



Emergence of Azole Resistant Candida Glabrata as an Important Cause of Hospital Acquired Infection: Its Risk Factors and Impact

Sarkar T*

¹Jamaica Hospital Medical Center, Internal Medicine, Richmond Hill, USA

Corresponding Author: **Taranika Sarkar** [ORCID ID](#)

Address: Jamaica Hospital Medical Center, Internal Medicine, Richmond Hill, NY, 11418, USA; E-mail: taranikasarkar14@gmail.com

Received date: 03 June 2020; **Accepted date:** 22 June 2020; **Published date:** 03 July 2020

Citation: Sarkar T. Emergence of Azole Resistant Candida Glabrata as an Important Cause of Hospital Acquired Infection: Its Risk Factors and Impact. *Asp Biomed Clin Case Rep.* 2020 Jul 03;3(2):141-46.

Copyright © 2020 Sarkar T. This is an open-access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium provided the original work is properly cited.

Introduction

Candida spp. colonizes the human host and coexists with members of the human microbiome. Candida glabrata are aggressive pathogens, have many virulence factors that lead to serious recurrent candidiasis. Their ability to form a complex biofilm, inability to form hyphae, and inability to secrete hydrolase lead to antifungal resistance. Candidemia is the fourth most common bloodstream infection [1]. Candidemia remains a major source of mortality and morbidity. Mortality among patients with invasive candidiasis is as high as 40%, even when patients receive antifungal therapy [2]. More than 90% of invasive diseases are caused by the 5 most common Candida spp. C. albicans, C. glabrata, C. tropicalis, C. parapsilosis, and C. krusei [3]. The distribution of Candida species has been changing over the last decade, with a decrease in the proportion of C. albicans and an increase in C. glabrata and C. parapsilosis. More than 50% of bloodstream infections are caused by non-albicans Candida [2,4]. The largest proportional increase in the USA is in C. glabrata, which accounts for one third or more of all candidemia isolates [5-7]. C. glabrata are associated with high mortality. Candida glabrata develop acquired resistance following exposure to antifungal agents [8]. 50% of C. glabrata are resistant to fluconazole [9,10]. Furthermore, 9% of C. glabrata that are resistant to

fluconazole are also resistant to the echinocandins [8,11].

Case History

A 32-yr. old female with a past medical history of cholecystectomy with common bile duct injury treated with hepaticojejunostomy reconstruction, colostomy, incisional hernia, small bowel obstruction presented with a chronic non-healing enterocutaneous fistula and failure to thrive (**Fig-1**). The patient had constant



Fig-1: Figure showing a fistula in the left lower abdomen

Case Report

10/10 abdominal pain in the left lower quadrant. Eating aggravated her pain and discharge from the fistula.

She had significant weight loss. She denied any history of recurrent fever, night sweats, diarrhea, or melena. On examination, she was cachectic and had left lower quadrant tenderness.

Laboratory investigations were significant for anemia of chronic disease (Hb 12.6 g/dL, hematocrit 36.5%, ferritin 444 ng/ml, serum Iron 25 mcg/dL, TIBC 188 mcg/dL, transferrin 135 mg/dL) and malnutrition (prealbumin 4.8 mg/dL). Anti-HIV 1 and HIV 2 antibody, HBsAg, and anti HCV antibody were non-reactive. PPD test was negative. Rest of the laboratory test were: WBC count of 11300 / cmm, adequate platelets, sodium of 134 mEq/L, potassium of 3.2 mEq/L, bicarbonate of 29 mEq/L.

CT scan abdomen and pelvis were significant for coloproctitis and fistula from small bowel through the anterior abdominal wall (Fig-2). The patient was



Fig-2: Linear hyperattenuating area extending from the structures inside to the anterior abdominal wall/median surgical wound consistent with enterocutaneous fistula evident

initially managed conservatively with total parenteral nutrition (TPN) and several ACELL and VAC (Vacuum-assisted closure) applications. Her electrolytes were monitored and replaced. A midline was placed for TPN. During the hospital course, she developed three episodes of infection ESBL E. coli UTI (Extended-spectrum beta-lactamase resistant E. coli urinary tract infection), ESBL E. coli Pneumonia and Enterococcus UTI for which she was treated with ertapenem and

vancomycin respectively. Fistulogram confirmed the presence of two fistulas (Fig-3) involving both jejunum

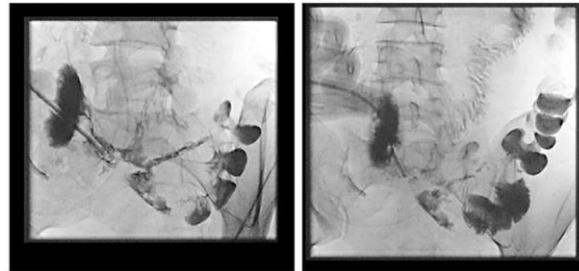
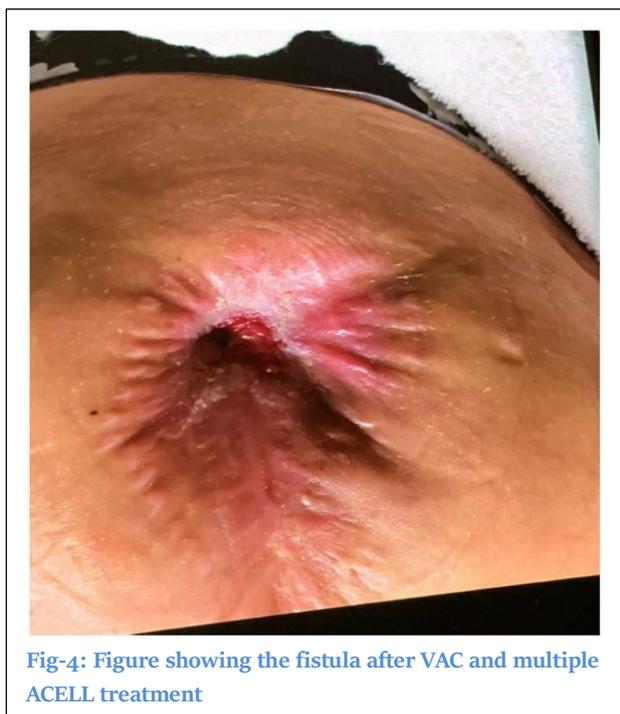


Fig-3: Fistulogram showing enterocutaneous fistula involving both jejunum and colon

and colon. The patient continued to have high fistula output and emesis with diet thus predisposing her to fluid electrolyte imbalance and malnutrition (low prealbumin). She also had recurrent episodes of bowel obstruction. The midline was removed with every fever spike but had to be replaced to continue her nutrition. Chronic intestinal failure secondary to short bowel syndrome (because of history of recurrent abdominal surgery leading to dense intraabdominal adhesions) was high in the differential which was thought to hinder her recovery. Gastroenterologist was consulted. Stool calprotectin was 446, thus increasing her likelihood of Crohn's disease. Colonoscopy could not be done as the patient had recurrent infections.

On hospital day 57, patients had a fever spike of 104, tachycardia, and hypotension. Preliminary blood culture was positive for yeast. Patient was started empirically on caspofungin. Ophthalmology was consulted to rule out endophthalmitis. The final blood culture showed Candida glabrata. Caspofungin was continued, repeated surveillance cultures were negative and antifungals were continued for 14 days. Patient had a repeat C. glabrata fungemia which was managed similarly as before. Patient improved with treatment and midline was placed to start TPN. Her discharge improved with regular follow up and VAC therapy and ACELL treatment (Fig-4). She needed to change her colostomy bag every three days and starting tolerating enteral nutrition. She gained 20 pounds and her prealbumin improved to 19. She was transferred to a tertiary care center for surgery of her complex fistula.



Discussion

C. glabrata lacks the ability to form hyphae and pseudohyphae. Hence initially it was classified under a separate genus *Torulopsis* and was later accepted in the genus *Candida*. *C. glabrata* fungemia is most often seen in older adults with low immunity or in patients with cancer. There have also been the incidence of hospital acquired infections in preterm newborns [12].

The spectrum of infections ranges from non-nosocomial vulvovaginal infections (complicated vulvovaginal candidiasis and recurrent vulvovaginal candidiasis) to severe, life-threatening invasive candidiasis. *C. glabrata* has emerged as an important hospital-acquired pathogen with a mortality rate of 49% [12]. A few decades ago, it was considered as a non-pathogenic saprophyte of the normal flora of healthy individuals. However, following the widespread and increased use of immunosuppressive therapy together with broad-spectrum antibiotic and antifungal therapies, the frequency of mucosal and systemic infections caused by *C. glabrata* has grown significantly. No unique clinical features are associated with *C. glabrata*. Often, the only manifestation is persistent fever in a patient whose condition is deteriorating and who is unresponsive to antimicrobial agents and has negative blood cultures.

C. glabrata secrete phospholipases, lipases, and hemolysins that contribute towards an extreme aggressiveness resulting in a low therapeutic response and serious recurrent candidiasis [12]. But pathogenicity was mainly attributed to moderate production of biofilm. They have the ability to form a compact biofilm structure in different multilayers with proteins, carbohydrates (e.g., β -1,3 glucans), and ergosterol in their matrixes. The biofilms help them to adhere to the surface of catheters. So central venous catheter removal with negative daily cultures are of great importance in treating these infections. Biofilms also help them to disseminate which leads to secondary metastatic infection in the kidney, lungs, spleen, liver, eyes, bones. These result in persistent fungaemia [12].

Multiple studies have been done to identify the risk factors for nosocomial *C. glabrata* bloodstream infection. Hospital environment favors infection owing to the interplay of carriage via the health care personnel hands which favor colonization and presence of risk factors [13]. Clearly identified risk factors are: length of stay, use of total parenteral nutrition, broad-spectrum antibiotics, central lines, abdominal surgery with particular risk among patients who have anastomotic leakage or have had repeat laparotomies, acute necrotizing pancreatitis, hematologic malignant disease, solid-organ transplantation, solid-organ tumors, hemodialysis, glucocorticoid use or chemotherapy for cancer, candida colonization, particularly if multifocal, mechanical ventilation > 48 hrs, multiple blood transfusions, APACHE II score of >10 [2].

Single risk factor is unlikely to predict invasive candidiasis, since all of these are very common in the hospital setting. Paphitou et al. [14] performed a retrospective review of all surgical ICU patients who stayed 4 days or longer over a year in a unit in the United States. Their findings showed that patients that had a combination of diabetes mellitus, new onset hemodialysis, use of total parenteral nutrition, and broad-spectrum antibiotics had a rate of invasive candidiasis of 16%, compared with 5% of patients that did not have the combination. Another study by Malani et al. [15] showed that the mean age \geq 60 years old,

use of broad-spectrum antibiotics were present in 86%, use of central intravenous catheters in 77%, stay in an ICU in 48%, renal insufficiency in 46% and receipt of parenteral nutrition in 45%.

Risk assessment strategies are thus used which increase the pretest likelihood of candidiasis. When a single uncommon risk factor, or a combination of two or more common risk factors are present there is a reasonable chance of developing the disease. It also demonstrated the rapidity with which these risk factors were achieved decided the type of candidiasis. It was day 8 in the no colonization group and LC groups and day 4 in the invasive candidiasis group. Risk factors can be divided into early and late. Early risk factors present at admission or at day 3 like total parenteral nutrition or central catheter previous SICU admissions or surgical procedures. Late risk factors hemodialysis, persistent leukocytosis, fever or hypothermia while taking antibiotics, use of broad-spectrum antibiotics, solid tumor, and lack of nutritional support. Central catheter for more than 72 hours and the use of mechanical ventilation on day 4 were significant predictors. The NEMIS Prospective Multicenter Study a prospective multicenter cohort study showed that independent risk factors like abdominal surgery was associated with higher risk (7.1). Vancomycin or an antibiotic agent with activity against anaerobic organisms (including combinations of imipenem, metronidazole, clindamycin, and the extended-spectrum penicillins/ β -lactamase-inhibitor drugs, such as ticarcillin/clavulanate, piperacillin/tazobactam, and ampicillin/sulbactam) were associated with increased risk.

The sensitivity of blood culture ranges from 21 to 71% [11]. Cultures may establish a diagnosis during the period when candida resides in the bloodstream, cultures of blood obtained from patients with deep seated infections often yield negative results. Candida mannan antigens and anti mannan antibodies and β -d-glucan are the primary surrogate markers for invasive candidiasis [16–18]. Nguyen et al. reported that an in-house PCR assay had a sensitivity of 89% [19]. Most of these tests are limited by low specificity. Because of the high mortality of invasive candidiasis, it's imperative to identify high risk patients which increases the

pretest likelihood of disease in that population.

In terms of treatment echinocandin was associated with better survival rates and greater clinical success in invasive candidiasis when compared to triazoles or amphotericin B [20]. Triazoles are preferred in the treatment of meningitis, endophthalmitis, and urinary tract as echinocandins cannot penetrate the barriers. Catheter Removal at any time point was associated with a reduction in mortality and higher clinical success rates [21–23]. As per 2016 Update by the Infectious Diseases Society of America choice of empiric antifungal therapy is decided on the basis of neutropenic vs non neutropenic patient. An echinocandin is the initial antifungal therapy for non neutropenic critically ill patient. Fluconazole, intravenous or oral, an acceptable alternative to an echinocandin as initial therapy in selected patients who are not critically ill. Testing for azole susceptibility is recommended for all bloodstream and other clinically relevant isolates. Transition from an echinocandin to fluconazole (usually within 5–7 days) is recommended for patients who are clinically stable, have isolates that are susceptible to fluconazole (e.g. *C. albicans*), and have negative repeat blood cultures following initiation of antifungal therapy. In neutropenic catheter removal is decided on an individual basis, ophthalmological evaluation is minimal during neutropenia, hence it performed within the first week after recovery from neutropenia.

Prophylaxis has also been tested in multiple trials. It has been shown that fluconazole prophylaxis in patients with recurrent abdominal surgery, recurrent gastrointestinal perforations or anastomotic leakage reduced the incidence of candidemia by approximately 50% [7]. But this strategy has not been shown to improve survival [24,25]. The major challenge is to select individual patients or subgroups that will benefit most from prophylaxis in order to limit the number needed to treat and to avoid emergence of resistance.

Conclusion

Candida glabrata are an important cause of Hospital Acquired Infection in our time. Spectrum of manifestation can range from low grade fever to fulminant shock. Unlike *Candida albicans* they are

associated with higher mortality and are usually resistant to azoles. MIC (minimum inhibitory concentration) is high for Amphotericin B as well. Resistance to echinocandins have also been reported. But this organism has not been extensively studied in terms of virulence, pathogenesis and host defense factors. Through our report we urge readers for the above. Also, the most important risk factor for the emergence of this species is the use of broad-spectrum antibiotic. Hence this underlines the urgency of antibiotic stewardship to prevent the emergence of azole-resistant *Non-albicans candida*.

Statement of funding

This work has not been funded by any institution or organization.

Acknowledgement

I would like to thank my attending Dr. Farshad Bagheri for his valuable feedback, Dr. Abhishek Das for his helpful suggestions in preparing this manuscript. I would also like to thank my mentor and Guru Sri Sri Ravi Shankar.

Conflict of Interest

The author would like to report that she has no conflict of interest in the above work.

References

[1] Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis.* 2004 Aug 1;39(3):309-17.

[2] Blumberg HM, Jarvis WR, Soucie JM, Edwards JE, Patterson JE, Pfaller MA, Rangel-Frausto MS, Rinaldi MG, Saiman L, Wiblin RT, Wenzel RP. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. *Clin Infect Dis.* 2001 Jul 15;33(2):177-86.

[3] Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, Reboli AC, Schuster MG, Vazquez JA, Walsh TJ, Zaoutis TE, Sobel JD. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2016 Feb 15;62(4):e1-50. [PMID: 26679628]

[4] Kullberg BJ, Arendrup MC. Invasive Candidiasis. *N Engl J Med.* 2015 Oct 8;373(15):1445-56. [PMID: 26444731]

[5] Snyderman DR. Shifting patterns in the epidemiology of nosocomial *Candida* infections. *Chest.* 2003 May;123(5 Suppl):500S-3S. [PMID: 12740235]

[6] Charlet R, Bortolus C, Barbet M, Sendid B, Jawhara S. A decrease in anaerobic bacteria promotes *Candida glabrata* overgrowth while β -glucan treatment restores the gut microbiota and attenuates colitis. *Gut Pathog.* 2018 Dec 3;10:50. [PMID: 30524506]

[7] Eggimann P, Francioli P, Bille J, Schneider R, Wu MM, Chapuis G, Chioloro R, Pannatier A, Schilling J, Geroulanos S, Glauser MP, Calandra T. Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients. *Crit Care Med.* 1999 Jun;27(6):1066-72. [PMID: 10397206]

[8] Arendrup MC, Patterson TF. Multidrug-Resistant *Candida*: Epidemiology, Molecular Mechanisms, and Treatment. *J Infect Dis.* 2017 Aug 15;216(suppl_3):S445-S451. [PMID: 28911043]

[9] Ruan SY, Lee LN, Jerng JS, Yu CJ, Hsueh PR. *Candida glabrata* fungaemia in intensive care units. *Clin Microbiol Infect.* 2008 Feb;14(2):136-40. [PMID: 18042196]

[10] Garnacho-Montero J, Díaz-Martín A, García-Cabrera E, Ruiz Pérez de Pipaón M, Hernández-Caballero C, Aznar-Martín J, Cisneros JM, Ortiz-Leyba C. Risk factors for fluconazole-resistant candidemia. *Antimicrob Agents Chemother.* 2010 Aug;54(8):3149-54. [PMID: 20498325]

[11] Lamoth F, Lockhart SR, Berkow EL, Calandra T. Changes in the epidemiological landscape of invasive candidiasis. *J Antimicrob Chemother.* 2018 Jan 1;73(suppl_1):i4-i13. [PMID: 29304207]

[12] Rodrigues CF, Rodrigues ME, Silva S, Henriques M. *Candida glabrata* Biofilms: How Far Have We Come? *J Fungi (Basel).* 2017 Mar 1;3(1):11. [PMID: 29371530]

[13] Fidel PL Jr, Vazquez JA, Sobel JD. *Candida glabrata*: review of epidemiology, pathogenesis, and clinical disease with comparison to *C. albicans*. *Clin Microbiol Rev.* 1999 Jan;12(1):80-96. [PMID: 9880475]

[14] Paphitou NI, Ostrosky-Zeichner L, Rex JH. Developing criteria for risk-stratified prophylaxis (PRX) of invasive candidiasis (IC) in the ICU. Abstr. M-1239. In 42nd Interscience Conference on Antimicrobial

Agents and Chemotherapy, San Diego 2002.

[15] Malani A, Hmoud J, Chiu L, Carver PL, Bielaczyc A, Kauffman CA. Candida glabrata fungemia: experience in a tertiary care center. *Clin Infect Dis.* 2005 Oct 1;41(7):975-81. [PMID: 16142662]

[16] Cornely OA, Bassetti M, Calandra T, Garbino J, Kullberg BJ, Lortholary O, Meersseman W, Akova M, Arendrup MC, Arikan-Akdagli S, Bille J, Castagnola E, Cuenca-Estrella M, Donnelly JP, Groll AH, Herbrecht R, Hope WW, Jensen HE, Lass-Flörl C, Petrikos G, Richardson MD, Roilides E, Verweij PE, Viscoli C, Ullmann AJ; ESCMID Fungal Infection Study Group. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients. *Clin Microbiol Infect.* 2012 Dec;18 Suppl 7:19-37. [PMID: 23137135]

[17] Lamoth F, Cruciani M, Mengoli C, Castagnola E, Lortholary O, Richardson M, Marchetti O; Third European Conference on Infections in Leukemia (ECIL-3). β -Glucan antigenemia assay for the diagnosis of invasive fungal infections in patients with hematological malignancies: a systematic review and meta-analysis of cohort studies from the Third European Conference on Infections in Leukemia (ECIL-3). *Clin Infect Dis.* 2012 Mar 1;54(5):633-43. [PMID: 22198786]

[18] Mikulska M, Calandra T, Sanguinetti M, Poulain D, Viscoli C; Third European Conference on Infections in Leukemia Group. The use of mannan antigen and anti-mannan antibodies in the diagnosis of invasive candidiasis: recommendations from the Third European Conference on Infections in Leukemia. *Crit Care.* 2010;14(6):R222. [PMID: 21143834]

[19] Nguyen MH, Wissel MC, Shields RK, Salomoni MA, Hao B, Press EG, Shields RM, Cheng S, Mitsani D, Vadnerkar A, Silveira FP, Kleiboeker SB, Clancy CJ. Performance of Candida real-time polymerase chain reaction, β -D-glucan assay, and blood cultures in the diagnosis of invasive candidiasis. *Clin Infect Dis.* 2012 May;54(9):1240-48. [PMID: 22431804]

[20] Andes DR, Safdar N, Baddley JW, Playford G, Reboli AC, Rex JH, Sobel JD, Pappas PG, Kullberg BJ; Mycoses Study Group. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. *Clin Infect Dis.* 2012 Apr;54(8):1110-22. [PMID: 22412055]

[21] Kollef M, Micek S, Hampton N, Doherty JA, Kumar A. Septic shock attributed to Candida infection: importance of empiric therapy and source control. *Clin Infect Dis.* 2012 Jun;54(12):1739-46. [PMID: 22423135]

[22] Horn DL, Ostrosky-Zeichner L, Morris MI, Ullmann AJ, Wu C, Buell DN, Kovanda LL, Cornely OA. Factors related to survival and treatment success in invasive candidiasis or candidemia: a pooled analysis of two large, prospective, micafungin trials. *Eur J Clin Microbiol Infect Dis.* 2010 Feb;29(2):223-29. [PMID: 20013016]

[23] Puig-Asensio M, Pemán J, Zaragoza R, Garnacho-Montero J, Martín-Mazuelos E, Cuenca-Estrella M, Almirante B; Prospective Population Study on Candidemia in Spain (CANDIPOP) Project; Hospital Infection Study Group (GEIH); Medical Mycology Study Group (GEMICOMED) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC); Spanish Network for Research in Infectious Diseases. Impact of therapeutic strategies on the prognosis of candidemia in the ICU. *Crit Care Med.* 2014 Jun;42(6):1423-32. [PMID: 24557426]

[24] Shorr AF, Chung K, Jackson WL, Waterman PE, Kollef MH. Fluconazole prophylaxis in critically ill surgical patients: a meta-analysis. *Crit Care Med.* 2005 Sep;33(9):1928-35; quiz 1936. [PMID: 16148461]

[25] Pelz RK, Hendrix CW, Swoboda SM, Diener-West M, Merz WG, Hammond J, Lipsett PA. Double-blind placebo-controlled trial of fluconazole to prevent candidal infections in critically ill surgical patients. *Ann Surg.* 2001 Apr;233(4):542-48. [PMID: 11303137]