Major Article

Revista da Sociedade Brasileira de Medicina Tropical 46(4):466-471, Jul-Aug, 2013
http://dx.doi.org/10.1590/0037-8682-0057-2013

Invasive candidosis: contrasting the perceptions of infectious disease physicians and intensive care physicians

Vanessa Schultz[1],[2], *Arnaldo Lopes Colombo*[3] *and Alessandro Comarú Pasqualotto*[2],[4]

[1]. Divisão de Doenças Infecciosas, Santa Casa Complexo Hospitalar, Porto Alegre, RS. [2]. Departamento de Ciências Básicas da Saúde, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS. [3]. Laboratório de Micologia Molecular, Divisão de Doenças Infecciosas, Universidade Federal de São Paulo, São Paulo, SP. [4]. Laboratório de Biologia Molecular, Santa Casa Complexo Hospitalar, Porto Alegre, RS.

ABSTRACT

Introduction: We analyze how infectious disease physicians perceive and manage invasive candidosis in Brazil, in comparison to intensive care unit specialists. **Methods**: A 38-question survey was administered to 56 participants. Questions involved clinicians' perceptions of the epidemiology, diagnosis, treatment and prophylaxis of invasive candidosis. $P < 0.05$ was considered statistically significant. **Results**: The perception that candidemia not caused by *Candida albicans* occurs in less than 10% of patients is more commonly held by intensive care unit specialists (p=0.018). Infectious disease physicians almost always use antifungal drugs in the treatment of patients with candidemia, and antifungal drugs are not as frequently prescribed by intensive care unit specialists (p=0.006). Infectious disease physicians often do not use voriconazole when a patient's antifungal treatment has failed with fluconazole, which also differs from the behavior of intensive care unit specialists (p=0.019). Many intensive care unit specialists use fluconazole to treat candidemia in neutropenic patients previously exposed to fluconazole, in contrast to infectious disease physicians (p=0.024). Infectious disease physicians prefer echinocandins as a first choice in the treatment of unstable neutropenic patients more frequently than intensive care unit specialists (p=0.013). When candidemia is diagnosed, most infectious disease physicians perform fundoscopy (p=0.015), whereas intensive care unit specialists usually perform echocardiograms on all patients (p=0.054). **Conclusions:** This study reveals a need to better educate physicians in Brazil regarding invasive candidosis. The appropriate management of this disease depends on more drug options being available in our country in addition to global coverage in private and public hospitals, thereby improving health care.

Keywords: Candidiasis. Candidemia. Invasive fungal infection. Medical education.

INTRODUCTION

Invasive fungal diseases have markedly increased in prevalence in recent decades[1]. Candidosis is currently recognized as one of the leading causes of death in critically ill patients. The overall mortality associated with invasive *Candida* infections is nearly 60%, with an attributable mortality as high as 40%[2]. In the USA and in many developed countries, *Candida* spp. have become the fourth leading cause of bloodstream infections (BSIs)[3]. Similar findings have been obtained in studies conducted in Brazil[1,2]. In addition, the costs of modern antifungal therapy have turned candidemia into one of the most expensive infections in clinical practice[4].

Address to: Dr. Alessandro Comarú Pasqualotto. Laboratório de Biologia Molecular/Hospital Dom Vicente Scherer. Av Independência 155, Heliponto, 90035-075 Porto Alegre, RS, Brasil.
Phone: 55 51 9995-1614; **Fax:** 55 51 3213-7491
e-mail: pasqualotto@ufcspa.edu.br
Received 11 March 2013
Accepted 10 July 2013

Understanding how physicians perceive a particular disease is a critical step in establishing priorities for educational programs directed at them. We therefore analyzed how infectious disease (ID) physicians manage invasive candidosis in Brazil, in comparison to intensive care unit (ICU) specialists. Only one similar report was found in the literature in which management choices by both specialties were compared[13].

METHODS

In the present study, we sequentially selected ID and ICU physicians working in tertiary care hospitals from three large Brazilian cities (Porto Alegre, Curitiba and São Paulo) who met the following criteria: I) they were board-certified by their respective medical societies; II) they worked in a tertiary care hospital with a minimum of 100 beds and at least one ICU; III) they had at least 3 years of clinical experience in their specialty after finishing medical residency; and IV) they had treated at least one patient with invasive fungal disease in the last year (pneumocystosis not included). Volunteers were mostly recruited during scientific meetings, during the years

2010-2011, and a single researcher applied the 38-topic survey to all participants. The study included questions related to the clinicians' perceptions on the epidemiology, diagnosis, treatment and prevention of invasive candidosis. Additional questions also addressed the institutions' capability to diagnose invasive *Candida* infections. This article did not require approval of the ethics committee because the participants were physicians, and any interventions had already been made. All participants freely signed informed consent forms, and their identities were kept secret. Data obtained in the survey were contrasted with the Infectious Diseases Society of America's (IDSA) recommendations for the treatment of candidemia[3] and also with previously published epidemiological data from the participating centers[1,2,5-7].Statistical analyses were performed using SPSS version 16.0 for Windows. Categorical variables were compared using chi-squared or Fisher's exact tests, wherever appropriate. $P < 0.05$ was considered statistically significant.

RESULTS

Participating physicians and institutions

In total, 56 clinicians from 19 hospitals were interviewed, including 22 ID specialists and 32 ICU physicians. Two physicians were certified in both areas and included in both groups. All participants worked in large tertiary hospitals (median of 700 hospital beds and 33 ICU beds; **Table 1)**. Hospitals were public (57.1%), private (17.9%), or mixed (25%). Most (92.9%) institutions were teaching hospitals. The main findings of this study are summarized in **Table 2.**

Hospitals' capabilities for diagnosing invasive *Candida* infections

Automated blood cultures and yeast identification at the species level were available for 96.4% and 90.9% of the participants, respectively. The lysis-centrifugation system method was available for 30.3%, whereas 1-3-β-d-glucan and *Candida* protein chain reaction (PCR) assays were available for 10.7% and 36.6%, respectively (with no difference in proportions between medical specialties). Antifungal susceptibility tests were accessible to 49.1% of the clinicians. The ICU physicians had a higher frequency of compulsory requests for susceptibility tests when candidemia was diagnosed than ID physicians (62.5% vs. 44.4%), but the difference was not statistically significant (p=0.434).

Awareness of the epidemiology of invasive *Candida* infections

The distribution of *Candida* species causing candidemia in each medical center was allegedly known by 80% of participants. However, 69.6% of the ICU physicians believed that the frequency of non-*Candida albicans* species was lower than 10% in their hospitals, in contrast to 31.2% of ID doctors (p=0.018). The proportion of *C. glabrata* infections causing candidemia was perceived to be lower than 10% by 90.9% of participants, with no difference between specialties.

Do physicians always treat patients with positive blood cultures for *Candida* spp.?

Whereas 95.8% of ID specialists affirmed that all patients with candidemia require antifungal treatment, this proportion was only 65.6% among ICU specialists (p=0.006). For ICU specialists, absence of sepsis was the main reason for potentially not offering antifungal drugs to a patient with candidemia (63.6%). Moreover, 45.4% of the ICU physicians who claimed not to treat their patients with antifungal drugs also reported not asking for routine eye examinations. Fundoscopy was performed systematically when treating a patient with candidemia by only 54.5% of those physicians surveyed (ID 65.2%, ICU 46.9%; p=0.178). The proportions of physicians reporting that eye examination was never requested were 13% and 43.8% (ID and ICU, respectively; p=0.015).

Primary antifungal treatment choices for candidemia

Nearly (96.4%) all participants expressed concerns regarding fluconazole use in patients with invasive *Candida* infections. However, fluconazole was the preferred antifungal drug for 91.1% of the interviewed physicians for treating non-neutropenic, stable patients with candidemia. For patients previously exposed to azoles, fluconazole remained the drug of choice for 46.9% and 12.5% of the ICU and ID physicians, respectively (p=0.024). Loading doses of fluconazole were prescribed by only 34.4% and 58.3% of the ICU and ID physicians (p=0.074), respectively, and none of the participants adjusted the fluconazole dose based on body weight. Moreover, 14.3% would consider fluconazole for the treatment of candidemia caused by *C. glabrata,* and 8.9% would use it for *C. krusei* infections, with no differences between medical specialties. Voriconazole was considered a reasonable second-line option in the treatment of patients with candidemia where fluconazole had failed by 42.9% of responders, and 75% of these were ICU physicians (p=0.019).

Many (33.9%) physicians would consider fluconazole as the drug of choice in the treatment of unstable patients with candidemia (ID 25%, ICU 40.6%; p=0.222). Echinocandins were preferred in such scenario by only 33.9% of the individuals surveyed (ID 45.8%, ICU 25.0%; p=0.103). The recommended caspofungin dosages for patients with candidemia were unknown to a quarter of the physicians interviewed, and 71.4% of these individuals were ICU physicians. Similarly, anidulafungin dosages were unknown to 46.4% of the participants, among whom 73% were ICU physicians.

Most (62.5%) ICU physicians were not aware of any limitation regarding the use of amphotericin B in *C. lusitaniae* infections. Additionally, 50% of ICU specialists were not able to comment on the use of echinocandins for *C. parapsilosis* or *C. guilliermondii* infections (p<0.001 for all comparisons with ID physicians).

For neutropenic patients with candidemia who were not previously exposed to azoles, fluconazole was the drug of choice for 75% of ICU and ID physicians. In the case of an unstable neutropenic patient, 46.8% of the ICU physicians preferred a polyene, either deoxycholate amphotericin B (31.2%) or a

TABLE 1 - Main characteristics of the hospitals participating in this study.

	Hosp A	Hosp B	Hosp C	Hosp D	Hosp E	Hosp F	Hosp G	Hosp H	Hosp I	Hosp J	Hosp L	Hosp M	Hosp N	Hosp O	Hosp P	Hosp Q	Hosp R	Hosp S	Hosp T
Number of ID specialists	2	2	1	1	3	1	3	1	0	2	1	1	1	1	0	1	3	0	0
Number of ICU specialists	0	12	1	0	5	0	3	0	1	7	0	0	0	0	1	0	2	1	1
Number of beds	880	1,200	900	300	635	170	237	170	300	743	780	150	500	180	800	270	700	150	108
Number of ICU beds	55	100	33	23	14	32	33	30	30	121	76	16	50	23	120	38	20	21	9
Diagnostic capacity (n)																			
Candida species identification																			
Y	2	12	2	1	8	1	6	1	0	0	1	1	1	1	1	1	5	1	1
N	0	0	0	0	0	0	0	0	1	8	0	0	0	0	0	0	0	0	0
UK	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Automated blood culture																			
Y	2	12	2	1	7	1	6	1	1	9	1	1	1	1	1	1	5	0	1
N	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
UK	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	1	0
Lysis-centrifugation system method																			
Y	0	12	0	0	0	0	0	0	0	1	1	0	1	0	0	0	1	0	1
N	2	0	1	1	1	1	2	1	0	2	0	1	0	1	0	1	1	0	0
UK	0	0	1	0	7	0	4	0	1	6	0	0	0	0	1	0	3	1	0
1-3-β-d-glucana																			
Y	2	0	1	0	1	0	0	0	0	4	0	0	0	0	0	0	0	0	0
N	0	0	0	1	5	1	3	1	1	2	1	1	1	1	0	1	3	0	0
UK	0	12	1	0	2	0	3	0	0	3	0	0	0	0	1	0	2	1	1
Candida PCR																			
Y	1	3	0	1	2	0	3	0	0	4	0	0	0	0	0	0	0	1	0
N	1	5	1	0	4	1	3	1	1	4	1	1	1	1	0	1	4	0	0
UK	0	4	1	0	2	0	0	0	0	0	0	0	0	0	1	0	1	0	1

Hosp: hospitals; ID: infectious disease specialist; Y: yes; N: no; UK: unknown; PCR: polymerase chain reaction; ICU: intensive care unit.

TABLE 2 - The main differences observed between ID and ICU specialists regarding perceptions and management of *Candida* infections.

	ID doctors (%)	ICU doctors (%)	P value
Perception that candidemia caused by *Candida* species other than *C. albicans* occurred in less than 10% of cases	31.2	69.6	0.018
Treatment of all patients with candidemia with antifungal drugs	95.8	65.6	0.006
Systematic removal of short-term central venous catheters	70.8	93.8	0.030
Use of voriconazole for patients in whom fluconazole failed	25.0	56.2	0.019
Fluconazole use for neutropenic patients previously exposed to azoles	12.5	46.9	0.024
Lack of knowledge on echinocandin dosage	29.2	68.8	0.003
Echinocandins as first-choice for unstable neutropenic patients	50.0	18.8	0.013
Fundoscopy never performed	13.0	43.8	0.015
Echocardiogram for all patients	16.7	46.6	0.054

ID: infectious disease specialist; ICU: intensive care unit specialist.

lipid formulation of amphotericin B (15.6%). Echinocandins were preferred by 50% and 18.8% of ID and ICU physicians, respectively, in such a context (p=0.013).

Combining antifungal drugs for the treatment of invasive *Candida* infections was an uncommon practice (10.7%; n=6). Most situations in which such practice was considered were in episodes of *Candida* endocarditis (n=3) and meningitis (n=2), or in the treatment of neutropenic patients (n=4).

Management of central venous catheters

Systematic removal of short-term management of central venous catheters **(**CVCs) was the usual practice for 93.8% of ICU specialists, in contrast to 70.8% of ID physicians (p=0.030). Regarding long-term CVCs, these proportions were 51.6% and 54.2%, respectively.

Frequency of blood culture after candidemia diagnosis

Following the diagnosis of candidemia, most participants (58.9%) reported obtaining additional blood cultures at 48-72h intervals until the clearance of candidemia was documented. No significant differences in this protocol were observed between ID and ICU physicians.

Echocardiographic examination

The proportion of physicians who requested an echocardiogram for patients with candidemia, persistent fever and blood cultures remaining positive for *Candida* spp. was 43.8% and 66.7% for ICU and ID physicians, respectively (p=0.089). **Table1** summarizes the results of the survey.

DISCUSSION

This study reveals that intensive care and infectious disease physicians in Brazil differ in several ways on how they understand the epidemiology of invasive *Candida* infections and on the clinical management of such conditions. Most physicians who were selected to participate in the study were based in large tertiary hospitals in which proper diagnostic facilities were apparently in place. Moreover, the epidemiology of candidemia had been well-documented over the preceding years in the medical centers in which these physicians were working[1,2,5-7]. We were surprised to see that, despite enjoying these advantages, a large proportion of the physicians who were interviewed demonstrated little knowledge regarding the epidemiology of invasive *Candida* infections. For instance, more than half of the participants declared that the frequency of candidemia caused by *Candida* species other than *Candida albicans* was lower than 10%; the actual proportion reported in most studies varies from 40% to 74%[8]. Additionally, more than 90% of the physicians were not aware of the increase of *C. glabrata* incidence that has been documented in some medical centers in Brazil[7,14,15]. As shown in **Table 1**, misunderstanding of the epidemiology of candidemia was particularly common among the ICU physicians.

In addition, ICU and ID physicians also had different views on the clinical use of antifungal susceptibility testing. Data obtained in this study showed that the ICU physicians were less aware of the importance of identifying *Candida* at the species level for predicting its susceptibility to antifungal drugs. For instance, *C. lusitaniae* is known to be amphotericin B-resistant, and both *C. guilliermondii* and *C. parapsilosis* have decreased *in vitro* susceptibility to echinocandins[9]. ICU physicians seemed to be particularly uninformed regarding these associations. In contrast, the frequency of compulsory requests for *in vitro* susceptibility tests was higher for the ICU physicians than for the ID physicians. This finding could be the result of sampling bias because many of the ICU physicians were working in the same hospital, and the requests for susceptibility tests could reflect institutional protocols. Moreover, many ICU physicians reported a willingness to use voriconazole for candidemic patients in which fluconazole had failed, which demonstrates a lack of

knowledge regarding cross-resistance in the triazole class. This lack of knowledge may be attributable to ICU physicians being less familiar with the IDSA's guidelines.

Several medical societies, including the IDSA, recognize the importance of antifungal drug treatment for all patients with candidemia[3]. This recommendation is justified by the high mortality associated with candidemia (at least 50%) and by the potential for metastatic complications in patients not treated with antifungal drugs[2]. However, 21.4% of the participants in this study appeared to not systematically treat candidemia, and most of these participants were ICU specialists (34.4%; p=0.008). It should be noted that no clinical or laboratory data are available to allow clinicians to safely select patients with transient episodes of candidemia that would not require treatment.

Fluconazole was the first-choice antifungal treatment for most physicians in this study, most likely because of their longstanding familiarity with fluconazole's safety profile and dosing. However, many physicians referenced the use of fixed doses of fluconazole rather than guiding therapy based on body weight; additionally, the administration of loading doses was frequently regarded as unimportant[3], with ICU and ID physicians registering similar opinions. Fluconazole was also preferred in situations in which the IDSA's guidelines recommend other therapeutic options.

One of the most striking findings of this study was the limited knowledge demonstrated by participants on the echinocandin class of antifungal drugs. Only 45.8% of ID physicians and 25% of ICU specialists reported using echinocandins as a first-line treatment for unstable patients with candidemia (p=0.154). This is in frank contrast to the latest guidelines for treating patients with candidemia[3]; in such a scenario, echinocandins are considered first-choice treatments. The limited availability of this antifungal class in the Brazilian market at the time of the survey in addition to the scarcity of resources at public hospitals, which comprised a large number of our sampling sites, may explain the apparently limited knowledge that the physicians had about this drug.

Removal of central venous catheters has been recommended in the IDSA's guidelines as an adjunct measure in the treatment of patients with candidemia[3] despite the controversy regarding this subject[10]. In this study, the ICU physicians endorsed a more aggressive approach regarding catheter management: 93.8% would remove catheters promptly, in comparison to 70.8% of ID physicians (p=0.030). As expected, these proportions were reduced to ~50% when long-term catheters were considered.

Another striking finding of this study was the limited frequency in which eye examination was performed in patients with candidemia, particularly by ICU physicians (~45%). Although fungal endophthalmitis is an uncommon condition, it may lead to blindness and requires specific and prolonged treatment once the diagnosis is made. Therefore, eye examination is recommended for all patients with candidemia[11]. In one investigation in Brazil, the frequency of eye examination in patients with candidemia was as low as 7.6%[12], which indicates the importance of educating healthcare professionals on this subject.

Consistent with this study's findings, Eggimann et al.[13] observed that many differences in management approaches between ICU and ID physicians also exist in Switzerland[13].

The present study reveals the need to better educate physicians in Brazil regarding invasive *Candida* infection, which is an important and aggressive infection with a high mortality if not correctly identified and treated. Nevertheless, the appropriate management of this disease depends on increasing the drug options available in our country and encouraging global coverage in private and public hospitals, thereby improving health care.

ACKNOWLEDGMENTS

We wish to thank all physicians who helped make this article possible by responding to the survey.

CONFLICT OF INTEREST

Drs. Pasqualotto and Colombo have consulted for and received research grants and speaker honoraria from Pfizer, MSD, Astellas and United Medical (Gilead). Dr. Shultz has no conflict of interest to declare.

REFERENCES

1. Colombo AL, Nucci M, Park BJ, Nouér SA, Arthington-Staggs B, Matta DA, et al. Epidemiology of Candidemia in Brazil: a Nationwide Sentinel Surveillance of Candidemia in Eleven Medical Centers. J Clin Microbiol 2006, 44:2816-2823.
2. Colombo AL, Guimarães T. Epidemiology of hematogenous infections due to *Candida* spp. Rev Soc Bras Med Trop 2003; 36:599-607.
3. Pappas PG, Kauffman CA, Andes D, Benjamin Jr DK, Calandra TF, Edwards Jr JE, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 48:503-535.
4. Olaechea PM, Palomar M, León-Gil C, Alvarez-Lerma F, Jordá R, Nolla-Salas J, et al. Economic impact of *Candida* colonization and *Candida* infection in the critically ill patient. Eur J Clin Microbiol Infect Dis 2004; 23:323-330.
5. Antunes AG, Pasqualotto AC, Diaz MC, d'Azevedo PA, Severo LC. Candidemia in a Brazilian tertiary care hospital: species distribution and antifungal susceptibility patterns. Rev Inst Med Trop Sao Paulo 2004; 46:239-241.
6. Colombo AL, Guimarães T, Silva LR, Almeida Monfardini LP, Cunha AK, Rady P, et al. Prospective observational study of candidemia in São Paulo, Brazil: incidence rate, epidemiology, and predictors of mortality. Infect Control Hosp Epidemiol 2007; 28:570-576.
7. Pasqualotto AC, Zimerman RA, Alves SH, Aquino VR, Branco D, Wiltgen D, et al. Take control over your fluconazole prescriptions: the growing importance of *Candida glabrata* as an agent of candidemia in Brazil. Infect Control Hosp Epidemiol 2008; 29:898-899.
8. Nucci M, Queiroz-Telles F, Tobón AM, Restrepo A, Colombo AL. Epidemiology of opportunistic fungal infections in Latin America. Clin Infect Dis 2010; 51:561-570.
9. Lyon GM, Karatela S, Sunay S, Adiri Y. Antifungal susceptibility testing of *Candida* isolates from the *Candida* surveillance study. J Clin Microbiol 2010; 48:1270-1275.
10. Pasqualotto AC, Severo LC. The importance of central venous catheter removal in patients with candidaemia: time to rethink our practice? Clin microbial Infect 2008; 14:2-4.

11. Pérez Blázquez E. Ophthalmoscopic examination in critically ill non-neutropenic patients: *Candida endophtalmitis*. Rev Iberoam Micol 2006; 23: 16-19.
12. Pasqualotto AC, Severo LC. Why don't we just do what we have to do? J infect 2005; 51:260-261.
13. Eggimann P, Calandra T, Fluckiger U, Bille J, Glauser MP, Marchetti O. Invasive candidiasis: comparison of management choices by infectious disease and critical care specialists. Intensive Care Med 2005; 31:1514–1521.
14. Colombo AL, Garnica M, Camargo LFA, Cunha CA, Bandeira AC, Borghi D, et al. *Candida glabrata*: na emerging pathogen in Brazilian tertiary care hospitals. Med Mycol 2013; 51:38-44.
15. Moretti ML, Trabasso P, Lyra L, Fagnani R, Resende MR, Cardoso LGO, et al. Is the incidence of candidemia caused by *Candida glabrata* increasing in Brazil? Five-year surveillance of *Candida* bloodstream infection in a university reference hospital in southeast Brazil. Med Mycol 2013; 51: 225-230.