

Candida BLOODSTREAM INFECTION: DATA FROM A TEACHING HOSPITAL IN MATO GROSSO DO SUL, BRAZIL

Marilene Rodrigues CHANG(1), Flávia Patussi CORREIA(1), Leonora Correa COSTA(1), Paula Cristhina Niz XAVIER(2), Durval Batista PALHARES(3), Deborah Ledesma TAIRA(1), Anamaria Mello Miranda PANIAGO(4), Elenir Rose Jardim Cury PONTES(5) & Vanessa Escobar MACHADO(6)

SUMMARY

The incidence of *Candida* bloodstream infection has increased over the past years. In the Center-West region of Brazil, data on candidemia are scarce. This paper reports a retrospective analysis of 96 cases of *Candida* bloodstream infection at a Brazilian tertiary-care teaching hospital in the state of Mato Grosso do Sul, from January 1998 to December 2006. Demographic, clinical and laboratory data were collected from medical records and from the hospital's laboratory database. Patients' ages ranged from three days to 92 years, with 53 (55.2%) adults and 43 (44.8%) children. Of the latter, 25 (58.1%) were newborns. The risk conditions most often found were: long period of hospitalization, utilization of venous central catheter, and previous use of antibiotics. Fifty-eight (60.4%) patients died during the hospitalization period and eight (13.7%) of them died 30 days after the diagnosis of candidemia. *Candida albicans* (45.8%) was the most prevalent species, followed by *C. parapsilosis* (34.4%), *C. tropicalis* (14.6%) and *C. glabrata* (5.2%). This is the first report of *Candida* bloodstream infection in the state of Mato Grosso do Sul and it highlights the importance of considering the possibility of invasive *Candida* infection in patients exposed to risk factors, particularly among neonates and the elderly.

KEYWORDS: Candidemia; Risk factors; Bloodstream infection; *Candida* spp.

INTRODUCTION

Systemic fungal infections are pathologies that particularly affect immunocompromised and severely ill patients¹. Epidemiological studies have shown an increasing incidence of bloodstream infection by yeasts of the genus *Candida*, given their colonization ability and opportunism and the therapeutic challenges arising from the development of resistance to some antifungal agents^{2,6}.

Candida infections are mostly endogenous and may result from proliferation or changes of the normal human microbiota, determined by risk factors such as long-term administration of broader-spectrum antibiotics, surgery, organ transplant, prematurity, use of invasive procedures (e.g. those involving catheters for nasogastric, urinary, parenteral nutrition, hemodialysis, or mechanic ventilation purposes), and other treatment actions^{3,7,11}.

The pathogenic potential of the genus varies considerably, and *C. albicans* is the species most frequently found in clinical samples^{1,4}. *C. parapsilosis* and *C. tropicalis*, however, are also regarded as important candidemia agents^{10,12}.

An additional aggravating factor is the high morbidity and mortality

rate associated with systemic candidemia, ranging from 40% to 60%, according to different studies^{1,2,9,11}.

Given the relevance of the issue and considering that the epidemiology of systemic *Candida* infections varies across regions and even across hospitals within a single region^{3,5,11}, the present study is focused on a series of candidemia cases that occurred at a teaching hospital located in the Center-West region of Brazil.

MATERIAL AND METHODS

A retrospective study was conducted to describe the prevalence of *Candida* species in blood cultures and the risk factors associated with candidemia at the tertiary-care teaching hospital of Universidade Federal de Mato Grosso do Sul (UFMS), in Campo Grande, Brazil.

The patients had been admitted to various hospital divisions - namely, adult intensive care center, medical clinic, surgical clinic, hematology sector, oncology division, parasitic infectious diseases, renal unit, neonatal intensive care unit, pediatric intensive care center, pediatric clinic, and nursery.

In order to be included in the study, a patient should have tested

(1) Department of Pharmacy-Biochemistry, Universidade Federal de Mato Grosso do Sul (UFMS), Campo Grande, MS, Brazil.

(2) Faculdade Estácio de Sá, Campo Grande, MS, Brazil.

(3) Department of Pediatrics, Universidade Federal de Mato Grosso do Sul, Campo Grande, MS, Brazil.

(4) Department of Clinical Medicine, Universidade Federal de Mato Grosso do Sul, Campo Grande, MS, Brazil.

(5) Department of Public Health, Universidade Federal de Mato Grosso do Sul, MS, Brazil.

(6) Graduate student, Graduate Program in Clinical Analyses, Conselho Regional de Farmácia de Mato Grosso do Sul, Campo Grande, MS, Brazil.

Correspondence to: Prof.² Dr.² Marilene Rodrigues Chang, R. Uricuri 582, 79060-040 Campo Grande, MS, Brasil. Tel.: +55-67-3345-3195. E-mail: marirchang@yahoo.com.br

positive to *Candida* spp. in at least one culture of blood drawn from a peripheral vein, in addition to exhibiting clinical evidence of sepsis.

The yeasts isolated from blood cultures were detected using a Bactec 9120 system (Becton Dickinson, INC, Sparks, MD). Positive samples were Gram-stained, grown on Sabouraud agar and brain-heart infusion agar, and incubated at 37 °C at room temperature until growth was observed. After screening with the germ tube test, the isolates were identified according to microscopic morphology on cornmeal - Tween 80 agar, auxanogram test, growth at 42 °C, and confirmation by means of an automated Vitek system (BioMérieux, St. Louis, MO, USA)⁸.

Medical records were reviewed and clinical data were analyzed in conjunction with the respective laboratory data using the software Epi Info 3.3.0.2 (Centers for Disease Control and Prevention, Atlanta, GA, USA). The study was approved by the Ethics Committee for Clinical Research of UFMS.

RESULTS

The cases of *Candida* bloodstream infection included in the study occurred in the period from January 1998 to December 2006, comprising 96 patients, 53 (55.2%) of them adults and 43 (44.8%) children. Of the pediatric patients, 20 were newborns (46.5%), 24 (55.8%) were premature, and 19 (44.2%) had very low birth weight. Fifty patients (52.1%) were male and 46 (48.2%) female. Ages ranged from three days to 92 years, with a mean of 30 years. Candidemia episodes were more frequent among newborns (20.8%) and elderly patients (21.9%).

Hospital stays lasted from four to 124 days, with a mean duration of 34 days. Most patients (63.5%) were admitted to the intensive care unit. Clinical and demographic data are reported in Table 1.

The most frequent comorbidities were pneumonia (43.8%) and gastrointestinal tract disease (33.4%). The underlying conditions more often observed were: hematological disease (leukemia, lymphoma), in 12 cases (12.5%); *diabetes mellitus*, in 10 (10.4%); and solid tumors, in nine (9.4%). The overall mortality rate was 56.3%, reaching as much as 80.9% (17/21) among adults older than 60 years and 70.0% (14/20) among newborns.

Table 2 shows the main conditions posing a risk of candidemia. For all age groups, invasive procedures and hospitalization for 15 days or longer were the occurrences most often associated with candidemia. Additional risk factors among pediatric patients included: hospital stay longer than 15 days (76.7%), prematurity (55.8%), and very low birth weight (44.2%). Overall, previous use of antibiotics occurred in 93 patients (97%), with 73% using four or more antibiotics. Most surgical (71.4%) and assisted-ventilation procedures (61.9%) were performed on patients older than 60 years.

C. albicans (44 cases; 45.8%) was the species most often isolated from blood cultures, followed by *C. parapsilosis* (33 cases; 34.4%), *C. tropicalis* (14; 14.6%), and *C. glabrata* (five; 5.2%). Table 3 shows the distribution of *Candida* species by three-year periods.

Mortality rates varied according to *Candida* species, being higher for *C. tropicalis* (12/14; 85.7%) and *C. glabrata* (4/5; 80.0%).

Table 1

Patients with candidemia according to age group underline conditions and outcome

| Characteristics | Patients (n = 96) | % |
|--------------------------------|-------------------|------|
| Age group * | | |
| 0 - 30 days | 20 | 20.8 |
| 31 days - 2 years old | 18 | 18.8 |
| >2 - 12 years old | 5 | 5.2 |
| >12 - 25 years old | 7 | 7.3 |
| >25 - 40 years old | 9 | 9.4 |
| >40 - 60 years old | 16 | 16.7 |
| >60 years old | 21 | 21.9 |
| Location | | |
| Nursery | 35 | 36.5 |
| ICU | 61 | 63.5 |
| Underlying diseases | | |
| Pulmonar disease | 42 | 43.8 |
| Gastrointestinal tract disease | 33 | 33.4 |
| Hematology disease | 12 | 12.5 |
| Diabetes mellitus | 10 | 10.4 |
| Neoplasia (solid tumors) | 9 | 9.4 |
| Evolution | | |
| Death | 58 | 60.4 |
| Discharge | 42 | 39.6 |

* Age at time first positive blood culture.

Fifty-nine patients (61.4%) received antifungal treatment. Fluconazole was administered to 34 patients and amphotericin B to six. Nineteen patients were treated with both antifungal drugs.

DISCUSSION

This is the first description of *Candida* bloodstream infection at a Brazilian tertiary-care teaching hospital in the Brazilian State of Mato Grosso do Sul. It provides information on species distribution and on the clinical features and outcomes among patients with candidemia.

The literature reports a progressive increase in candidemia frequency in hospitalized patients^{1,5}. These infections are generally difficult to diagnose, are refractory to treatment, and have an attributable mortality rate of 40-60%^{1,2,5,6}.

In agreement with other studies^{6,9,10,11}, most episodes of candidemia seen in this series of cases occurred in adults and children in intensive care units - the very wards were critical patients remain bedridden and are subject to alterations in defense mechanisms or to compromised anatomical barrier, secondary to invasive medical procedures.

Patients in extreme age ranges were the most susceptible, with fatal outcomes in all those older than 80 years. Overall, the underlying conditions and comorbidities identified in this study were similar to those reported in other investigations^{2,4}.

Table 2
Risk factor for the development of candidemia according to age group. Teaching Hospital of the Federal University of Mato Grosso do Sul (UFMS), Brazil, 1998 to 2006

| Risk factor | Pediatrics | Adults | Adults |
|---------------------------------|-----------------------------|----------------------------------|--------------------------|
| | 3 days ≤ 12 years n = 43 | > 12 to < 60 years old n = 32 | > 60 years old n = 21 |
| Hospitalization > 15 days | 33 (76.7) | 19 (52.4) | 14 (66.7) |
| Very-low-birth-weight* | 19 (44.2) | - | - |
| Prematurity** | 24 (55.8) | - | - |
| Central venous catheter use | 40 (93.0) | 27 (84.4) | 15 (71.4) |
| Other foreign bodies /catheters | 33 (76.7) | 22 (68.8) | 16 (76.2) |
| Assisted ventilation | 26 (60.4) | 13 (40.6) | 13 (61.9) |
| Antibiotics use | | | |
| Third-generation cephalosporin | 30 (69.7) | 10 (47.6) | |
| Vancomycin | 34 (79.1) | 19 (61.3) | 10 (47.6) |
| Carbapenems | 22 (51.2) | 12 (38.7) | 11 (52.4) |
| Surgical procedure | 19 (44.1) | 20 (62.5) | 15 (71.4) |

* Birth-weight < 2500 g, ** Old gestational age ≤ 37 weeks.

Table 3

Cause of fungemia: distribution of *Candida* species over time. Teaching Hospital at the Federal University of Mato Grosso do Sul (UFMS), Brazil, 1998-2006

| Species | 1998-2000 | 2001-2003 | 2004-2006 |
|--------------------------------------|-----------|-----------|-----------|
| <i>Candida albicans</i> (n = 44) | 11 (35.5) | 16 (53.3) | 17 (48.6) |
| <i>Candida parapsilosis</i> (n = 33) | 12 (38.7) | 7 (23.3) | 14 (40.0) |
| <i>Candida tropicalis</i> (n = 14) | 7 (22.6) | 5 (16.7) | 2 (5.7) |
| <i>Candida glabrata</i> (n = 5) | 1 (3.2) | 2 (6.7) | 2 (5.7) |
| Total | 31 (32.3) | 30 (31.2) | 35 (36.5) |

Chi-squared test for trend. Non-*albicans* species were added together.

The present results add evidence to the already recognized risk of invasive candidemia, especially in neonatal and elderly inpatients. Use of central venous catheter and previous administration of antibiotics were the principal conditions posing a risk of candidemia, irrespective of age. Prolonged hospital stays may also have collaborated with the occurrence of bloodstream infection. These conditions are already recognized as important factors of risk for opportunistic infections, among them those caused by *Candida* spp.^{2,3,4,11}.

The capacity of yeasts to attach to a wide range of inanimate surfaces (such as those of intravascular devices) and to form biofilms in glucosilated solutions seems to protect them from immune responses and antimicrobial agents⁷. This may explain why *Candida* species were associated with the use of central venous catheters and parenteral nutrition in the present study¹⁰. Gastrointestinal disorders were observed in 30-40% of the patients, an occurrence that may have favored yeast invasion into the bloodstream⁵.

In the present investigation, *C. albicans* was the species most often isolated from both adult and pediatric patients, although its yearly frequency did not significantly differ from those of other *Candida* species ($p = 0.303$).

In the past three years, however, cases of *C. parapsilosis* outnumbered those from previous years, while cases of *C. tropicalis* decreased in number (Table 3). That increase may be associated with interventional therapy, including the growing use of central venous catheters, parenteral nutrition, and large-spectrum antibiotics for long periods¹⁰. Although the literature reports *C. parapsilosis* as being more frequent in pediatric patients^{1,6,10,11,12}, the present study did not reveal any significant difference between adults (34.0%) and children (34.9%).

C. tropicalis was more often isolated from adult patients, a finding consistent with other studies^{4,12} reporting that this species is not common in pediatric patients, and even less so among neonates. *C. glabrata* was more frequent in adults (4/5).

Mortality rates for each *Candida* species were similar to those revealed by studies carried out in southern Brazil, where *C. glabrata* and *C. tropicalis* were associated with the highest death rates².

The high mortality rate (56.3%) in the present series, similar to that found in other studies^{1,2,4,5,10}, is a strong reason for health teams to be aware of risk factors potentially leading to *Candida* spp. infection - a reminder that prevention and control methods should be pre-emptively implemented.

In the present case series, only 59 patients (61.4%) received antifungal treatment. The absence of treatment may be attributed to a lack of clinical recognition that candidemia can occur in severely ill patients or to delays in obtaining blood culture results.

These are relevant issues in the management of patients, as pre-emptive therapy should be instituted earlier whenever infections of fungal etiology are suspected.

Cases of candidemia are possibly underestimated in the hospital investigated, since this retrospective study only included documented infections, and blood cultures may often lack adequate sensitivity¹. Candidemia is thus of greater prevalence than the available data may suggest, since blood culture, albeit a gold standard test, can possibly identify only a small fraction of the total number of cases. PCR-based assays are expected to provide further assistance in the future, increasing the sensitivity of screening methods¹².

The present findings corroborate the relevance of epidemiological studies in monitoring bloodstream infections.

RESUMO

Infecção na corrente sanguínea por *Candida* spp. dados de um hospital universitário em Mato Grosso do Sul, Brasil

A incidência de infecções na corrente sanguínea causada por *Candida* spp. tem aumentado nos últimos anos. Na região Centro-Oeste do Brasil, os dados sobre candidemia são escassos. Realizamos uma análise retrospectiva de casos de infecção na corrente sanguínea por *Candida* em um hospital terciário de ensino de Mato Grosso do Sul. Noventa e seis episódios diagnosticados de janeiro de 1998 a dezembro de 2006 foram incluídos no estudo. Os dados demográficos e clínicos foram obtidos de prontuários; os dados laboratoriais provieram de registros do laboratório hospitalar. Dos pacientes, 43 (44,8%) eram crianças e 53 (55,2%) adultos, com idades variando de três dias a 92 anos. Das crianças, 25 (58,1%) eram recém-nascidas. As condições de risco mais encontradas foram: prolongado tempo de internação, uso de cateter venoso central e uso prévio de antibióticos. Cinquenta e oito (60,4%) pacientes foram a óbito durante a hospitalização e oito (13,7%) deles foram a óbito 30 dias após o diagnóstico de candidemia. *Candida albicans* (45,8%) foi a espécie mais prevalente seguida por *C. parapsilosis* (34,4%), *C. tropicalis* (14,6%) e *C. glabrata* (5,2%). Esta é a primeira descrição de infecção na corrente sanguínea por espécies de *Candida* em Mato Grosso do Sul, confirmando a importância da suspeita clínica de infecções invasivas por tais microrganismos na evolução de pacientes expostos a fatores de risco, principalmente no caso de idosos e neonatos.

ACKNOWLEDGMENTS

This study was supported by Fundação de Apoio ao Desenvolvimento do Ensino, Ciência e Tecnologia do Estado de Mato Grosso do Sul

(FUNDECT), Brazil, grant 41/100.115/2004. Thanks are given to Floriano Campoçano and Maína O. Nunes for providing technical support.

REFERENCES

1. ABELSON, J.A.; MOORE, T.; BRUCKNER, D.; DEVILLE, J. & NIELSEN, K. - Frequency of fungemia in hospitalized inpatients over 11 years at a tertiary care institution. **Pediatrics**, 116: 61-67, 2005.
2. AQUINO, V.R.; LUNARDI, L.W.; GOLDANI, L.Z. & BARTH, A.L. - Prevalence, susceptibility profile for fluconazole and risk factors for candidemia in a tertiary care hospital in southern Brazil. **Braz. J. infect. Dis.**, 9: 411-418, 2005.
3. BLUMBERG, H.M.; JARVIS, W.R.; SOUCIE, J.M. *et al.* - Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. **Clin. infect. Dis.**, 33: 177-186, 2001.
4. CHENG, M.F.; YANG, Y.L.; YAO, T.J. *et al.* - Risk factors for fatal candidemia caused by *Candida albicans* and non-*albicans Candida* species. **BMC infect. Dis.**, 5: 1-5, 2005.
5. COLOMBO, A.L. & GUIMARÃES, T. - Epidemiologia das infecções hematogênicas por *Candida* spp. **Rev. Inst. Med. trop. S. Paulo**, 36: 599-607, 2003.
6. DIEKEMA, D.J.; MESSER, S.A.; BRUEGGEMANN, A.B. *et al.* - Epidemiology of candidemia: 3-year results from the emerging infections and the epidemiology of Iowa organisms study. **J. clin. Microbiol.**, 40: 1298-1302, 2002.
7. KOJIC, E.M. & DAROUICHE, R.O. - *Candida* infections of medical devices. **Clin. Microbiol. Rev.**, 17: 255-267, 2004.
8. LACAZ, C.S.; PORTO, E.; MARTINS, J.E.C.; HEINS-VACCARI, E.M. & MELO, N.T. - **Tratado de Micologia médica**. São Paulo, Sarvier, 2002.
9. LUPETTI, A.; TAVANTI, A.; DAVINI, P. *et al.* - Horizontal transmission of *Candida parapsilosis* candidemia in a neonatal intensive care unit. **J. clin. Microbiol.**, 40: 2363-2369, 2002.
10. MEDRANO, D.J.A.; BRILHANTE, R.S.N.; CORDEIRO, R.A. *et al.* - Candidemia in a Brazilian hospital: the importance of *Candida parapsilosis*. **Rev. Inst. Med. trop. S. Paulo**, 48: 17-20, 2006.
11. PEMÁN, J.; CANTÓN, E.; ORERO, A. *et al.* - Estudio multicéntrico sobre la epidemiología de las candidemias en Españã. **Rev. iberoamer. Micol.**, 19: 30-35, 2002.
12. ROILIDES, E.; FARMAKI, E.; EVDORIDOU, J. *et al.* - *Candida tropicalis* in a neonatal intensive care unit: epidemiologic and molecular analysis of an outbreak of infection with an uncommon neonatal pathogen. **J. clin. Microbiol.**, 41: 735-741, 2003.

Received: 22 January 2008

Accepted: 6 August 2008