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Invasive Fungal Disease in an Intensive Care Unit of Tertiary Care Hospital of Bangladesh

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Abstract

Background: Invasive fungal infections (IFIs) represent a major challenge in intensive care units (ICUs) globally, contributing significantly to morbidity and mortality among critically ill patients. It is crucial to comprehend the dynamics of these infections in Bangladesh, considering its unique healthcare environment and tropical climate, to enhance management and prevention strategies effectively. ***Materials and Methods:*** The study was designed as a retrospective cohort study. Data was collected from fungal surveillance database of non-covid ICU of Dhaka Medical college for a period ranging from July 2022 to April 2024. The study enrolled 205 patients based on specific criteria. It aimed to identify the prevalence & resistance pattern of invasive fungal species. Statistical Package for Social Science (SPSS) version 25.0 was used for data analysis. ***Results:*** In the study of 205 ICU patients, demographic analysis revealed a predominance of males (65.37%) and an age distribution skewed towards those aged 30-60 years (46.34%). Common comorbidities included diabetes (20.00%), hypertension (24.88%), chronic kidney disease (10.24%), and COPD (14.63%). Invasive procedures, such as central venous lines (44.88%), were prevalent, alongside notable rates of fungal infection (8.29%), primarily involving Candida species. Resistance patterns among fungal-positive blood samples showed significant resistance to Amphotericin B, Caspofungin, and Voriconazole (50% each), while Fluconazole and Flucytosine exhibited no resistance. Species analysis identified Candida albicans, Candida tropicalis, and Candida auris with varying mortality rates (100%, 80%, and 66.67%, respectively). ***Conclusion:*** High mortality rates associated with Candida species underscore the urgent need for effective antifungal strategies tailored to local resistance patterns. Continued surveillance and improvements in infection prevention and control measures are essential to mitigate the impact of emerging resistant pathogens like Candida auris in healthcare settings.

Keywords: Invasive Fungal Disease, Fungal Infection, Anti-fungal.

INTRODUCTION

Fungi are eukaryotic organisms with membrane-bound organelles and defined nuclei, distinguishing them from bacteria. They exist in the environment and can be part of the human flora. Fungal infections range from mild skin or mucosal infections to severe, life-threatening invasive infections involving organs like the kidneys, liver, and brain. Fungi mainly exist as yeasts, molds, or dimorphic forms. Yeasts are single-celled and reproduce by budding, while molds consist of thread-like filaments (hyphae). Fungal infections are classified as superficial, cutaneous, subcutaneous, endemic, or opportunistic. Invasive fungal infections occur when fungi penetrate deep tissues, often affecting immunocompromised individuals and leading to prolonged illness [1].

According to the updated definition of invasive fungal diseases (IDFs) European Organization for Research and Treatment of Cancer and the Mycoses Study Group classified IFDs into three categories: "proven," "probable," and "possible." A patient can be classified as having proven IFD if fungi are detected by microscopy, culture of sterile material or blood, tissue nucleic acid diagnosis, or DNA sequencing, regardless of their immune status [2,3].

More than 150 million people globally suffer from serious fungal diseases, which significantly increase the risk of illness and death. In intensive care units, fungal infections account for 29 to 45% of bloodstream infections [4]. Regional studies reveal varying burdens among countries and populations, hindered by inadequate surveillance systems, underreporting, and diagnostic challenges outside specialized settings. Risk factors include central venous catheters, ICU stays, prolonged antibiotic use, comorbidities, and invasive medical procedures. Early detection and management remain challenging, particularly in resource-limited settings with slow diagnostic tests [5]. The Global Action Plans for Fungal Infections prioritize improving diagnosis and treatment for diseases such as cryptococcal meningitis, Pneumocystis pneumonia, disseminated histoplasmosis, chronic pulmonary aspergillosis, and fungal keratitis to enhance public health outcomes [6-10].

Fungal infections in Bangladesh display a diverse range, with numerous studies detailing their epidemiology, clinical characteristics, and diagnostic challenges. Superficial mycoses and dermatomycoses are prevalent across rural areas and tertiary hospitals. Candida bloodstream infections were estimated at 5 per 100,000 (8100 cases), primarily affecting critically ill patients unresponsive to initial antibiotics, leading to emergence of drug-resistant strains. Invasive aspergillosis, mainly affecting leukemia and COPD patients, was estimated at 5166 cases [11]. Histoplasmosis was documented in 16 cases, primarily disseminated, and suspected in 21 cases with HIV infection. Emerging deep mycoses include cases of blastomycosis, mucormycosis, renal aspergillosis, pulmonary aspergilloma, and cryptococcal meningitis. These findings underscore the increasing importance of identification of fungal species and systemic antifungal treatments in critical care settings in Bangladesh [12-15].

The Rationale of the study:

Invasive fungal infections (IFIs) are a significant cause of morbidity and mortality among critically ill patients in intensive care units (ICUs) worldwide. These infections lead to prolonged hospital stays, increased healthcare costs, and high mortality rates. Given Bangladesh's unique healthcare challenges and tropical climate, studying these infections in this region is particularly critical.

ICU patients are at increased risk for fungal infections due to factors such as prolonged antibiotic use, invasive procedures, and immunosuppression. Despite this, there is a scarcity of data on the prevalence and species distribution of fungal infections in Bangladeshi ICUs, hindering the development of targeted treatment protocols. Insights from this study could contribute to the global understanding of fungal infections, particularly in tropical and resource-limited settings, and lead to improved diagnostic, prophylactic, and therapeutic strategies, thereby enhancing patient care and outcomes in ICUs.

METHODOLOGY

Study Design:

This study was designed as a Retrospective cohort study conducted in the Non-COVID ICU at the Department of Anesthesia, Pain, Palliative & Intensive Care, Dhaka Medical College, Dhak. Data was collected from fungal surveillance database of non-covid ICU of Dhaka Medical college for a period ranging from July 2022 to April 2024. Total 205 patients are enrolled in the study based on inclusion and exclusion criteria. The main outcome variable studied was the prevalence of invasive fungi in different specimens and identification of fungal species in selected cases.

Participant Selection:

After the initial study design data was obtained from ICU database of fungal surveillance database. The study included patients aged 13 years and older, of both sexes, admitted to the ICU of Dhaka Medical College Hospital. This includes patients with chronic lung conditions (asthma, COPD), undergoing hemodialysis, diagnosed with diabetes, receiving chemotherapy or immunosuppressive drugs (≥7 days), or diagnosed with AIDS. Also included are patients at risk of healthcare-associated infections (postoperative care, urinary catheters, tracheal intubation, ventilatory support, IV cannula, other invasive procedures). Additionally, patients undergoing prolonged injectable antibiotic treatment (>7 days), those with hospital stays exceeding 7 days, and those with a history of taking steroids or antibiotics for more than 2 weeks prior to hospitalization are included.

Data Collection & evaluation parameters:

Patient socio-demographic information, duration of hospitalization, history of invasive or non-invasive procedures, use of invasive medical devices, systemic antimicrobial exposures, and past medical was searched from intensive care unit fungal surveillance record.

Statistical analysis:

Following collection of the data, all data were edited and encoded into a statistical software named statistical program Statistical Package for Social Science‘(SPSS) version 25.0. In this study, continuous data was displayed as mean ± standard deviation if normally distributed and were compared by unpaired t-test. But when data was abnormally distributed it was expressed as median, interquartile ranges (IQR) and was compared using the Mann-Whitney test between both groups. Qualitative data were expressed as frequency, percentage (%) and compared using Kaplan-Meier curve with log-rank test. Diagnostic accuracy measures of sensitivity and specificity were calculated with 95 % exact binomial confidence intervals (CIs). In the whole study, significance level was set $p<0.05$ in all cases.

RESULTS

This was a retrospective study conducted in Non-COVID ICU, Department of Anesthesia, Pain, Palliative& Intensive Care DMCH. Patient. The main objective of the study is to identify the burden of fungal infection in ICU and detecting species as well as identifying the resistance pattern of antifungal drugs.

In the study involving 205 intensive care unit (ICU) patients, demographic and clinical characteristics were analyzed to understand patterns of invasive fungal disease surveillance. The patient cohort predominantly comprised males (65.37%) compared to females (34.63%). Age distribution showed a majority in the 30-60 years category (46.34%), followed by those aged 18-30 years (24.88%) and over 60 years (22.93%), with a smaller proportion under 18 years (5.85%).

Common comorbidities included diabetes (20.00%), hypertension (24.88%), chronic kidney disease (10.24%), and chronic obstructive pulmonary disease (COPD) (14.63%), with other comorbid conditions making up 30.24% collectively.

Table 1: Demographic and clinical characteristics

N=205		**n (%)**
Gender	Male	134 (65.37%)
	Female	71 (34.63%)
Age, years	<18	12 (5.85%)
	18–30	51 (24.88%)
	30-60	95(46.34%)
	>60	47 (22.93%)
Co-morbidity	Diabetes	41(20.00%)
	Hypertension	51 (24.88%)
	Chronic kidney disease	21 (10.24%)
	COPD	30 (14.63%)
	Others	30.24%
Invasive procedures	CV line	92 (44.88%)
	Dialysis catheter	15 (7.32%)
	Urinary catheter	205 (100%)
	Craniotomy	8 (3.90%)
	Laparotomy	12 (5.85%)

Regarding invasive procedures, a significant portion of patients had central venous lines (44.88%), while a smaller percentage underwent procedures like dialysis catheter insertion (7.32%), craniotomy (3.90%), and laparotomy (5.85%). Notably, all patients required urinary catheters due to their critical care status.

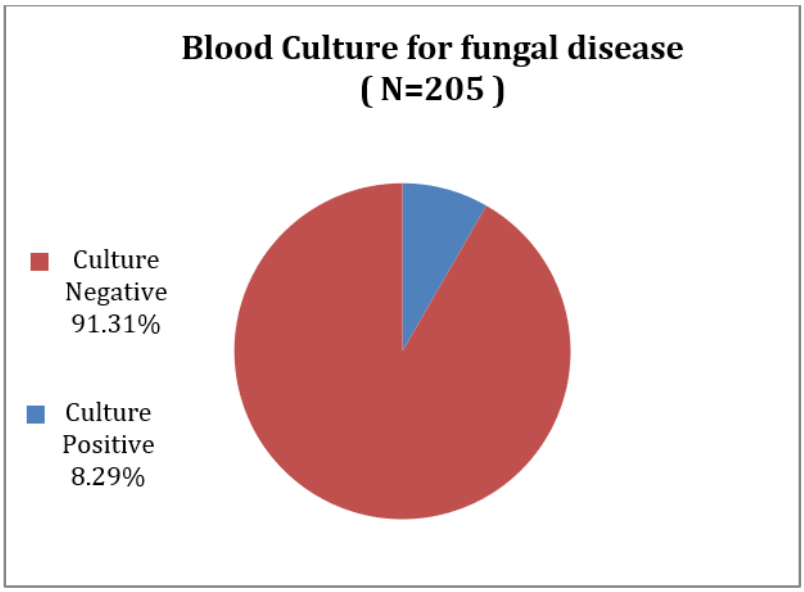

Figure 1: Blood culture of fungal disease

Among 205 patients 8.29% of patients tested positive for different fungal species.

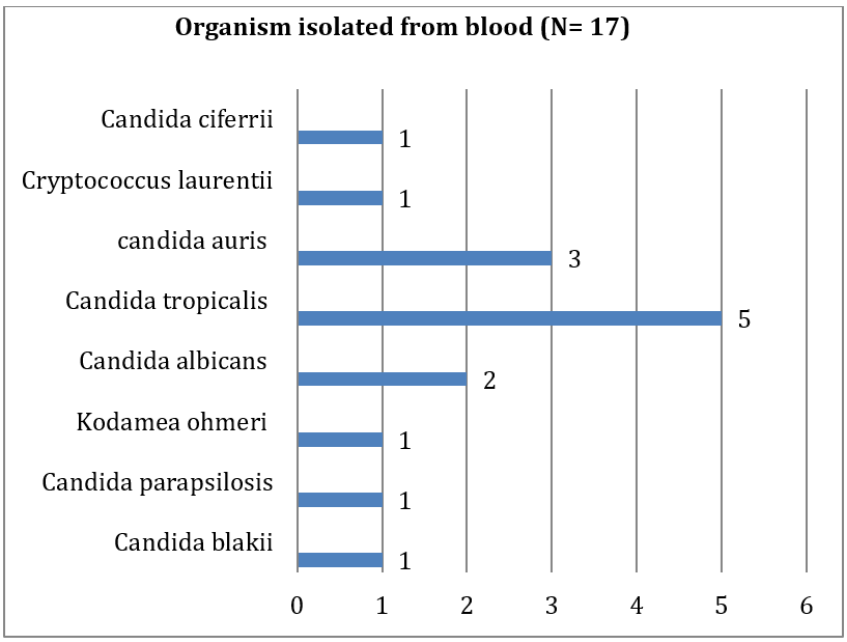

Figure 2: Organism isolated from blood

In Figure 2 Species analysis (N=17) of the organism isolated from blood revealed Candida blakii, Candida parapsilosis, Kodamea ohmeri, Cryptococcus laurentii, Candida ciferrii, were isolated from 1 patient's blood where as Candida albicans, Candida tropicalis, Candida auris were isolated from 3,5 and 2 patients' respectively.

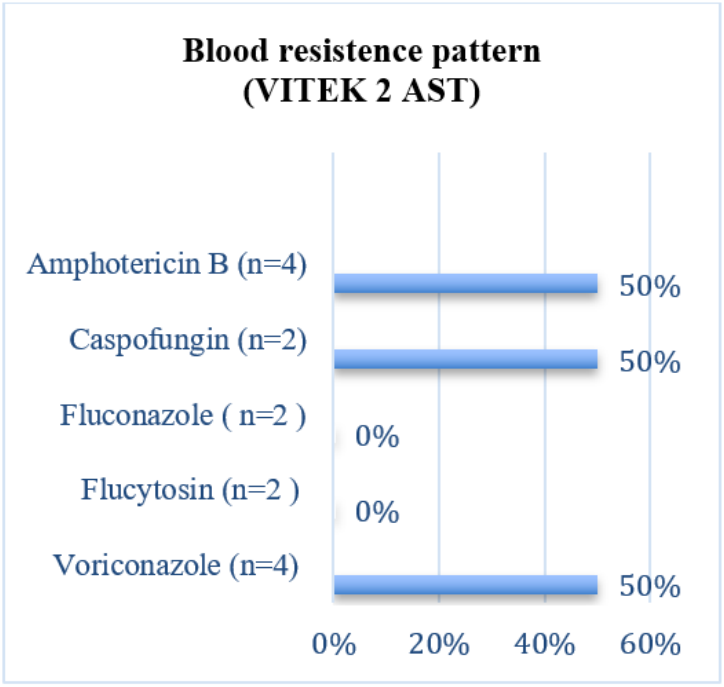

Figure 3: Blood resistance pattern

Figure 3 revealed Blood resistance pattern of fugal positive blood sample. It showed 50% resistance to Amphotericin B (n=4), Caspofungin (n=2) and Voriconazole (n=4). No resistance was found against Fluconazole (n=2) and Flucytosin (n=2).

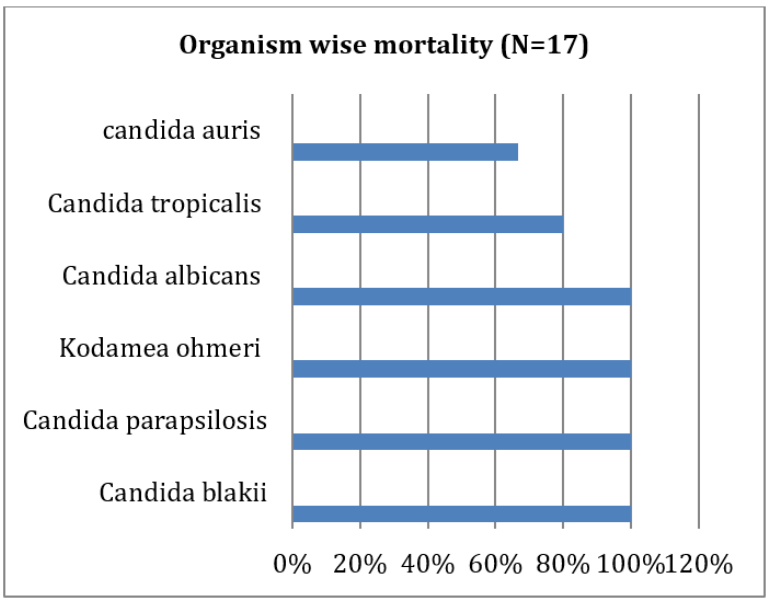

Figure 4. Organism wise mortality

Analysis of culute positive samples demonstrates Candida blakii, Candida parapsilosis, Kodamea ohmeri, Candida albicans were associated with 100% mortality whereas candida tropicalis and Candida auris were associated with 80% and 66.67 % mortality respectively. Cryptococcus laurentii and Candida ciferrii were associated with no mortality.

DISCUSSION

The incidence of candidemia varies widely across countries. With a conservative estimate of 5 cases per 100,000 population, approximately 8,100 cases are projected annually in Bangladesh [19]. However, these numbers are likely underestimated, necessitating further data for more accurate modeling. In contrast, invasive aspergillosis (IA) is minimally recognized in Bangladesh. Among adults over 40 years old, estimated COPD prevalence is approximately 7.2%, totaling 2,481,444 patients [20]. Assuming 13% of these patients are hospitalized annually and 1.3% develop IA, an estimated 4,194 IA cases would occur each year in this population. Overall, both invasive candidemia and aspergillosis represent significant health burdens in Bangladesh.

This retrospective cohort study was conducted in the Non-COVID Intensive Care Unit (ICU) of the Department of Anesthesia, Pain, Palliative, and Intensive Care at DMCH. The study aimed to assess the prevalence of fungal infections among ICU patients and identify fungal species associated with mortality. A total of 205 patients were enrolled in the study, among whom 8.29% tested positive for various fungal species.

Species analysis of isolated organisms from blood cultures (N=17) revealed that Candida blakii, Candida parapsilosis, Kodamea ohmeri, Cryptococcus laurentii, and Candida ciferrii were each isolated from one patient. Candida albicans, Candida tropicalis, and Candida auris were isolated from 3, 5, and 2 patients, respectively." Invasive aspergillosis was recognized from no patient which is opposed to the concept of probable prevalence of aspergillosis in ICU patients. But from the few selective specimens which were analyzed Candida auris was isolated which is a matter of concern.

Candida auris (C. auris) is a drug-resistant yeast that has emerged globally, causing invasive infections and healthcare-associated outbreaks with high mortality rates ranging from 30-72% [21]. It primarily affects hospitalized patients with severe medical conditions. In this study Candida auris was isolated from patients having prolonged ICU stay and having bed sore. Candida auris manifests in various clinical forms, including bloodstream infections, intra-abdominal candidiasis, and superficial infections [2-23]. Patients can remain colonized with C. auris for extended periods, and it can persist on healthcare surfaces [24]. Standard healthcare disinfectants are often ineffective against this resilient yeast, contributing to its persistence and emergence [25]. So, Candida auris identification necessitates the need for further improvement of Infection Prevention and Control (IPC) standards.

In this study Candida albicans Candida blakii and Candida parapsilosis was associated with 100% mortality. Globally,*C. Albicans* accounts for 50% of all causes of fungal sepsis in the intensive care unit, with a mortality rate of between 40 and 70% [26]. High resistance to antifungal may be attribute to high mortality in this study cohort of Candida species isolates.

The study analyzed the resistance patterns of fungal isolates from blood samples. Results indicated significant resistance among fungal isolates, with 50% showing resistance to Amphotericin B, Caspofungin, and

Voriconazole. Conversely, no resistance was observed against Fluconazole and Flucytosine.

Amphotericin B (AmB) is generally considered an effective agent for IFD. It was initially introduced in the late 1950s as the first polyene antifungal drug. It gained popularity for its broad spectrum of activity, low resistance rates, and effective clinical and pharmacological properties. However, its use is limited by side effects such as nephrotoxicity and infusion reactions. To address these issues, newer formulations of AmB, such as AmB lipid complex, liposomal AmB, and AmB colloidal dispersion, were developed. In this study alarmingly 50% of isolates show resistance.

Though considered an effective antifungal agent to various fungal strains in this study cohort from selected samples showed 50 % resistance to Caspofungin. The only known mechanism of C. albicans clinical resistance to caspofungin and other echinocandins is the occurrence of point mutations in the FKS1 [27]. This resistance pattern need to be further studied.

Opposed to available data, in this study Fluconazole & Flucytosine resistance was nil. Fluconazole is fungistatic rather than fungicidal, so treatment provides the opportunity for acquired resistance to develop in the presence of this antifungal. In the developed world, *C. albicans* has a low incidence of fluconazole resistance, approximately 0.5–2% [28]. *C. tropicalis*, *C. parapsilosis*, and *C. glabrata*, on the other hand, have higher rates at 4–9%, 2–6%, and 11–13%, respectively. The emerging yeast *C. auris* can exhibit a rate of resistance to fluconazole as high as 93% [29]. But in this study cohort though Candida auris was isolated but Fluconazole resistance was absent.

The emergence of drug-resistant pathogens like Candida auris highlights a pressing need for robust infection prevention and control measures. Healthcare facilities must implement stringent protocols to mitigate transmission risks and optimize patient care. Moreover, the study's findings on antifungal resistance patterns underscore the complexity of managing fungal infections, necessitating continuous surveillance and the development of new therapeutic options.

Efforts to address fungal infections in critical care settings should prioritize multidisciplinary approaches involving infectious disease specialists, microbiologists, and infection control practitioners. Collaborative research initiatives can further elucidate the epidemiology and resistance mechanisms of fungal pathogens, paving the way for targeted interventions and improved patient outcomes.

Limitations of the study:

This study has several limitations. The study is retrospective in nature. So, all some variables of interest had to be excluded. The sample analysis of study cohort only included blood sample. As a result potential specimen like sputum, tracheal aspirate, broncho-alveolar lavage or, urine were left unexplored from where fungi could be isolated.

Authors' Conclusion:

Fungal infections in intensive care settings pose significant challenges due to their potential resistance to commonly used antifungal agents and varying mortality rates associated with different fungal species. The findings underscore the importance of vigilant monitoring and appropriate management strategies tailored to the specific fungal pathogens encountered in clinical practice.

Recommendation

Further studies needed to validate the resistance pattern and prevalent fungal pathogens for tailoring management of invasive fungal infection.

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