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Clinical profile of candidemia in critically ill Patients

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Abstract

Blood stream infection due to candida is an important cause of sepsis contributing to mortality and morbidity of critically ill patients. Many studies done across the world have shown that the incidence of candidemia is more in critical care settings compared to general wards. This is due to multiple organ dysfunctions in critically ill necessitating the use of broad spectrum antibiotics, invasive central venous and arterial lines, and total parenteral nutrition. Those who undergo gastrointestinal tract surgeries, develop pancreatitis, sustain burns etc are also at increased risk of development of candidemia. Candidemia in critical care settings can arise either exogenously or endogenously. Exogenous candidemia usually occurs due to breaches in infection prevention and control strategies like in the case of central line associated candidemia. Endogenous candidemia occurs as a result of collateral damage due to unscrupulous use of broad spectrum antibiotics and translocation of candida in the gut following total parenteral nutrition, gastrointestinal tract surgeries, necrotising pancreatitis , extensive burns etc. Collateral damage and thereby selecting out of candida in the gut can be addressed only by antimicrobial stewardship.

This retrospective descriptive study was done to identify the clinical profile of candidemia in patients admitted to critical care intensive care unit at GMC Thiruvananthapuram between January 2016 and January 2018. Total 40 patients were included in this study. Those who were Immunocompromised were excluded from the study.Average age of patients with

candidemia in the study was 44 years. Gender distribution was 18 males [45%] and 22 females [55%]. Average day at which candidemia was detected was 19.5 days from symptom onset. But it was 13.4 days from symptom onset for patients with necrotising pancreatitis . All the patients with candidemia [100%] were on broad spectrum antibiotics for more than 7 days. Of the patients with candidemia, 80.8% of patients had central venous catheters in situ at time of detection of candidemia of which 50.6% showed differential time to positivity more than two hours suggestive of CLABSI, 75.9% of patients were on mechanical ventilation, 70% were in severe sepsis, 20.5% had received total Parenteral nutrition [TPN], 17.5% had necrotising pancreatitis and history of gastrointestinal surgical procedure was present in 35% cases. Average duration of broad spectrum antibiotic use prior to development of candidemia was 17.5 days. Central venous catheters were present for an average of 12.6 days prior to development of candidemia. The most common species was Candida Tropicalis 14 [35%], Albicans 10 [25%], Parapsilosis 5 [12.5%], Auris 5 [12.5%], Haemulonni 2 [5%], Candida Glabrata 2 [5%] and Candida Krusei 2 [5%]. Of the 5 patients with Candida auris, 100% had resistance to fluconazole and Amphotericin B. 20 % [1 patient] had caspofungin resistance. Overall mortality due to candidemia was 25% and that due to Candida auris was 33.3%.

Keywords: Candidemia, Critically Ill, Candida tropicalis, Antifungal resistance, Candida auris, CLABSI

Introduction

Blood stream infection due to candida is an important cause of sepsis contributing to mortality and morbidity of critically ill patients.

Candidemia represents the fourth and sixth leading cause of healthcare associated sepsis in European and US studies respectively [1, 2]. Data on the clinical and epidemiological profile of candidemia is available from large series of laboratory based [3] and population based surveillance studies [4], as well as from studies pertaining to high risk populations like those on chemotherapy, immunosuppressive drugs, neonates [5, 6], post-transplant patients, post gastrointestinal surgery and those who are critically ill [7, 8]. Recent increase in incidence of candidemia is probably attributed to the prolonged survival of critically ill patients and change in the demographic characteristic of the patient population [10, 11]. The epidemiology of candidemia varies from region to region, from hospital to hospital and sometimes even from ICU to ICU in the same hospital. This makes it necessary to have continuous surveillance programs to monitor the incidence, species distribution and antifungal susceptibility profile. Candidemia is associated with high attributable mortality, increased cost of care and duration of hospitalisation [12]. Attributable mortality due to candidemia varies from 5 % to 71% [13] depending on the patient population. Emergence of resistance to azoles is a major challenge to be considered while designing the prophylactic and pre-emptive treatment strategies for candidemia. Emergence of candida auris has been reported from almost all hospitals across the globe. Due to the unique infection prevention and control and therapeutic challenges posed by it, Candida Auris has recently been termed “Candida superbug” due to its resistance profile, especially its non-susceptibility to fluconazole and variable susceptibility to amphotericin and echinocandins .In the ICU scenario,without optimal infection control.it will be

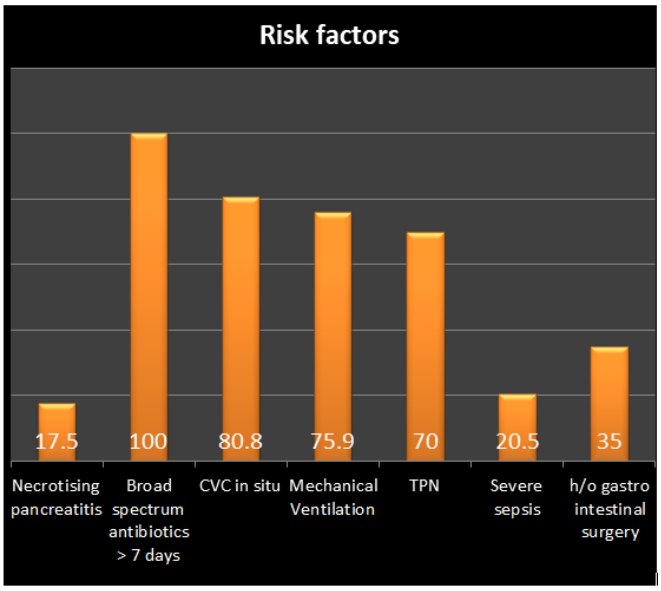
difficult to get rid of Candida Auris just like Acinetobacter species, as it displays clonal inter and intra-hospital transmission. This retrorospective study was done over a period of two years to assess the clinical profile, risk factors and outcomes of patients with candidemia in critical care ICU.

Methods

This retrospective study was done in critical care intensive care unit of Government Medical College Hospital, Thiruvananthapuram. Study period was from January 2016 to January 2018.Patients with malignancy, HIV and those on chemotherapy or immunosuppressive drugs were excluded from the study. Patients with blood culture positive for candida [vitek 2 biomeriux] were included in the study. Species level identification and Susceptibility was determined using VITEK 2 YST ID colorimetric cards. In case of candida haemulonii and famata, the isolate was subjected to MALDI-TOF and in case of Candida Auris confirmed by MALDI-TOF. Clinical profiles, risk factors and outcomes were studied and data with regard to these were extricated from clinical charts. An episode of candidemia was defined as ≥ 1 positive candida isolate in a blood culture drawn from a peripheral vein along with signs and symptoms compatible with candidemia. Episodes were considered as separate if they occurred ≥1 month apart. Catheter related candidemia was diagnosed when blood drawn from catheter and peripheral line flagged positive for the same candida isolate with no evidence of infection at any other site to account for candida blood stream infection. A differential time to positivity of ≥ 2 hours was used to diagnose catheter related candidemia.

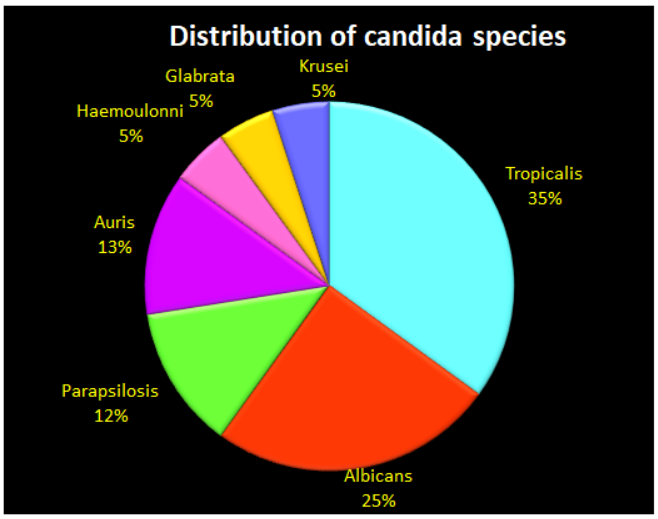
Results

Total 40 patients were included in this study. Average age of patients with candidemia in the study was 44 years. Gender distribution was 18 males [45%] and 22 females [55%]. Average day at which candidemia was detected was 19.5 days from symptom onset. But it was 13.4 days from symptom onset for patients with necrotising pancreatitis . All the patients with candidemia [100%] were on broad spectrum antibiotics for more than 7 days. Of the patients with candidemia, 80.8% of patients had central venous catheters in situ at time of detection of candidemia of which 50.6% showed differential time to positivity more than two hours suggestive of CLABSI, 75.9% of patients were on mechanical ventilation, 70% were in severe sepsis, 20.5% had received total Parenteral nutrition [TPN], 17.5% had necrotising pancreatitis and history of gastrointestinal surgical procedure was present in 35% cases.



Average duration of broad spectrum antibiotic use prior to development of candidemia was 17.5 days. Central venous catheters were present for an average of 12.6 days prior to development of candidemia. The most

common species was Candida Tropicalis 14 [35%], Albicans 10 [25%], Parapsilosis 5 [12.5%], Auris 5 [12.5%], Haemulonni 2 [5%], Candida Glabrata 2 [5%] and Candida Krusei 2 [5%].



Of the 5 patients with Candida auris, 100% had resistance to fluconazole and Amphotericin B. 20 % [1 patient] had caspofungin resistance. Overall mortality due to candidemia was 25% and that due to Candida auris was 33.3%.

Discussion

Many studies done across the world have shown that the incidence of candidemia is more in critical care settings compared to general wards. This is due to multiple organ dysfunction in critically ill necessitating the use of broad spectrum antibiotics, invasive central venous and arterial lines, and total parenteral nutrition. Those who undergo gastrointestinal tract surgeries, develop pancreatitis, sustain burns etc are also at increased risk of development of candidemia. Candidemia in critical care settings can arise either exogenously or endogenously. Exogenous candidemia usually occurs due to breaches in infection prevention and control strategies like in the case of central line associated candidemia. Endogenous candidemia occurs as a result of collateral damage due to unscrupulous use of broadspectrum antibiotics and translocation of candida in the gut following total parenteral nutrition, gastrointestinal tract surgeries, necrotising pancreatitis , extensive burns etc. Collateral damage and thereby selecting out of candida in the gut can be addressed only by antimicrobial stewardship.

An increased incidence of candidemia in nosocomial settings has been shown by many studies in the last fifteen years . Candidemia was more frequently diagnosed among patients aged 61 to 80 years, with a progressive increase of the mean age over time[12]. In our study mean age of patients with candidemia was 44years, with 55% of patients being female and 45% male. Multiple studies from across the world suggests that the increase in the incidence of candidemia is related not only to an increased number of immunocompromised patients, but also to the aging of the population [15]. In our study Immunocompromised patients were not included. In a population based active surveillance for culture confirmed candidemia across four sites in United States from 2012-2016 [Mitsuru Toda et al], the crude annual incidence of candidemia was highest among adults aged ≥65 years (25.5 per 100,000 population) followed by infants aged <1 year. The crude annual incidence was higher among males (9.4) than among females (8.0) and was approximately 2 times greater among blacks than among nonblacks (13.7 versus 5.8). In contrast to this result, in our study 55% of patients with candidemia were females. As per study by Mitsuru Toda et al, one third of cases occurred in patients who had undergone a surgical procedure in the 90 days before the candidemia diagnosis, 77% occurred in patients who had received systemic antibiotics in the 14 days before the diagnosis, and 73% occurred in patients who had had a central

venous catheter (CVC) in place within 2 days before the diagnosis. In our study 35% of patients had undergone gastrointestinal surgery prior to diagnosis of candidemia, 100% of patients with diagnosed candidemia had received broad spectrum antibiotics for more than 7 days and 80.8% had central line in situ of which 50.6% had CLABSI. As per study by Mitsuru Toda et al, ten percent were in patients who had used injection drugs in the past 12 months [16]. In our study none of the patients gave history of injection drug use. The median time from admission to candidemia diagnosis was 5 days with an interquartile range [IQR] of 0–16 days [16). In our study, mean time from symptom onset at which candidemia was diagnosed was 19.5 days and in those with necrotizing pancreatitis it was 13.4 days. Among 2,662 cases that were treated in adults aged >18 years, 34% were treated with fluconazole alone, 30% with echinocandins alone, and 34% with both [16]. In our study 80% patients with candidemia were treated with fluconazole, 12.5% with echinocandins and 7.5% with a combination of fluconazole and echinocandins. All cases of candida auris were treated with echinocandins. As per study by Mitsuru Toda et al, the all-cause in-hospital case-fatality ratio was 25% for any time after admission; the all-cause in-hospital case-fatality ratio was 8% for <48 hours after a positive culture for *Candida* species [16]. In our study, the all cause in hospital case-fatality rate due to candidemia was 25%. The crude mortality for candidemia in various studies ranges from 30 - 81% as evident from studies of Bassetti *et al*. (43.5%), Singh *et al* (50.6%), Chakrabarti *et al* (54.3%), and Bougnoux *et al*. (61.8%). Apparently lower case fatality rate observed in our study is due to the fact that our study did not include candidemia in immunocompromised patients. As per study by Mitsuru Toda et al *Candida albicans* accounted for 39% of cases, followed by *Candida glabrata* (28%) and *Candida parapsilosis* (15%). Overall, 7% of isolates were resistant to fluconazole and 1.6% were resistant to echinocandins, with no clear trends in resistance over the 5-year surveillance period [16]. In our study, the most common species identified was Candida Tropicalis 14 [35%] followed by C.Albicans 10 [25%], C. Parapsilosis 5 [12.5%],C. Auris 5 [12.5%],C. Haemulonni 2 [5%], Candida Glabrata 2 [5%] and Candida Krusei 2 [5%]. Of the 5 patients with Candida auris ,100% had resistance to fluconazole and Amphotericin B. 20 % [1 patient] had caspofungin resistance. Overall mortality due to candidemia was 25% and that due to Candida auris was 33.3%.

Similar to observations in our study,recent studies have shown an increase in the incidence of candidemia due to non-albicans *Candida*, with the isolation rate ranging from 50 to 96% from tertiary care centers in India. *C. tropicalis* and *C. parapsilosis* are an emerging cause of candidemia in India. In a systematic epidemiological study on intensive care unit (ICU)-acquired candidemia across India, vast spectrum of agents (31 Candida species) were implicated for candidemia with most prevalent species being Candida tropicalis (41.6 %) as observed [17]. Azole and multidrug resistance were seen in 11.8 and 1.9 % of isolates [17]. Public sector hospitals reported a significantly higher presence of the relatively resistant C. auris (8.2 %) and C. rugosa (5.6 %) [17]. The 30-day crude and attributable mortality rates of candidemia patients were 44.7 and 19.6 %, respectively. [17]

Conclusion

This study demonstrates that Candidemia is an important cause of mortality and morbidity in critically ill patients, especially in those with prolonged ICU stay, use of broad spectrum antibiotics, presence of central venous catheters, mechanical ventilation, pancreatitis and those in severe sepsis. Non-albicans candida were more common than candida albicans. Candida Tropicalis was the commonest species responsible for candidemia. Emergence of candida Auris is a major concern from therapeutic and infection control perspective. Due to multi drug resistance exhibited, antifungal susceptibility testing is very important for Candida Auris. In this study,12.5% of candida isolates were found to be Candida Auris with 100% resistance to amphotericin B and fluconazole and 20% resistance to caspofungin.

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