Research Article

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Candidemia A Review Over 5 Years at A 300 Beds Military Hospital (Serving Military Personnel and Their Families) In the United Arab Emirates

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Abstract

We report the occurrence of 93 episodes of candidemia over 5 years (2010-2014). Non Albicans Candida outnumbered Albicans as blood stream isolates. Candida Parapsilosis with intermediate sensitivity to fluconazole was the most prevalent isolate. New species never isolated before emerged in the last year (Krusei, Guilliermondii and Lusitanii). Central line use and antifungal therapy are discussed as possible factors leading to the change in Candida species and sensitivity. In view of the unusual sensitivity of C.parapsilosis and the emergence of new C.species prospective studies are required to evaluate candidemia risk factors, especially central line use and antifungal treatment patterns in order to formulate appropriate preventive and therapeutic recommendations.

Introduction

Candida is yeast responsible for most of the systemic invasive fungal infections in humans. The incidence of systemic Candida infections, particularly bloodstream infections (Candidemia), has increased significantly in recent years, being the fourth most common pathogen isolated in blood cultures in the USA [1-3]. In Europe, it ranks among the ten most frequently isolated pathogens, and in a survey of intensive care units (ICUs) worldwide, the prevalence of Candidemia was found to be 6.9 per 1000 patients [4].

In the past, almost all the isolates responsible for bloodstream infections were *C. Albicans*, whereas in recent years a growing proportion of episodes of Candidemia have been caused by Candida species other than Albicans. During the past two decades, most healthcare institutions have reported a progressive shift in the species of Candida. Although *C. Albicans* remains the predominant strain in many countries, non-Albicans species are increasingly common and may be responsible for over 50% of Candidemias [5-7].

In the United Arab Emirates the epidemiology and prevalence of Candidemia was reported by the Faculty of Medicine at UAE University in 60 episodes, over 6 years (1995-2001): Albicans 43% ranked first followed by Tropicalis 13% and Glabrata 13% then Parapsilosis 5% [8]. In Qatar of total 201 episodes of Candidemia identified Candida albicans was the most common species isolated (33.8 %; n = 68), whereas non-Albicans Candida species represented 66.2 % (n = 133) of the episode [9]. In Saudi Arabia, in 2 retrospective reviews of Candidemia reported, one over nine years (1996–2004) found Candida Albicans the most frequent Candida species (53%), followed by Candida Tropicalis (19%), Candida Parapsilosis (16%), and Candida Glabrata (7%) [10]. while the second reported over 5 years (1995-2000) found Candida parapsilosis the most frequent Candida species (44%) followed by Candida Tropicalis (25%) then Candida Albicans (19%) [11].

The epidemiology of invasive Candida infections and the increase in non Albicans Candida with potential alteration in sensitivity to antifungal drugs has significant implications for the choice of the appropriate management strategy. Therefore this retrospective review of the microbiology laboratory records, for the period from 1st January 2010 till end of December 2014 was carried out to evaluate the prevalence of candidemia at Zayed Military Hospital (ZMH), determine the occurrence of non Albicans Candida and define the sensitivity pattern of Candida isolates to the tested antifungals.

Materials and Methods

Standard methods were used to identify isolated fungi and test their sensitivity. Laboratory culture bottles were incubated in the automated Bact Alert (Bio MerieuxSA) for 5 days. Blood cultures with the presumptive visualization of yeast cells in the gram stain were subcultured in the Candida Chome Agar and Sabourad Dextrose Agar and incubated for 24 to 48hoursat35degreescelcius. Candida species isolated on cultures were identified by means of VITEK2YST (Fungal identification card) whereas susceptibility results for azole antifungals and echinocandins were reported as per laboratory standards institute document M27S4 [12].

Data collection

The microbiology culture logbooks for the period Jan 1st 2010 till Dec. 31st 2014 were reviewed. All blood cultures that grew Candida were identified. Patient location when Candidemia occurred, blood collection method (whether via a central line or peripheral venous puncture), Candida species, sensitivity to antifungal drugs, total count of positive blood culture episodes (bacterial/fungal) were recorded.

Results

Of 1347 total episodes of positive blood cultures 93 grew Candida. Twenty four episodes occurred in patients admitted to general wards and 69 from the critical care area. *C. Parapsilosis* was the most common isolate (30) followed by Tropicalis (29) then Albicans (16), Glabrata (12), Krusei (2), Guilliermondii (1), Lusitanii (1) and unidentified species (2) (Table 1).

Species	*Parapsilosis*	*Tropicalis*	*Albicans*	*Glabrata*	*Guillier Mondi*	*Krusei*	*Lusitaniae*	?	Total
2010	5	12	5	0	0	0	0	0	22
2011	6	5	3	3	0	0	0	1	17
2012	9	5	4	3	0	0	0	0	21
2013	8	4	2	3	0	0	0	0	17
2014	2	3	2	3	1	2	1	1	15
Sum	30	29	16	12	1	2	1	2	93

Table 1: Distribution of Candida species per year of occurrence.

C. Albicans and *C. Tropicalis* were sensitive to Fluconazole in all isolates. *C. Glabrata* was sensitive in 11 out of 12 patients. *C. Parapsilosis* was sensitive to fluconazole in only 6 isolates and had intermediate sensitivity in 22 isolates, sensitivity not available for 2 isolates. Blood cultures were drawn from central venous access (37 episodes). *C.Parapsilosis* was isolated from (16) of them followed by Albicans (10), Tropicalis (9) and Kruseii (2).

Discussion

Invasive Candidiasis is a disease of modern medicine, especially in developing countries where modern advances in medical therapeutics are being introduced. Broad-spectrum antibiotics, indwelling intravenous catheters, prosthetic devices, hyperalimentation fluids, cancer treatment with cytotoxic agents, use of immunosuppressives for organ transplantation have led to the emergence of Candida [1]. Similar to litterature reports Candida has emerged as a common pathogen with high prevalence at ZMH as 93 episodes of Candidemia occured over 5 years from Jan 1st 2010 till Dec 31st 2014. Candida accounted for 6.9% of all positive blood culture isolates (bacterial and fungal) and an average of 19 ± 4 episodes per year occured over the study period. Recent reports show that more than 50% of all Candidemia episodes occur in a patient population usually hospitalized in internal medicine wards. This population, in contrast to previous association with intensive care units and immunocompromised neutropenic patients is at risk of systemic Candidiasis in view of multiple co morbidities, such as older age, need for parental nutritionorbacterial infections episodes [13].

In this study the majority of Candidemia episodes still occurred in critical care area, 69 compared to 24 from general wards with a ratio approximately 3:1. A shift to non-Albicans species occurred during the study period as Candida Albicans (17.2% of fungemias) ranked 3rd after Candida Parapsilosis (32.2%) and Candida Tropicalis (31.1%). Of note as well a change in the epidemiology of Candidemia happened during 2014 as new species never isolated before emerged, such as Krusei (2), Guilliermondii (1), Lusitanii (1) and others (2). Figure 1 Overall the trend in Candida species showed a decline in Albicans and a rise in Parapsilosis and others. Possible explanation to the predominance of non Albicans species may be related to the spectrum of medical services offered at ZMH causing a selection in the population at risk of Candidemia and as a result, a predominance of certain Candida species over others. As an example Neutropenia and bone marrow transplantation predispose to systemic fungal infections caused by Candida Tropicalis and Candida Krusei however bone marrow transplant is not performed at ZMH.

Additional services not provided at ZMH include treatment of hematologic malignancies, solid organ transplantation and neonatal /pediatric intensive care. On the other hand treatment of solid tumors and follow up for various organ transplant recipients on immunosuppressive therapy is offered. Intensive care units are combined medical /surgical units and overflow of patients requiring ICU care are often admitted to CCU if required. In addition the prevalence of Candida Parapsilosis can be attributed to known risk factors that include the presence of central lines, hyperalimentation and the use of antifungal therapy [1,14]. Although neonatal age is a known risk factor for *C. Parapsilosis* this does not apply to our situation as neonatal ICU and neonatal service are not available at ZMH.

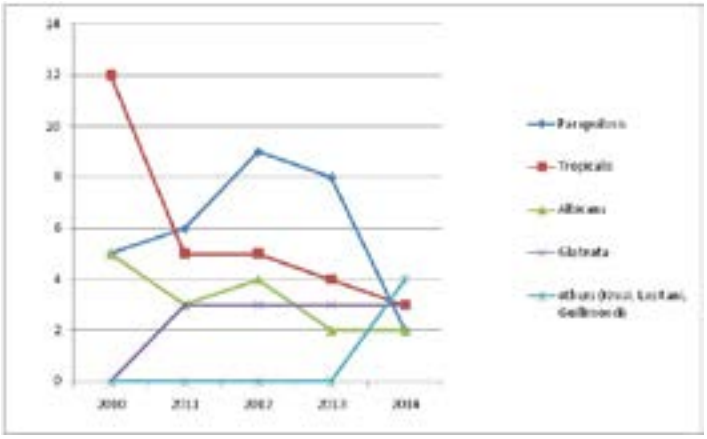

Figure 1: Changing trends in Candida species over time.

In this study the frequency of central line use is reflected by the large number of positive blood cultures obtained via central lines 37 (39.7%) compared to 56 peripheral draws. Figure 2. *C. Parapsilosis* was the most frequently isolated candida species

from blood drawn via central lines and accounted for 43% (16) of them followed by Albicans in 27% (10), Tropicalis 24% (9) and kruseii 5% (2) (Figure 3).

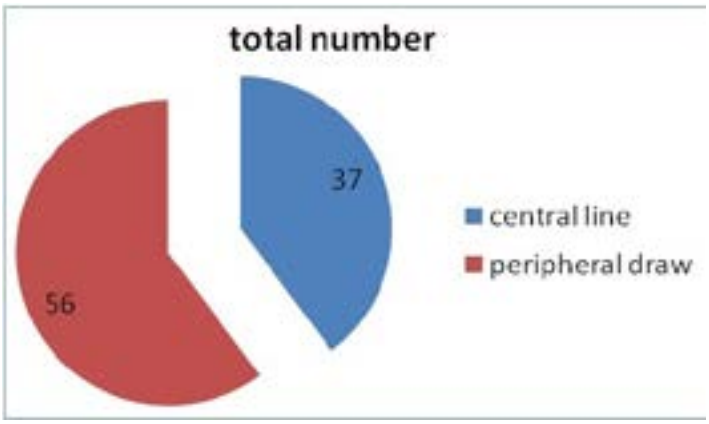

Figure 2: Site of blood culture.

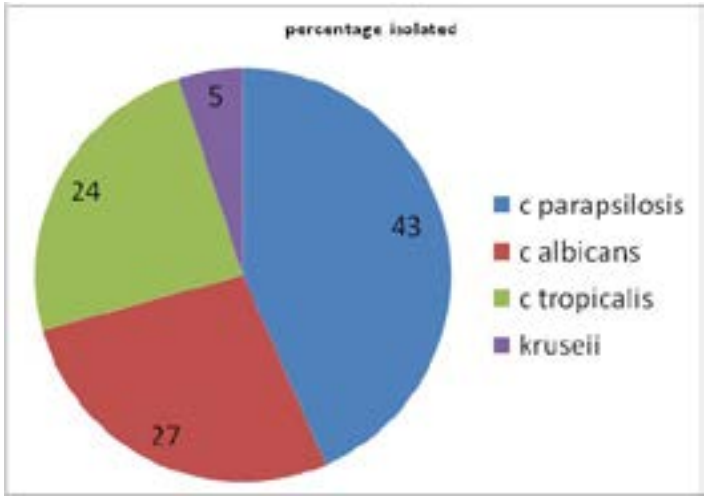

Figure 3: Candida species isolated from blood cultures drawn via central lines.

Another important factor that may have contributed to the emergence of non Albicans species is the antifungal use [14,15]. A widespread use of fluconazole has been associated with the development of infections due to non-Albicans species that are intrinsically resistant to fluconazole or have developed resistance during treatment. The fluconazole exposure can be considered either on a patient level, for example, in case of long-term fluconazole prophylaxis that predisposes patients to *C. krusei* infection, or on the level of a ward or hospital, when bulk consumption can change ecology of Candida species [15-17]. The relationship with a heavy consumption of an antifungal and an increase in minimum inhibitory concentration to antifungals has been established not only for azoles, but also for echinocandins. Previous therapy with echinocandins seems to predispose to emergence of echinocandin resistant strain due to the development of mutations in FKS genes coding for β-1,3-glucan-synthase [18,19].

The sensitivity of *C. Albicans, C. Tropicalis* and *C. Glabrata* to Fluconazolewas 100%, 100% and 91.6%, respectively. *C. parapsilosis* was sensitive to fluconazole in only 21.4% (6 isolates) and intermediate in (78.6%) 22 isolates. Candida Parapsilosis, now the most commonly isolated species at our institution represents a therapeutic challenge as it is only 20% sensitive to fluconazole, considerably less than what is reported in the literature. *C. Parapsilosis* is also known to be intrinsically less susceptible with higher minimum inhibitory concentration (MIC) values for echinocandins however this seems not to influence the outcome of treatment with these agents as the clinical response to echinocandins is generally satisfactory [20]. In view of rising concerns about the growing prevalence of antifungal resistance the updated IDSA Candida treatment guideline advocates testing for azole susceptibility in clinically relevant Candida isolates. Testing for echinocandin susceptibility should also be considered in patients who have had prior treatment with echinocandins and among those who have infection with *C. glabrata* or *C. parapsilosis* [21]. Antifungal susceptibility tests are currently standardized as the Clinical and Laboratory Standards Institute (CLSI) MIC clinical break point for Candida species have been lowered and are now consistent with the European Committee on Antimicrobial Susceptibility Testing (EUCAST), which makes reporting worldwide Candida nonsusceptibility rates much easier [22]. Routine susceptibility testing is essential for species causing invasive infections, in case of antifungal prophylaxis or previous exposure and in patients who do not respond to treatment [21].

The updated IDSA treatment guidelines also indicate that echinocandins are at present the best choice for patients who are severely ill or possibly infected with fluconazole resistant strains. An echinocandin can be used as first line treatment of Candidemia rather than an azole antifungal. The reason is that azoles are static while echinocandins are cidal. In addition echinocandins are more active in the setting of line sepsis in view of the biofilm formed in case of infected catheter. If the removal of a central venous catheter is absolutely contraindicated or not feasible, initiating agents active against biofilm such as echinocandins or liposomal amphotericin and then switching to an oral treatment, such as fluconazole is therefore recommended as a step-down approach [21].

Conclusions

Non Albicans Candida has outnumbered Albicans as blood stream isolate in the past 5 years with *Candida Parapsilosis* being the most prevalent isolate. Initiating treatment with an intravenous antifungal such as an echinocandin and then switching to an oral treatment, such as fluconazole once final identification and sensitivity results are available is an acceptable therapeutic option at present.In view of the unusual sensitivity pattern of *C. parapsilosis* and the emergence of new Candida species prospective studies are required to evaluate candidemia risk factors, especially central line use and antifungal treatment patterns in order to formulate appropriate preventive and therapeutic recommendations tailored to our local hospital environment.

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