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LETTER TO THE EDITOR

Mortality associated with candidemia in non-neutropenic cancer patients is not less compared to a neutropenic cohort of cancer patients

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Mortality from candidemia has remained high despite advances in diagnosis, treatment, prophylaxis, and infection control [1]. Multicentric studies from Indian intensive care units have previously reported a 30-day crude mortality of about 45% [2]. Cancer patients with neutropenia are at an increased risk and are often put on antifungal prophylaxis. The aim of this study was to compare the incidence and all-cause mortality associated with candidemia in non-neutropenic cancer patients with a neutropenic cohort of cancer patients in an oncology hospital in eastern India.

In this retrospective observational study, data were analyzed from May 2011 to January 2017 from a cancer and stem cell transplantation center in eastern India. During this period, 17,000 patients were admitted, 16,528 blood cultures were collected (from 6140 patients), and candidemia was detected in 89 blood cultures from 63 patients (BacT/ALERT blood culture; identification and susceptibility by Vitek 2, bioMérieux, France). One patient with non-malignant disease was removed from the analysis.

The candidemia rate was 5.2 per 1000 admissions (89/17,000). Species isolated included *Candida tropicalis* (17), *C. albicans* (15), *C. parapsilosis* (15), *C. haemulonii* (6), *C. glabrata* (5), *C. norvegensis* (2), and one each of *C. kefyr*, *C. krusei*, and *C. lusitaniae*. One of the limitations of our study was that matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) or DNA sequencing was not used for confirming the identification of *Candida* species. VITEK is sometimes known to misidentify *C. auris* as *C. haemulonii*.

In our study, hematolymphoid and solid-organ malignancies were in 22 (34.9%) and 41 (65.1%) patients, respectively. Seven patients were lost to follow-up within day 30 of candidemia (four from the neutropenic group and three from the non-neutropenic group); 6/7 patients were on palliative care for advanced malignancies and one patient went to a neighboring country. The patients who were lost to follow-up were considered dead (4/7 were neutropenic) while analyzing the results.

Thirty-one patients (31/63, 49.2%) with candidemia were neutropenic (absolute neutrophil counts <500/μL within 10 days). The median lymphocyte count of the neutropenic cohort was 136 cells/μL (interquartile range 52 to 335 cells/μL). Fifteen out of 31 patients (48.4%) had concurrent bacteremia (13 with Gram-negative bacilli, of which seven were multidrug resistant; two with Gram-positive cocci). The 30-day all-cause mortality of the neutropenic candidemic patients was 38.7% (12/31) (Table 1).

Thirty-two patients (32/63, 50.8%) with candidemia were non-neutropenic. Of them, 27 (84.4%) patients without neutropenia had intra-abdominal surgery (24 gastro-intestinal

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Table 1 Profile of patients with candidemia at the Tata Medical Center, Kolkata, India

	Neutropenic patients (n = 31)	Non-neutropenic patients(n = 32)	p-Value (univariate)	p-Value (multivariate)
Age, median (interquartile range)	14.7 years (5.8 to 50.4 years)	61.4 years (53 to 66.5 years)	**<0.01**	Not calculated
Gender ratio (male:female)	1.2:1	1.3:1	NS	Not calculated
Neutrophil count, median (range)	20 (6 to 63) cells/μL	5683.5 (2552 to 8257) cells/μL	**<0.01**	**Comparator group**
Lymphocyte count, median (range)	136 (52 to 335) cells/μL	402 (219 to 619) cells/μL	**<0.01**	**<0.01**
Antifungal prophylaxis received	29% (9/31)	9.4%(3/32)	NS	**<0.01**
Candida species detected	*C. albicans* (5), *C. parapsilosis* (7), *C. tropicalis* (11), *C. glabrata* (2), *C. haemulonii* (2), and one each of *C. kefyr*, *C. norvegensis*, *C. pelliculosa*, and *C. lusitaniae*	*C. albicans* (10), *C. parapsilosis* (8), *C. tropicalis* (6), *C. glabrata* (3), *C. haemulonii* (4), and one each of *C. krusei* and *C. norvegensis*	Not calculated	Not calculated
Fluconazole resistance or sensitivity dose dependent (SDD)	16.1% (5/31)	21.9% (7/32)	NS	NS
Abdominal surgery	0% (0)	84.4% (27/32)	Not calculated	**<0.01**
Concurrent bacterial infection	48.4% (15/31)	56.3% (18/32)	NS	**<0.01**
Received echinocandin therapy (empirical/targeted)	41.9% (13/31)	37.5% (12/32)	NS	**<0.01**
Received fluconazole only therapy (empirical/targeted)	25.83% (8/31)	59.4% (19/32)	**0.01**	**<0.01**
Received treatment with broader spectrum antifungal agents (echinocandin/amphotericin/voriconazole) (empirical/targeted)	67.7% (21/31)	40.6% (13/32)	**0.04**	Not calculated
Hypotension requiring vasopressor support	32.3% (10/31)	46.9% (15/32)	NS	**<0.01**
All-cause mortality at day 30	38.7% (12/31)	43.8% (14/32)	NS	**<0.01**

One terminally ill palliative care patient did not receive any antifungal therapy

NS: not statistically significant

surgery; two urologic surgery; one gynecologic cancer surgery). The median lymphocyte count of the non-neutropenic candidemic patients was 402 cells/μL. Eighteen out of 32 (56.3%) patients without neutropenia had concurrent bacteremia (15 with Gram-negative bacilli, of which 14 were multidrug resistant; three were Gram-positive cocci, of which one was a vancomycin-resistant *Enterococcus*). The 30-day all-cause mortality of the non-neutropenic candidemic patients was 43.8% (14/32).

When patients with candidemia who died was compared to those who survived, hypotension requiring vasopressor support ($p < 0.01$) and intra-abdominal surgery ($p < 0.01$) were significant predictors of mortality. Neutropenia was of borderline significance ($p = 0.13$) in predicting mortality using multivariate statistics. The odds ratio of mortality was 4.32 (95% confidence interval [CI] 1.39 to 13.49) for those candidemia patients with hypotension requiring vasopressor support.

We noted that the all-cause mortality from candidemia can be similar in the neutropenic and non-neutropenic cohorts. Although the numbers were small, it also appeared that the effect of antifungal prophylaxis on reducing incidence or mortality from candidemia in the neutropenic cohort is less. It is noteworthy that the drug-resistant *Candida* species were as common in the non-neutropenic cohort, the group that did not receive antifungal prophylaxis compared to neutropenic patients where antifungal prophylaxis was more widely used. These results, if confirmed by larger multicentric studies, would have significant implications for strategies to diagnose, prevent, and treat candidemia, especially in the non-neutropenic cancer patients. The reasons for similar incidence and outcome of candidemia in cancer patients irrespective of neutrophil count are multifactorial. These include risk factors like: (a) multiple healthcare exposures and hospital admissions, (b) greater use of broad-spectrum antibiotics for the treatment of repeated episodes of bacterial infections, (c) use of central line for the administration of chemotherapy, intensive care support, and total parenteral nutrition (TPN), (d) greater use of TPN due to difficulty of enteral nutrition, (e)

immunocompromised status due to chemotherapy, radiotherapy, or radical surgery. Most patients on neutropenia are, however, at a higher risk of fungal infections and are put on antifungal prophylaxis, especially in those with hematologic malignancies (for example, patients on high-risk acute lymphoblastic leukemia on fluconazole, those with acute myeloblastic leukemia on voriconazole, and those undergoing stem cell transplantation on posaconazole). However, these prophylactic strategies are targeted for certain periods when the risk is estimated to be highest (during a period of neutropenia post-chemotherapy). Any unexpected episode of neutropenia or cell-mediated immune dysfunction may predispose patients to *Candida* infection. Infection control measures such as adequate care of central lines and good hand hygiene practices also play an important part in preventing *Candida* infections. Again, the level of precaution taken in non-neutropenic patients may be unwittingly low compared to neutropenic patients, leading to *Candida* infections in the non-neutropenic group. *Candida* is also a normal commensal of the human gut, and any breach in the structural or functional integrity of the gut (either due to chemotherapy or abdominal surgery) may predispose patients to candidemia. We have noted in our cohort of non-neutropenic patients a significant proportion (Table 1) having abdominal surgery for cancer.

Cancer patients with candidemia even without neutropenia have a significant chance of mortality. In a cancer cohort, fungemia (90% due to *Candida*) occurred in 0.23% of patients, ranging from 0.15% in patients with solid tumors to 1.55% in hematopoietic stem cell transplantation recipients. The 4-week survival rate was 64%. The study identified baseline septic shock (odds ratio [OR] 3.04, 95% CI 1.22–7.58) and tachypnea as poor prognostic factors (OR 2.95, 95% CI 1.66–5.24) [1]. Concurrent bacterial infections (especially with multidrug-resistant Gram-negative bacteria) could have played a major role in the high mortality as seen in our patient cohort (concurrent bacterial infections were detected in 52.4% [33/63] of patients in our study).

Cancer patients with clinical suspicion of fungal infection irrespective of neutrophil count need prompt workup for adequacy of treatment, focal sources of sustained infection, and potential superinfections. Instituting appropriate antifungal therapy before the onset of vasopressor-requiring hypotension is critical for the prevention of mortality. In a study from the Memorial Sloan Kettering Cancer Center in the USA, it was reported that, for cancer patients with candidemia, the incubation period accounts for a significant amount of time, compared with the provider notification and antifungal initiation times, and is associated with in-hospital mortality [3]. In another study from Turkey among cancer patients, intensive care unit stay, being and remaining neutropenic, APACHE III score, and disseminated disease were independent prognostic factors [4]. Strategies to shorten the diagnostic time, such as utilizing polymerase chain reaction (PCR)-based methods, along with low threshold of starting antifungal therapy in at-risk patients may help reduce in-hospital mortality [3, 5].

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Compliance with ethical standards

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References

1. Cornely OA, Gachot B, Akan H, Bassetti M, Uzun O, Kibbler C et al; EORTC Infectious Diseases Group (2015) Epidemiology and outcome of fungemia in a cancer cohort of the Infectious Diseases Group (IDG) of the European Organization for Research and Treatment of cancer (EORTC 65031). Clin Infect Dis 61:324–331
2. Chakrabarti A, Sood P, Rudramurthy SM, Chen S, Kaur H, Capoor M et al (2015) Incidence, characteristics and outcome of ICU-acquired candidemia in India. Intensive Care Med 41:285–295
3. Taur Y, Cohen N, Dubnow S, Paskovaty A, Seo SK (2010) Effect of antifungal therapy timing on mortality in cancer patients with candidemia. Antimicrob Agents Chemother 54:184–190
4. Uzun O, Ascioglu S, Anaissie EJ, Rex JH (2001) Risk factors and predictors of outcome in patients with cancer and breakthrough candidemia. Clin Infect Dis 32:1713–1717
5. Avni T, Leibovici L, Paul M (2011) PCR diagnosis of invasive candidiasis: systematic review and meta-analysis. J Clin Microbiol 49: 665–670