importantes, principalmente no hospital estudado, pois assim medidas preventivas podem ser realizadas contras as infecções.

Palavras-chaves: *Candida*; Infecções Nosocomiais; *Candida albicans*; Antifúngicos.

Evaluación de infecciones por *Candida* en un hospital universitario de la región del Vale do Paraíba, Estado de São Paulo, Brasil: distribución de especies, colonización, factores de riesgo y susceptibilidad antifúngica

RESUMEN

La presente investigación tuvo como objetivo realizar un estudio epidemiológico, registrando la prevalencia de *Candida* spp. que causa infección, bien como la colonización, distribución de diferentes especies en especímenes clínicos de diversos sectores de un hospital universitario, factores de riesgo y su susceptibilidad a las drogas antifúngicas. En un período superior a un año, se aislaron e identificaron 100 muestras de *Candida* de 67 pacientes, las cuales 74% fueron caracterizadas como colonización y 26% como infección nosocomial. *C. albicans* fue la más frecuente (40%), seguida de *C. tropicalis* (25%), *C. parapsilosis* (21%), *C. glabrata* (9%), *C. rugosa* (2%), *C. novergensis* (1%), *C. krusei* (1%) y *C. guilliermondii* (1%). Las especies *Candida* no *albicans* representaron un 71,4% de los casos de colonización y 52,1% de infección. *C. albicans* fue la especie más común encontrada en las secreciones y en la sangre. *C. parapsilosis* fue la más aislada de las muestras del catéter venoso, mientras que *C. tropicalis* y *C. glabrata* fueron las especies más frecuentemente aisladas en sondas. Las alas hospitalarias con el mayor número de levaduras fueron las Unidades de Terapia Intensiva (45%). La falencia renal y los múltiples traumas las enfermedades de base más frecuentes y los principales factores de riesgo para colonización o infección fueron la terapia con antibióticos y procedimientos invasivos. La mayoría de las muestras presentó una alta susceptibilidad para los agentes antifúgicos estudiados. Investigaciones epidemiológicas de esos agentes en el ambiente hospitalario son bastante importantes, principalmente en el hospital estudiado, ya que así, medidas preventivas pueden ser tomadas contra las infecciones.

Palabras clave: *Candida*; Infecciones Nosocomiales; *Candida albicans*; Antifúngicos.

REFERENCES

1 Sandven P, Giercksky KE, Group N and The Norwegian Yeast Study. Yeast colonization in surgical patients with intra-abdominal perforations. Eur J Clin Microbiol Infect Dis. 2001 Jul;20(7):475-81.

2 Deorukhkar SC, Saini S, Mathew S. Non-*albicans* *Candida* infection: an emerging threat. Interdiscip Perspect Infect Dis. 2014 Oct;(ID6159158):1-7.

3 Warnock DW. Trends in the epidemiology of invasive fungal infections. Nihon Ishinkin Gakkai Zasshi. 2007;48(1):1-12.

4 Barton M, O'Brien K, Robinson JL, Davies DH, Simpson K, Asztalos E, et al. Invasive candidiasis in low birth weight preterm infants: risk factors, clinical course and outcome in a prospective multicenter study of cases and their matched controls. BMC Infect Dis. 2014 Jun;14:327.

5 Batista GC, Krebs VL, Ruiz LS, Auler ME, Hahn RC, Paula CR. Oral colonization: a possible source for candidemia in low-weight neonates. J Mycol Med. 2014 Jun;24(2):81-6.

6 Oliveira VK, Ruiz LS, Oliveira NA, Moreira D, Hahn RC, Melo AS, et al. Fungemia caused by *Candida* species in a children's public hospital in the city of São Paulo, Brazil: study in the period 2007-2010. Rev Inst Med Trop Sao Paulo. 2014 Jul-Aug;56(4):301-5.

7 Puig-Asensio M, Ruiz-Camps I, Fernandez-Ruiz M, Aguado JM, Munoz P, Valerio M, et al. Epidemiology and outcome of candidaemia in patients with oncological and haematological malignancies: results from a population-based surveillance in Spain. Clin Microbiol Infect. 2015 May;21(5):491e1-10.

8 Marol S, Yucesoy M. Molecular epidemiology of *Candida* species isolated from clinical specimens of intensive care unit patients. Mycoses. 2008 Jan;51(1):40-9.

9 Bhatt M, Sarangi G, Paty BP, Mohapatra D, Chayani N, Mahapatra A, et al. Biofilm as a virulence marker in *Candida* species in nosocomial blood stream infection and its correlation with antifungal resistance. Indian J Med Microbiol. 2015 Feb;33(5):112-4.

10 Sahbudak Bal Z, Yilmaz Karapinar D, Karadas N, Sen S, Onder Sivis Z, Akinci AB, et al. Proven and probable invasive fungal infections in children with acute lymphoblastic leukaemia: results from an university hospital, 2005-2013. Mycoses. 2015 Apr;58(4):225-32.

11 Kurtzman CP, Fell JW, Boekhout T. The yeasts, a taxonomic study. 5th ed. Philadelphia: Elsevier Science; 2011.

12 Donnelly SM, Sullivan DJ, Shanley DB, Coleman DC. Phylogenetic analysis and rapid identification of *Candida dubliniensis* based on analysis of ACT1 intron and exon sequences. Microbiology. 1999 Aug;145(Pt 8):1871-82.

13 Clinical and Laboratory Standards Institute. Reference method for broth dilution antifungal susceptibility testing of yeasts: document M27-A3. 3rd ed. Wayne: CLSI; 2008.

14 Clinical and Laboratory Standards Institute. Reference method for broth dilution antifungal susceptibility testing of yeast: fourth informational supplement: CLSI document M27-S4. Wayne: CLSI; 2012.

15 Caggiano G, Puntillo F, Coretti C, Giglio M, Alicino M, Manca M, et al. *Candida* colonization index in patients admitted to an ICU. Int J Mol Sci. 2011 Oct;12(10):7038-47.

16 Nucci M, Anaissie E. Revisiting the source of candidemia: skin or gut? Clin Infect Dis. 2001 Dec;33(12):1959-67.

17 Ruping MJ, Vehreschild JJ, Cornely OA. Patients at high risk of invasive fungal infections: when and how to treat. Drugs. 2008 Oct;68(14):1941-62.

18 Garbino J, Lew DP, Romand JA, Hugonnet S, Auckenthaler R, Pittet D. Prevention of severe *Candida* infections in nonneutropenic, high-risk, critically ill patients: a randomized, double-blind, placebo-controlled trial in patients treated by selective digestive decontamination. Intensive Care Med. 2002 Dec;28(12):1708-17.

19 Eggimann P, Que YA, Revelly JP, Pagani JL. Preventing invasive *Candida* infection. Where could we do better? J Hosp Infect. 2015 Apr;89(4):302-8.

20 De Rosa FG, Garazzino S, Pasero D, Di Perri G, Ranieri VM. Invasive candidiasis and candidemia: new guidelines. Minerva Anestesiol. 2009 Jul-Aug;75(7-8):453-8.

21 Colombo AL, Guimaraes T. Epidemiology of hematogenous infections due to *Candida* spp. Rev Soc Bras Med Trop. 2003 Sep-Oct;36(5):599-607.

22 Ruiz LS, Sugizaki MF, Montelli AC, Matsumoto FE, Pires MFC, Silva BCM, et al. Fungemia by yeasts in Brazil: ocurrance and phenotypic study of strains isolated at the Public Hospital, Botucatu, São Paulo. J Mycol Medical. 2005 Mar;15(1):13-21.

23 Hinrichsen SL, Falcao E, Vilella TA, Colombo AL, Nucci M, Moura L, et al. Candidemia in a tertiary hospital in northeastern Brazil. Rev Soc Bras Med Trop. 2008 Jul-Aug;41(4):394-8.

24 Bruder-Nascimento A, Camargo CH, Sugizaki MF, Sadatsune T, Montelli AC, Mondelli AL, et al. Species distribution and susceptibility profile of *Candida* species in a Brazilian public tertiary hospital. BMC Res Notes. 2010 Jan;3(1):1-5.

25 Hoffmann-Santos HD, Paula CR, Yamamoto AC, Tadano T, Hahn RC. Six-year trend analysis of nosocomial candidemia and risk factors in two intensive care hospitals in Mato Grosso, midwest region of Brazil. Mycopathologia. 2013 Dec;176(5):409-5.

26 Matsumoto FE, Gandra RF, Ruiz LS, Auler ME, Marques SA, Pires MF, et al. Yeasts isolated from blood and catheter in children from a public hospital of São Paulo, Brazil. Mycopathologia. 2002 Sep;154(2): 63-9.

27 Morace G, Borghi E. Fungal infections in ICU patients: epidemiology and the role of diagnostics. Minerva Anestesiol. 2010 Nov;76(11):950-6.

28 Tao F, Jiang R, Chen Y, Chen R. Risk factors for early onset of catheter-related bloodstream infection in an intensive care unit in china: a retrospective study. Med Sci Monit. 2015 Feb;21:550-6.

29 Pfaller MA. Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment. Am J Med. 2012 Jan;125(1 Suppl):S3-13.

30 Srinivasan A, Lopez-Ribot JL, Ramasubramanian AK. Overcoming antifungal resistance. Drug Discov Today Technol. 2014 Mar;11:65-71.

Received / Recebido em / Recibido en: 20/8/2015
Accepted / Aceito em / Aceptado en: 28/3/2016