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Original Article

Assessing the Impact of Broad-Spectrum Antibiotics on Fungal Infection Rates in ICU Patients: Implications for Patient Safety

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ABSTRACT

Background: Invasive Fungal Infections (IFIs) are on the rise, notably among critical care patients in the Intensive Care Unit (ICU) undergoing treatment with Broad Spectrum Antibiotics (BSAs). These antibiotics, designed to combat a wide range of bacteria, inadvertently disrupt the body's microbial balance, creating an environment favorable for opportunistic fungi, particularly *Candida albicans*, leading to severe infections. ICU patients, often with multiple risk factors, are at heightened risk. **Aim and Objectives:** This study aimed to assess the incidence of fungal infections in ICU patients treated with broad-spectrum antibiotics, highlighting the potential implications for patient outcomes and antibiotic stewardship in healthcare settings. **Materials and Methods:** A cross-sectional observational study was conducted in the intensive care unit of Dhiraj General Hospital, Vadodara, Gujarat. Patients aged between 18-65 years who received broad-spectrum antibiotics for more than five days were included in the study. Patients with additional risk factors for developing fungal infections in the ICU, such as diabetes mellitus or corticosteroid therapy, were excluded. Relevant data were collected from patients' medical records using a predefined proforma. The study aimed to determine if broad-spectrum antibiotics were independently associated with the development of fungal infections in ICU patients. **Results:** The study unveiled a significant incidence of fungal infections in patients on broad-spectrum antibiotics. Among the 71 patients, 9.8% (7 individuals) met criteria for fungal infection development, emphasizing the need for vigilant monitoring. **Conclusion:** The use of broad-spectrum antibiotics in the ICU is strongly linked to an increased risk of fungal infections. To mitigate this risk, healthcare providers should consider dose adjustments, narrow-spectrum antibiotics and prompt fungal infection diagnosis and treatment. Diagnosing fungal infections remains challenging due to confounding factors, comorbidities and high diagnostic costs. Therefore, it's advisable to restrict broad-spectrum antibiotic use, such as third-generation cephalosporins and carbapenems, to reduce invasive fungal infection risk and antibiotic-resistant strains. Close monitoring of patients for fungal infection signs during broad-spectrum antibiotic treatment is essential.

Keywords: Invasive Fungal Infections, Intensive Care Unit, Antibiotic-Resistant Strains.

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INTRODUCTION

Patients in the Intensive Care Unit (ICU) are particularly susceptible to infections due to various factors. Many ICU admissions are a consequence of existing infections, some patients suffer from severe underlying illnesses that weaken their immune systems and the presence of numerous invasive medical devices further increases the risk of infection (Vincent *et al.*, 2020). In the context of hospital care, especially in surgical and ICU settings, antibiotics are among the most commonly prescribed medications (Perveen., *et al.* 2018). It's worth noting, however, that a substantial proportion of antibiotic prescriptions, potentially up to 50%, may be unnecessary (da Fonseca Pestana Ribeiro and Park. 2020). Notably, antibiotics such as Ceftriaxone, Meropenem and Cefoperazone+Sulbactam are frequently administered in the ICU (Joshi., *et al.* 2023). Beta-Lactam Antibiotics (BLAs) are the predominant class of antibiotics used in the ICU. ICU patients display various pathophysiological characteristics that give rise to specific Pharmacokinetic (PK) and Pharmacodynamic (PD) considerations, increasing the risk of underdosage and the need for tailored antibiotic therapy (Guilhaumou *et al.*, 2019). Invasive Fungal Infections (IFIs) have seen an increasing incidence in recent times (Borjian Boroujeni *et*

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al., 2021). The most common nosocomial fungal infection among humans, invasive candidiasis, is closely linked to antibiotic use as a modifiable iatrogenic risk factor, although the underlying mechanisms remain elusive (Drummond *et al.*, 2022). IFIs, which are a significant cause of nosocomial bloodstream infections, can result in severe conditions in patients with various underlying health issues and host factors (Li *et al.*, 2020). *Candida albicans*, like numerous other microbial species, resides in the human gastrointestinal system. The gut microbiota's substantial impact on fungal growth is increasingly evident, dating back to the discovery in the 1960s that human antibiotic use could trigger Candida overgrowth (Pérez 2021). Early diagnosis of invasive fungal infections is vital due to the associated morbidity and mortality. Nonetheless, making an early diagnosis is challenging because of the nonspecific symptoms and radiographic findings (Haydour *et al.*, 2019). Effective utilization of laboratory testing, including antigen testing, serological assays and PCR-based methods, plays a pivotal role in swiftly and accurately identifying fungal infections (Hage *et al.*, 2019). The human microbiota harbors organisms such as Candida spp., capable of causing opportunistic infections in healthy individuals and life-threatening conditions like invasive candidiasis (Drummond *et al.*, 2022). To enhance patient outcomes, the judicious use of antibiotics is imperative (Kayambankadzanja *et al.*, 2020). This study is conducted at Dhiraj General Hospital, Vadodara, which houses a well-established critical care unit, including an ICU where broad-spectrum antibiotics are regularly administered to a significant patient population. This unique context provides an ideal opportunity to explore the potential link between broad-spectrum antibiotics and invasive fungal infections. By focusing on this specific hospital, we can gather local data and assess how broad-spectrum antibiotic use influences fungal infection rates among the hospital's patients. The insights gained from this research have the potential to inform clinical practices and interventions, aiming to reduce fungal infections in critical care settings, ultimately improving patient safety and outcomes, particularly within the Dhiraj General Hospital.

Invasive

Fungal Infections (IFIs) have been increasingly documented within healthcare facilities, with a particular prevalence among critical care patients, notably those in the Intensive Care Unit (ICU) receiving Broad Spectrum Antibiotics. Despite this emerging concern, there is a paucity of comprehensive literary evidence addressing this issue. This study seeks to bridge this knowledge gap by investigating the incidence of fungal infections in the specific context of broad-spectrum antibiotic use. By delving into this underexplored area, our research aims to contribute to the understanding of how the incidence of fungal infections can be mitigated. This includes optimizing antibiotic usage, with a particular focus on the prudent application of broad-spectrum antibiotics. The overarching goal of this study is to provide healthcare professionals with data-driven insights that can lead to more judicious antibiotic practices and ultimately decrease the occurrence of fungal infections in the critical care setting. The research endeavors to enhance patient safety and care outcomes within the ICU, reinforcing the imperative need for a comprehensive examination of this critical issue.

MATERIALS AND METHODS

In this cross-sectional observational study conducted over six months in the Intensive Care Unit (ICU) of Dhiraj General Hospital, Vadodara, Gujarat, we investigated the incidence of fungal infections among patients aged 18 to 65 years who had received broad-spectrum antibiotics. Ethical approval was obtained from the Sumandeep Vidyapeeth Institutional Ethics Committee (SVIEC/ON/PHAR/BNPG21/NOV/22/23). A total of 71 ICU patients were included and informed consent was obtained from them and, where necessary, from their relatives. Patients with pre-existing risk factors such as diabetes mellitus, corticosteroid therapy, or those already on broad-spectrum antibiotics before admission were excluded. Data collection involved recording details of antibiotic duration, dose and frequency. After five days of antibiotic therapy, fungal infection diagnosis was initiated through laboratory cultures, with subsequent identification of fungal species and administration of appropriate antifungal treatment. The data were analyzed using Microsoft Excel, representing quantitative data as percentages and mean±standard deviation. The incidence of fungal infection was calculated as part of the analysis, contributing to our understanding of the impact of broad-spectrum antibiotics on fungal infections in ICU patients (Figure 1).

RESULTS

The study was carried out in the Medical Intensive Care Unit (MICU) at Dhiraj Hospital. In our study, the total sample size comprised 71 patients. Among them, 7 patients developed fungal infections after the administration of broad-spectrum antibiotics, accounting for 0.098% of all the patients included in our study. Patients were diligently screened on a daily basis for a period of four months until we reached our desired sample size. We continued to monitor patients until we achieved the designated sample size. The majority of patients in the study (38%) were in the 51-60 age groups, followed by the 41-50 age group (28%), with the 31-40 age group accounting for 9.8% and the 21-30 age group at 5.6%. The mean age of the patients was 50.23±10.79, indicating that the average age of the study population is approximately 50 years. Out of the total patients, 60.56% were male, while 39.43% were female, suggesting that fungal infections in ICU patients receiving broad-spectrum antibiotics do not exhibit significant gender bias. The data also reveals the presence of various comorbidities in the patient population. The most prevalent comorbidity was hypertension, observed in 32.39% of the patients. Other comorbidities included alcoholic conditions

(7.04%), aortic stenosis (2.81%), asthma (2.81%), COPD (2.81%), Cerebrovascular Accident (CVA) (1.40%), filariasis (1.40%), anemia (1.40%), Ischemic Heart Disease (IHD) (1.40%), liver disease (1.40%), tuberculosis (1.40%) and Rheumatic Heart Disease (RHD) (4.22%). It's noteworthy that a significant proportion of patients (38.02%) had no reported underlying diseases (Table 1).

Out of the 71 patients included in the study, 7 (9.85%) developed a fungal infection. Notably, none of the patients who received Salbactum, Augmentin, Cefotaxime, Ceftriaxone, Ciprofloxacin, Meropenem, Tazobactum, or Clindamycin developed a fungal infection. However, when patients were prescribed two or three antibiotics, the percentage of patients who developed a fungal infection increased to 4.22%. Furthermore, one patient who received four antibiotics developed a fungal infection, representing a 1.41% rate. These findings collectively suggest that patients who are administered multiple antibiotics may be at an elevated risk of developing fungal infections when compared to those receiving a single antibiotic (Figure 2 and Table 2).

In the total population under study, 30% were addicted to smoking, 31% were addicted to smokeless tobacco and 34% were addicted to alcohol. Out of the 71 samples tested, 7 samples (approximately 10%) showed the presence of fungal elements, while 64 samples (about 90%) did not exhibit any fungal elements. Regarding the specific fungal components, the first component, Candida Non Albicans, was observed in 5 patients. The second component, Yeast budding cells, was identified in 2 patients. The remaining patients, who did not exhibit a fungal infection,

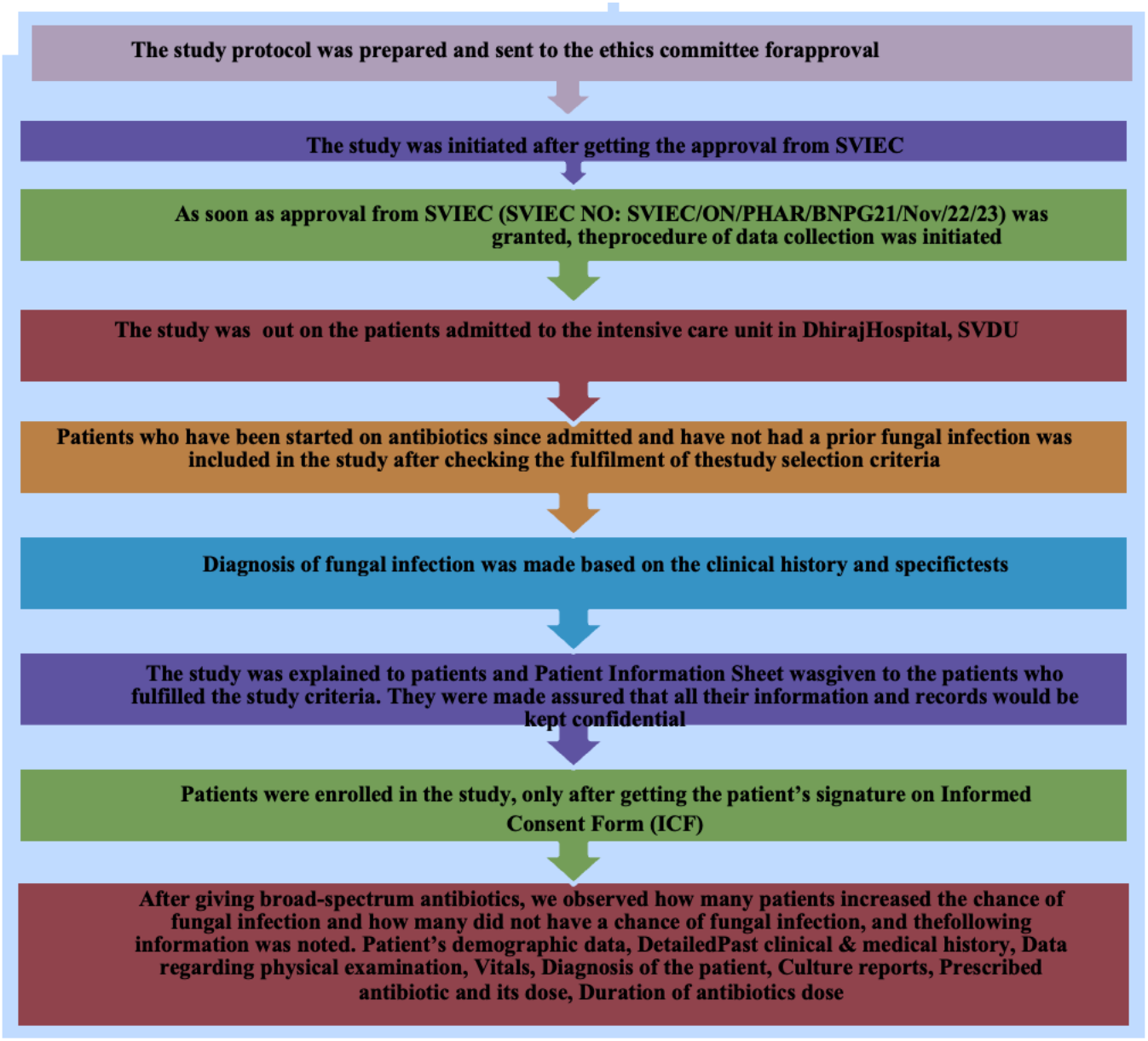

Figure 1: Schedule of the study.

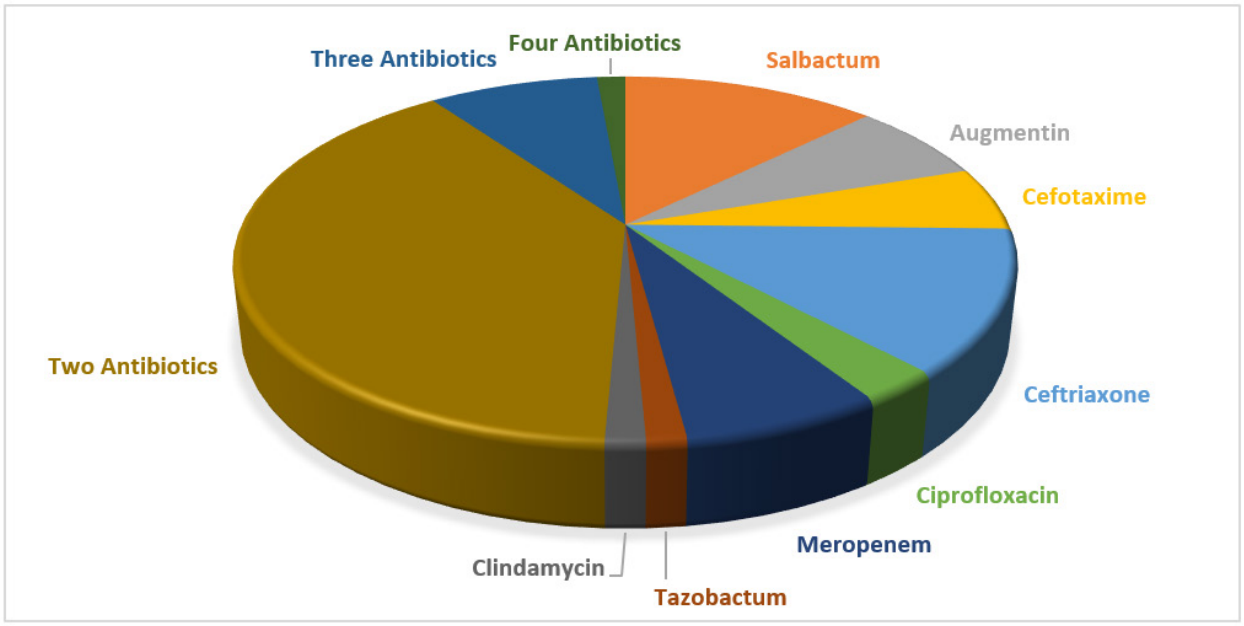

Figure 2: Prescribed Antibiotics.

Table 1: Baseline Characteristics.

	Total No. 71
Age	**No. of Patients (%)**
≤20 years	01 (1.4)
21-30 years	04 (5.6)
31-40 years	07 (9.8)
41-50 years	20 (28)
51-60 years	27 (38)
≥60 years	12 (16.9)
Mean age (Mean±SD)	50.23±10.79
Gender	
Male	43 (60.56)
Female	28 (39.43)
Comorbidities	
Alcoholic	05 (7.04)
Anemia	01 (1.40)
Aortic Stenosis	02 (2.81)
Asthmatic	02 (2.81)
COPD	02 (2.81)
CVA	01 (1.40)
Filariasis	01 (1.40)
Hypertension	23 (32.39)
IHD	01 (1.40)
Liver disease	01 (1.40)
Tuberculosis	01 (1.40)
RHD	03 (4.22)
No Disease	27 (38.02)

accounted for a frequency of 64. Among these findings, 5 patients who tested positive for fungal infection received a daily dose of 200 mg of fluconazole administered intravenously. Additionally, two patients who tested positive for fungal infection were administered a dose of 50 mg of caspofungin twice daily (Table 3).

DISCUSSION

In our study conducted within the Medical Intensive Care Unit (MICU) of Dhiraj Hospital, a total of 71 patients met the inclusion and exclusion criteria. Among these, 60% were male and 38% were female. Following the initiation of broad-spectrum antibiotic therapy, seven patients developed fungal infections in conjunction with various broad-spectrum antibiotics. A separate study involving 105 patients found that 82.9% received antibiotics known to impact anaerobic gut flora, such as imipenem, vancomycin, ceftazidime, metronidazole, clindamycin, or ampicillin-sulbactam. Additionally, 44.5% used prophylactic ofloxacin. Patients on ofloxacin, aminoglycosides, or azithromycin (antibiotics not affecting anaerobic flora) displayed higher rates of *C. albicans* infection (58.9% vs. 33.7%, p=0.04). Conversely, those on third-generation cephalosporins, carbapenems, glycopeptides and broad-spectrum penicillin were at a greater risk of developing invasive Aspergillus spp. Infections (Soysa *et al.*, 2008). Bajpai *et al.*'s review underscores the growing significance of fungi as clinical pathogens, particularly in critically ill patients, including those who are immunocompromised. *Candida, Cryptococcus* and filamentous fungi are frequently encountered in clinical settings (Bajpai *et al.*, 2019). Another study suggests that broad-spectrum antibiotic exposure in preterm neonates without underlying illness is associated with an increased risk of Invasive Fungal Infections (IFIs) (Esaiassen *et al.*, 2017). This study also concluded

that both Carbapenem monotherapy and its combination with amikacin resulted in a significant increase in *Candida albicans* concentration (Samonis *et al*., 2013). In a study encompassing 71 critically ill patients, all of whom were administered various broad-spectrum antibiotics such as meropenem, salbactam, ceftriaxone, clindamycin, augmentin and ciprofloxacin, those who received these antibiotics as monotherapy did not develop Candida spp. infections. However, patients who received combinations of these broad-spectrum antibiotics exhibited a potential risk for such infections. Peres Bota *et al*.'s prospective study among critically ill patients (28 infected patients) unveiled that those with an ICU stay exceeding 24 hr predominantly suffered from bacterial infections (89%), while 11% met the criteria for Candida infection. This study further underscored the association between broad-spectrum antibiotic therapy and increased fungal growth in patients previously colonized, suggesting that curtailing antibiotic usage may serve as a preventive measure against fungal infections (Peres-Bota *et al*., 2004; Tian *et al*., 2018). Typically, the likelihood of developing a fungal infection increases in patients exposed to broad-spectrum antibiotics for more than 5 to 15 days. However, our study revealed that patients who developed fungal infections had received antibiotics for a duration ranging from 5 to 9 days. In a prospective study conducted in New Delhi, the focus was on children with acute leukemia and persistent febrile neutropenia. The study revealed a concerning prevalence of Invasive Fungal Infection (IFI) at 22.97% among those who were not on antifungal prophylaxis. Predictors of IFI included abnormal chest X-rays and clinical sinusitis and these factors played a significant role in influencing patient outcomes, including mortality or discharge (Kumar *et al*., 2018). A retrospective analysis in Germany spanning from 2002 to 2016 delved into fungal infections in patients with pancreatic necrosis and pseudocysts, involving 113 patients and 187 Fine-needle aspirations. Notably, approximately 46% of these patients were found to have fungal pancreatic infections, primarily caused by Candida species. This risk was significantly associated with pre-FNA antibiotic use (p=0.003) and the duration of treatment (Reuken *et al*., 2018). In a study, focusing on patients with severe acute pancreatitis, fungal infections, predominantly *Candida albicans*, were identified in 36% of cases. Prolonged hospital stays (exceeding 4 weeks) and extended courses of antibiotics were found to increase the risk of fungal infections (Eggimann *et al*., 2015). Considering the insights from these studies, the initial hypothesis put forward to explain the occurrence of fungal

Table 2: Data according to broad-spectrum antibiotics use.

Drugs (Single and combination)	No. of patients received	No. of patient developed fungal infection	Drugs	No. of patients received	No. of patient developed fungal infection
Salbactum	08		Meropenem Clindamycin	01	
Augmentin	05		Salbactum Meropenem	01	
Cefotaxime	04		Tazobactum Levofloxacin	01	
Ceftriaxone	09		Meropenem Augmentin	01	
Ciprofloxacin	02		Azithromycin Ceftriaxone	01	
Meropenem	05		Meropenem Ceftriaxone	01	
Tazobactum	01		Meropenem Linezolid	01	
Clindamycin	01		Azithromycin Augmentin	01	
Salbactum Azithromycin	03		Clindamycin Ceftriaxone	01	
Azithromycin Meropenem	04	02	Meropenem Ciprofloxacin	01	
Augmentin Levofloxacin	02		Clindamycin Augmentin	01	
Salbactum Clindamycin	02		Tazobactum Clindamycin Augmentin	02	01
Augmentin Linezolid	02	01	Azithromycin Clindamycin Augmentin	01	
Tazobactum Clindamycin	05	01	Meropenem Clindamycin Ciprofloxacin	01	01
Levofloxacin Ceftriaxone	02		Meropenem Tazobactum Clindamycin Augmentin	01	01

Table 3: Data according to Age and Gender Distribution.

Age group (years)	Gender		Total
	Female	Male	
≤ 20	1	0	1
21-30	3	1	4
31-40	2	5	7
41-50	7	13	20
51-60	8	19	27
≥ 61	7	5	12
Total	28	43	71
Data according to addiction			
Addiction			**Frequency (%)**
Smoking			30
Tobacco			31
Alcohol			34
Data according to the diagnosis of fungal infection (culture test)			
Result			**Frequency**
Fungal elements seen			07
No fungal elements seen			64
Total			71
Data according to the diagnosis of fungal infection (culture test)			
Result			**Frequency**
Fungal elements seen			07
No fungal elements seen			64
Total			71
Data according to the diagnosis of fungal infection (culture test)			
Name (isolated species)			**Frequency (%)**
Candida Non Albicana			05
Yeast budding cells			02
NA			64
Total			71
Data according to treatment of fungal infection			
Name of drug	**Dose**	**No. of patient received among the positive for fungal infection**	**Frequency**	**ROA**
Fluconazole	200 mg	05	OD	IV
Caspofungin	50 mg	02	BD	IV

infections in the current study is that modifications in antibiotic treatment, which led to a reduction in early deaths caused by bacterial infections, might have rendered the patients more susceptible to secondary events like fungal infections. In simpler terms, the new antibiotic regimen indirectly contributed to the emergence of fungal infections. Consequently, it is imperative to closely monitor patients receiving broad-spectrum antibiotics for the development of fungal infections.

CONCLUSION

In conclusion, our study highlights a strong link between the use of broad-spectrum antibiotics in ICU settings and a heightened risk of fungal infections. These findings reinforce the need for

prudent antibiotic stewardship to protect patient health and minimize complications. Limiting the use of broad-spectrum antibiotics, such as third-generation cephalosporins and carbapenems, when narrower-spectrum options are available, may reduce the incidence of Invasive Fungal Infections (IFI) and help curb antibiotic resistance. Early identification and intervention for fungal infections are vital, particularly given the complex health profiles of ICU patients. The substantial costs and diagnostic complexities of fungal infections further stress the importance of careful antibiotic selection. By encouraging a restrained approach to antibiotic use, healthcare providers can improve patient outcomes, lower healthcare costs and support broader public health efforts against antibiotic resistance. An evidence-based, vigilant strategy in ICUs can ultimately reduce the societal burden of these infections and enhance patient care in critical care settings.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

IFIs: Invasive Fungal Infections; **BSAs:** Broad Spectrum Antibioticsl; **BLAs:** Beta:lactam antibiotics; **PK:** Pharmacokinetic; **PD:** Pharmacodynamic; **C. albicans:** *Candida albicans*; **MICU:** Medical Intensive Care Unit; **ROA:** Route of Administration; **FNA:** Fine needle aspiration; **ICU:** Intensive Care Unit.

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