Infection and Drug Resistance

Dovepress
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ORIGINAL RESEARCH

Effectiveness and Safety of Empirical Antifungal Strategies in Critically Ill, Non-Neutropenic Patients: A Multi-Center Observational Study

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Introduction: Invasive fungal infections (IFIs) are a major cause of morbidity and mortality in critically ill patients. While early empirical antifungal therapy (EAFT) is a common strategy to combat diagnostic delays, the choice of agent and its overall benefit remain debated. This study evaluates the clinical outcomes and safety profiles associated with different empirical antifungal strategies in non-neutropenic ICU patients with suspected IFIs.

Methods: A retrospective observational study was conducted on 324 non-neutropenic patients who received EAFT in eight ICUs from 2015 to 2023. Data on demographics, comorbidities, treatments, and outcomes were collected from medical records. The primary endpoints were survival, clinical improvement, and incidence of confirmed fungal infection. Mortality predictors were identified using multivariate logistic regression.

Results: Among the 324 patients, the overall in-hospital mortality rate was 78.70%. Mortality was significantly lower in the group receiving fluconazole (63.16%) compared to those receiving caspofungin (76.80%), liposomal amphotericin B (75%), and anidulafungin (84.83%) (p = 0.028). Regarding safety, fluconazole demonstrated the lowest incidence of hepatotoxicity (13.16%) and nephrotoxicity (7.89%). In contrast, anidulafungin was associated with the highest rate of hepatotoxicity (33.79%, p=0.035), and caspofungin was associated with the highest rate of nephrotoxicity (39.52%, p=0.003). Only 17.28% of patients achieved clinical improvement. After the initiation of EAFT, a fungal infection was confirmed in only 7.41% of patients.

Conclusion: Fluconazole-based EAFT was associated with lower mortality rates compared to other antifungal agents. However, with a confirmed fungal infection rate of only 7.41%, these findings suggest that current patient selection for EAFT is suboptimal. The high overall mortality, coupled with the low infection confirmation rate, underscores the need for improved risk stratification tools to ensure the judicious use of antifungals in this critically ill population.

Keywords: empirical antifungal therapy, invasive fungal infections, intensive care unit, mortality, fluconazole

Introduction

Invasive fungal infections (IFIs), predominantly invasive candidiasis (IC), are a major threat in the intensive care unit (ICU) and rank among the primary causes of morbidity and mortality in critically ill patients.[1,2] General ICU mortality rates for IC are reported at 40–60%, increasing to 80–90% in those with septic shock.[3–5] *Aspergillus* infections are the second leading cause of IFIs in ICU patients.[6]

These fungal infections are challenging to treat and are associated with extended hospitalizations, costly therapeutic measures, and a greater need for health care resources.[7,8] Since conventional microbiological methods of identification take 3–5 days and many results late in the course of the disease, many clinicians prefer the option of early empirical antifungal therapy (EAFT) rather than postponing treatment while waiting for microbiological confirmation.[9–11]

https://doi.org/10.2147/IDR.S579631
Received: 20 November 2025
Accepted: 10 February 2026
Published: 18 February 2026

Independent studies have indicated an association between early appropriate antifungal therapy and reduced mortality in such critically ill patients.[9,10]

Recent guidelines recommend initiating echinocandin therapy in all critically ill patients who have risk factors for IC, as well as unexplained fever; this recommendation is particularly emphasized in patients with risk factors and septic shock.[12,13] Risk factors for IC include colonization with Candida, severity of illness, exposure to broad-spectrum antibiotics, recent extensive surgery (especially in the abdomen), necrotizing pancreatitis, dialysis, parenteral nutrition, corticosteroid therapy, and central venous catheters.[14,15] Although clinical predictive models such as the *Candida* Score have been developed to identify high-risk patients, they are generally characterized by high negative predictive values (NPV) but low positive predictive values (PPV).[16,17] While high NPV allows clinicians to rule out infection in low-risk patients, the modest PPV often leads to the over-initiation of empirical antifungal therapy in patients who do not have invasive disease.[17,18] This creates a challenging clinical dilemma, balancing the risk of missed treatment against the consequences of unnecessary antifungal exposure.

Despite those theoretical advantages, clinical trials assessing the effectiveness of EAFT have shown mixed results, with several not demonstrating reduced mortality when azoles or echinocandins were compared to placebo in non-neutropenic critically ill patients.[19–22]

Moreover, the majority of current evidence is derived from randomized trials or observational studies in Western populations.[10,23,24] There remains a significant knowledge gap regarding the real-world effectiveness and safety of EAFT strategies in Middle Eastern ICU settings, where differences in local epidemiology, resistance patterns, and patient comorbidities may influence outcomes. This ongoing clinical challenge, coupled with the persistent limitations of current diagnostic methods[19,21] highlights the scarcity of high-quality evidence to inform comprehensive management of IFI in our specific region.

Therefore, the primary objective of this study was to evaluate the real-world clinical outcomes and safety profiles associated with different EAFT strategies in terms of mortality and clinical outcomes in critically ill, non-neutropenic patients. A secondary objective was to determine the incidence of proven IFI after the initiation of empirical therapy.

Method

Study Design and Setting

This multicenter observational study was conducted in the medical and surgical ICUs of several tertiary care facilities in Madinah, Saudi Arabia, from January 2015 through July 2023.

Patient Selection and Data Collection

A total of 1185 patients who received antifungal therapy (caspofungin, anidulafungin, fluconazole, or amphotericin B) were screened through hospital information systems. The inclusion criteria were: (1) critically ill adults (≥18 years) who were non-neutropenic, (2) an ICU stay of at least 48 hours, and (3) initiation of empirical antifungal therapy (EAFT) based on clinical suspicion of an invasive fungal infection (IFI). Given the high contamination rates in urine and sputum samples, patients with *Candida*-positive cultures from these sources were included and monitored until microbiological eradication, which served as the endpoint for assessing EAFT efficacy.

Patients with a proven invasive fungal infection, defined as a positive fungal culture from a normally sterile site (eg, blood) at the time of EAFT initiation, were excluded. In contrast, patients with *Candida* colonization from non-sterile sites (eg, urine, sputum) were eligible for inclusion, as such colonization is a key risk factor that frequently triggers the initiation of empirical therapy in the ICU setting. Additional exclusion criteria included neutropenia (absolute neutrophil count <500 cells/μL) and pregnancy. Demographics, laboratory values, microbiological findings, clinical parameters, and treatment details were extracted from medical records. While clinical parameters were collected, severity of illness scores such as APACHE II or SOFA were not consistently documented in the medical records across all centers during the study period. Consequently, these scores could not be calculated retrospectively, and the Charlson Comorbidity Index was utilized to assess patient complexity. Bacterial infections, pathogen isolation, and concurrent antibiotic treatment were

documented. Outcome variables included clinical improvement, ICU length of stay, and hospital admission and discharge dates. The Candida score was calculated at the initiation of antifungal therapy to predict early benefit from treatment.

Definitions

Key study definitions, including those for EAFT, clinical improvement, and antifungal-related toxicities, are summarized in Table 1. The risk assessment scoring systems are presented in Table 2.

Study Outcomes

The study primary outcome was in-hospital mortality. Secondary endpoints were clinical improvement and incidence of proven IFI. Safety outcomes consisted of antifungal-associated adverse events.

Table 1 Key Study Definitions and Scoring Systems

Term	Definition
Empirical Antifungal Therapy[9,25]	Administration of antifungals based on either: • Persistent fever after 4–7 days of antibiotic therapy OR • Clinical suspicion without definitive diagnosis
Clinical Improvement[25]	Composite of: Hemodynamic stability Successful extubation Improved Glasgow Coma Score Decreased inflammatory markers
Hepatotoxicity[26]	Any of the following: 1. AST/ALT >5× ULN or ALP >2× ULN on two occasions ≥24h apart 2 Total bilirubin >2.5 mg/dL with elevated liver enzymes 3. INR >1.5 with elevated liver enzymes
Nephrotoxicity (AKI)[26]	Any of the following: 1. SCr increase ≥0.3 mg/dL within 48h 2. SCr increase ≥1.5× baseline within 7 days 3. Urine output <0.5 mL/kg/h for 6h
Hypersensitivity Reaction[26]	Immune system overreaction, including allergic responses

Table 2 Prognostic and Risk Assessment Scoring Systems

Score	Components	Interpretation
Fungal Infection Risk Assessment **Candida Score**[18]	Severe sepsis (2 points) TPN (1 point) Surgery (1 point) Multifocal colonization (1 point)	< 3 points: 2.3% risk 3 points: 8.5% risk 4 points: 16.8% risk 5 points: 23.6% risk
Prognostic/Comorbidity Assessment **Charlson Comorbidity Index**[27]	**Point system for comorbidities***: 1 point: Myocardial infarction (MI), Congestive heart disease (CHF), Peripheral vascular disease (PVD), Cerebrovascular disease (CVD), Dementia, Chronic pulmonary disease, Rheumatologic disease, Peptic ulcer disease (PUD), Mild liver disease, diabetes. 2 points: Hemiplegia, Moderate to severe renal disease (CKD), Diabetes with chronic complications, Cancer without metastases, Leukemia, Lymphoma. 3 points: Moderate to severe liver disease 6 points: Metastases solid tumor, AIDS	Mild: 1–2 Moderate: 3–4 Severe: ≥5

Notes: * The total Charlson Comorbidity Index score is calculated by summing the assigned weights for all documented comorbidities present in the patient.

https://doi.org/10.2147/IDR.S579631

Statistical Analysis

Stata 16.1 (Stata Corporation, College Station, Texas, USA) was used for data analysis. Comparisons between groups employed Chi-square tests for categorical variables and Student's t-tests or Mann–Whitney *U*-tests for continuous variables, as appropriate. Factors associated with hospital mortality were analyzed by logistic regression. Variables with a p-value < 0.10 in the bivariate analysis were entered into the multivariate model using a backward stepwise selection method. Missing data were handled using a complete-case analysis approach; patients with significant missing data regarding primary outcome variables were excluded from the final analysis. A $p < 0.05$ was regarded as statistically significant.

Ethics Approval and Informed Consent

This study was conducted in compliance with the Declaration of Helsinki. Ethical approval was obtained from the Institutional Review Board (IRB), General Directorate of Health Affairs in Madinah (IRB Log No: 23–023; National Registration Number with NCBE-KACST: H-03-M-84). Due to the retrospective nature of the study and the high mortality rate among participants, the requirement for informed consent was waived by the IRB, and patient data were anonymized and maintained with strict confidentiality.

Results

The characteristics of the 324 patients who received EAFT and their relationship to hospital mortality are detailed in Table 3. Overall in-hospital mortality was 78.70%. The non-survivor group was significantly older than the survivor group (median age 65 vs 48 years, $p < 0.001$). In the bivariate analysis, numerous factors were associated with a significantly higher mortality rate. These included comorbidities such as diabetes mellitus and chronic renal failure

Table 3 Characteristics of 324 Patients Who Received EAFT and Their Relationship to Hospital Mortality

Characteristic	Hospital Discharge Status		*p*-value
	Alive (n=69)	Dead (n = 255)	
Demographic characteristics			
Median age (years)	48	65	**< 0.001**
Age group, n (%)			
< 65 years	32 (19.39)	133 (80.61)	0.394
≥ 65 years	37 (23.27)	122 (76.73)	
Sex male, n (%)	50 (24.75)	152 (75.25)	0.051
Hospital name			
Hospital 1	40 (16.88)	197 (83.12)	**0.001**
Hospital 2	29 (33.33)	58 (66.67)	
Reason for admission, n (%)			
Sepsis/septic shock	7 (14.29)	42 (85.71)	**0.041**
Respiratory distress	12 (12.77)	82 (87.23)	
Neurological causes	9 (30)	21 (70)	
Metabolic Disorders	2 (28.57)	5 (71.43)	
Others	39 (27.08)	105 (72.92)	
Underlying conditions and status, n (%)			
Diabetes	22 (12.94)	148 (87.06)	**< 0.001**
Immunosuppression	4 (30.77)	9 (69.23)	0.394
Myocardial infarction	2 (13.33)	13 (86.67)	0.453
Ischemic heart disease	7 (10.45)	60 (89.55)	**0.015**

(*Continued*)

Table 3 (Continued).

Characteristic	Hospital Discharge Status		*p*-value
	Alive (n=69)	Dead (n = 255)	
Congestive heart failure	1 (4.55)	21 (95.45)	**0.047**
Peripheral vascular disease	1 (8.33)	11 (91.67)	0.264
Cerebral vascular accident	9 (18.37)	40 (81.63)	0.579
Hypertension	20 (12.50)	140 (87.50)	**< 0.001**
Neurological disorder	13 (32.50)	27 (67.50)	0.065
Chronic pulmonary disease	8 (21.62)	29 (78.38)	0.959
Cancer	1 (25)	3 (75)	0.858
Chronic renal failure	5 (6.85)	68 (93.15)	**0.001**
Liver disease	2 (15.38)	11 (84.62)	0.595
Sepsis/septic shock	7 (13.73)	44 (86.27)	0.150
Presence of bacteremia	23 (18.25)	103 (81.75)	0.286
Candida colonization	20 (13.25)	131 (86.75)	**0.001**
No colonization	50 (28.74)	124 (71.26)	**0.002**
Sputum colonization	9 (18)	41 (82)	
Urine colonization	8 (13.11)	53 (86.89)	
Sputum and urine colonization	2 (5.13)	37 (94.87)	
Incidence of fungal infection confirmed by culture	2 (8.33)	22 (91.67)	0.107
Candida score, n (%)			
≤ 2	47 (24.74)	143 (75.26)	0.072
> 2	22 (16.42)	112 (83.58)	
Charlson comorbidity index, n (%)			
None (0)	25 (55.56)	20 (44.44)	**< 0.001**
Mild (1–2)	18 (27.69)	47 (72.31)	
Moderate (3–4)	18 (19.57)	74 (80.43)	
Severe (>4)	8 (6.56)	114 (93.44)	
Mechanical ventilation, n (%)	53 (17.38)	252 (82.62)	**< 0.001**
Central catheter, n (%)	58 (18.65)	253 (81.35)	**< 0.001**
No. of prescribed antibiotics during antifungal therapy, n (%)			
< 2	19 (33.33)	38 (66.67)	**0.030**
2–4	38 (17.51)	179 (82.49)	
> 4	12 (24)	38 (76)	
No. of bacterial infections, n (%)			
1-3	60 (22.14)	211 (77.86)	0.401
> 3	9 (16.98)	44 (83.02)	
No. of sites of bacterial infection, n (%)			
1-3	58 (23.11)	193 (76.89)	0.140
> 3	11 (15.07)	62 (84.93)	
Presence of Multidrug-Resistant Organisms	46 (20.09)	183 (79.91)	0.409
Empiric antifungal agents, n (%)			
Fluconazole	14 (36.84)	24 (63.16)	**0.028**
Caspofungin	29 (23.20)	96 (76.80)	
Anidulafungin	22 (15.17)	123 (84.83)	

(*Continued*)

Table 3 (Continued).

Characteristic	Hospital Discharge Status		*p*-value
	Alive (n=69)	Dead (n = 255)	
Liposomal Amphotericin B	4 (25)	12 (75)	
Median duration of antifungal therapy	8	8	0.997
Median hospital duration before empiric antifungal initiation	12	13	0.712
Median length of stay in ICU (days)	24	23	0.327

Note: Bold values indicate statistical significance (p < 0.05).

(p < 0.001), as well as *Candida* colonization (p = 0.001). Additionally, a high Charlson comorbidity index (p < 0.001) and the need for mechanical ventilation (p < 0.001) were significant predictors.

Regarding treatment, empirical fluconazole was associated with a significantly lower mortality rate (63.16%). This was statistically significant compared to caspofungin (76.80%), anidulafungin (84.83%), and liposomal amphotericin B (75%) (p = 0.028).

The independent risk factors for in-hospital mortality were determined using a multivariate logistic regression model (Table 4). Notably, while the choice of empirical antifungal agent was associated with mortality in the bivariate analysis, it did not retain statistical significance in the multivariate model after adjusting for confounders such as mechanical ventilation and comorbidity burden. After adjusting for potential confounders, a higher Charlson comorbidity index was associated with increased odds of mortality (Adjusted OR 1.18 per point increase; 95% CI: 0.63–1.73; $p < 0.001$). The need for mechanical ventilation more than doubled the odds of mortality (Adjusted OR 2.14; 95% CI: 0.44–3.84; p=0.014). Conversely, *Candida* colonization was associated with lower odds of mortality in the adjusted model (Adjusted OR 0.85; 95% CI: 0.06–1.64; p=0.034).

Clinical improvement, as defined in the Methods (Table 1), was achieved in 17.28% (56 of 324) of patients. As detailed in Table 5, the lack of clinical improvement was significantly associated with the use of mechanical ventilation (p<0.001) and central venous catheters ($p < 0.001$). Among antifungal agents, fluconazole was associated with the highest rate of clinical improvement (34.21%), a statistically significant difference compared to other agents ($p = 0.001$).

The incidence of major adverse events is summarized in Table 6. Statistically significant differences were observed between the antifungal agents for both hepatotoxicity and nephrotoxicity. Anidulafungin was associated with the highest rate of hepatotoxicity (33.79%, p = 0.035). Conversely, caspofungin was associated with the highest rate of nephrotoxicity (39.52%, p = 0.003). Fluconazole was associated with the lowest incidence of both hepatotoxicity (13.16%) and nephrotoxicity (7.89%).

As detailed in Table 7, a fungal infection was microbiologically confirmed in only 24 of the 324 patients (7.41%) after the initiation of EAFT. There was no statistically significant difference in the incidence of confirmed infection between the different antifungal agents used (p=0.415). Similarly, neither the median duration of antifungal therapy (p=0.140) nor the presence of *Candida* colonization (p=0.231) was significantly associated with a confirmed fungal infection.

Table 4 Multivariate Model of Independent Risk Factors for Hospital Mortality

Variable	Adjusted OR (95% CI)	*p*-value
Chronic pulmonary disease	0.23 (0.07–0.76)	0.015
Candida colonization	0.85 (0.06–1.64)	0.034
Charlson comorbidity index	1.18 (0.63–1.73)	< 0.001
Mechanical ventilation	2.14 (0.44–3.84)	0.014

Table 5 Univariate Analysis of Factors Associated with Clinical Improvement

Variable	Clinical Improvement		*P*-value
	Yes (n = 56)	No (n = 268)	
Use of mechanical ventilation, n (%)	42 (13.77)	263 (86.23)	**< 0.001**
Use of central venous catheter, n (%)	47 (15.11)	264 (84.89)	**< 0.001**
Empiric antifungal agents, n (%)			
Fluconazole	13 (34.21)	25 (65.79)	**0.001**
Caspofungin	27 (21.60)	98 (78.40)	
Anidulafungin	13 (8.97)	132 (91.03)	
Liposomal	3 (18.75)	13 (81.25)	
Amphotericin B			
Median duration of antifungal therapy	8	8	0.937
No. of bacterial infections, n (%)			
1-3	50 (18.45)	221 (81.55)	0.209
>3	6 (11.32)	47 (88.68)	
No. of sites of bacterial infection, n (%)			
1-3	49 (19.52)	202 (80.48)	**0.048**
>3	7 (9.59)	66 (90.41)	
Presence of Multidrug-Resistant Organisms	34 (14.85)	195 (85.15)	0.072
Median length of stay in ICU (days)	20	24	0.174
No. of prescribed antibiotics during antifungal therapy, n (%)			
<2	17 (29.82)	40 (70.18)	**0.021**
2–4	31 (14.29)	186 (85.71)	
>4	8 (16)	42 (84)	
Immunosuppression	3 (23.08)	10 (82.72)	0.573

Note: Bold values indicate statistical significance ($p < 0.05$).

Table 6 Association Between Antifungal Agents and Major Side Effects

Antifungal Agent	Hepatotoxicity	Nephrotoxicity	Hypokalemia	Hypomagnesemia
Fluconazole	5 (13.16)	3 (7.89)	12 (31.58)	3 (7.89)
Caspofungin	28 (22.40)	49 (39.52)	28 (22.40)	22 (17.60)
Anidulafungin	49 (33.79)	44 (30.34)	32 (22.07)	15 (10.34)
Liposomal Amphotericin B	5 (31.25)	4 (25)	7 (43.75)	1 (6.25)
***p*-value**	0.035	0.003	0.171	0.184

Table 7 Variables Associated with Fungal Infection

Variable	Incidence of Fungal Infection		*p*-value
	Yes (n = 24)	No (n = 300)	
Empiric antifungal agents, n (%)			
Fluconazole	4 (10.53)	34 (89.47)	0.415
Caspofungin	12 (9.60)	113 (90.40)	
Anidulafungin	7 (4.83)	138 (95.17)	
Liposomal	1 (6.25)	15 (93.75)	
Amphotericin B			
Median duration of antifungal therapy	9	8	0.140
Candida colonization	14 (9.27)	137 (90.73)	0.231

https://doi.org/10.2147/IDR.S579631

Discussion

Our multicenter study of 324 non-neutropenic patients who required intensive care and received EAFT has provided several important insights into treatment outcomes. The overall in-hospital mortality rate of 78.70% is similar to previous studies that have shown a dismal prognosis in ICU patients with possible fungal infection.[23,28] Interestingly, fluconazole resulted in lower mortality rates (63.16%) than echinocandins, albeit compared to current IDSA recommendations.[12] The low incidence of proven fungal infections (7.41%) among treated patients underscores the persistent issue of adequate patient selection for empirical therapy and corroborates previous reports regarding the limitations of current diagnostic strategies.[29]

The in-hospital mortality rates observed in our study (63–85% for different antifungal agents) were significantly higher than those reported in the previous literature. This stands in contrast with several international reports, including the one by Trifi et al's (36–40.2%), Jacobs et al's (22–54%), and Hasan et al's (10.39–19.44%).[28,30,31] These differences likely represent our population's greater comorbidity burden and illness severity. However, our finding that fluconazole was associated with decreased mortality (63.16%) is consistent with several important studies. Both Garey et al and Zhang et al studies similarly demonstrated improved survival with early fluconazole therapy (HR 0.57, 95% CI 0.44–0.74, $p<0.001$).[10,24]

It is crucial to interpret the mortality difference between antifungal agents with caution. While fluconazole was associated with lower raw mortality rates, this finding is likely subject to confounding by indication. In clinical practice, echinocandins are often reserved for patients with higher severity of illness, septic shock, or suspected resistance, whereas fluconazole is frequently prescribed to more stable patients. Indeed, when our analysis was adjusted for severity markers such as mechanical ventilation and comorbidity burden, the choice of antifungal agent was no longer an independent predictor of survival. This suggests that the underlying patient condition, rather than the drug itself, was the primary driver of mortality outcomes.

A key paradoxical finding from our study was the role of *Candida* colonization. While associated with higher mortality in the bivariate analysis, it emerged as an independent predictor for survival in the multivariate model (Adjusted OR 0.85). This suggests a complex interaction. It is possible that colonization serves as a crucial clinical trigger, prompting clinicians to initiate antifungal therapy or provide more aggressive supportive care, thereby mitigating its initial risk. Alternatively, it may be a marker of a more chronic state of illness in survivors, rather than a driver of acute mortality. This counterintuitive result highlights the need for further research to understand the precise role of colonization in ICU patient outcomes.

Mechanical ventilation was consistently identified as a strong predictor of worse outcomes across studies, although to varying degrees. Our observed mortality in ventilated patients (82.62%, $p<0.001$) was higher than in most reports, including Cui et al's study (32.2%) and Trifi et al's findings (76–78.7%).[28,32] The association between illness severity scores had more uniformity, with our findings for the Charlson comorbidity index (adjusted OR 1.18, $p<0.001$) being similar to those of Garey et al. APACHE II score results (OR 1.13, $p<0.05$).[24] In contrast to some studies, we did not find a significant association between the timing of EAFT initiation and in-hospital mortality in our cohort.[17,24] The median time to therapy was similar between survivors and non-survivors. This may be due to the overall high acuity of our patient population, in which the underlying severity of illness and comorbidities were the dominant drivers of outcome, potentially masking any benefit from earlier therapy. It is also possible that a threshold for irreversible organ damage had already been crossed for many patients by the time EAFT was considered. Nevertheless, the principle of early and appropriate antimicrobial therapy remains a cornerstone of sepsis management, even if its effect was not statistically evident in our specific population.[23]

Our findings have important implications for clinical practice. First, they argue for early EAFT in high-risk patients, particularly with fluconazole, despite the existence of conflicting evidence from randomized trials.[33,34] Second, they elucidate the need for better risk stratification tools, as existing methods have variable utility in various patient groups.[35] The contrasting findings regarding the prognostic value of Candida colonization indicate that future studies are warranted to clarify its value as a risk marker. Given the low prevalence of confirmed disease (7.41%) and the modest positive predictive value of current clinical scores, future research should prioritize diagnostic-driven strategies—such as rapid

biomarker integration—that can improve PPV and reduce unnecessary empirical exposure, rather than focusing solely on comparative drug efficacy.

Limitations and Strengths

Several methodological caveats warrant consideration when interpreting our findings. Key limitations include the potential for selection and information bias inherent to retrospective analyses, the absence of randomization, and the inability to compute APACHE scores due to missing data. Incomplete documentation also limited the assessment of antifungal-related gastrointestinal and hypersensitivity reactions (although such events are unlikely), and the source of blood cultures (central versus peripheral) was not consistently specified. In addition, *Candida* species were not identified at colonization sites, and the classification of ICU type was missing at one participating center, which operated a mixed unit.

Despite these limitations, the study has several important strengths. To our knowledge, this is the first comprehensive analysis of the mortality benefit of EAFT in both medical and surgical ICU settings, and it provides actionable insights for clinical practice. The use of fungal colonization as an inclusion criterion enabled more refined risk stratification compared with most previous studies. The inclusion of both surgical and medical ICU patients, particularly those with post-gastrointestinal operations and acute pancreatitis, enhances the generalizability of the findings to high-risk populations. Furthermore, the investigation of timing effects, together with the evaluation of the Candida score, offers valuable concepts for the timely initiation of EAFT. Despite the aforementioned limitations, these findings make a meaningful contribution to the growing body of evidence on EAFT in critically ill patients.

Conclusion

This multicenter retrospective observational study on empirical antifungal therapy (EAFT) in non-neutropenic ICU patients observed a significant association between fluconazole use and lower in-hospital mortality compared to other antifungal agents. Regarding safety, fluconazole was associated with a lower incidence of hepatotoxicity and nephrotoxicity compared to echinocandins and liposomal amphotericin B. However, the low rate of confirmed fungal infections remains a significant challenge in optimizing treatment. Mechanical ventilation, Candida colonization, and high Charlson comorbidity scores were identified as strong independent predictors of poor outcomes. Despite its limitations, the study underscores the need for more effective diagnostic tools and risk stratification methods to enhance EAFT utilization in this complex patient population.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Bassetti M, Garnacho-Montero J, Calandra T, et al. Intensive care medicine research agenda on invasive fungal infection in critically ill patients. *Intensive Care Med*. 2017;43(9):1225–1238. doi:10.1007/s00134-017-4731-2
2. Ostrosky-Zeichner L, Al-Obaidi M. Invasive fungal infections in the intensive care unit. *Infect Dis Clin*. 2017;31(3):475–487. doi:10.1016/j.idc.2017.05.005
3. Logan C, Martin-Loeches I, Bicanic T. Invasive candidiasis in critical care: challenges and future directions. *Intensive Care Med*. 2020;46(11):2001–2014. doi:10.1007/s00134-020-06240-x
4. Al-Dorzi HM, Sakkijha H, Khan R, et al. Invasive candidiasis in critically ill patients: a prospective cohort study in two tertiary care centers. *J Intensive Care Med*. 2020;35(6):542–553. doi:10.1177/0885066618767835
5. Eggimann P, Bille J, Marchetti O. Diagnosis of invasive candidiasis in the ICU. *Ann Intens Care*. 2011;1(1):37. doi:10.1186/2110-5820-1-37
6. Alan MS. *Clinical Features of Invasive Fungal Infections: Aspergillosis, Candidiasis and Mucormycosis*. 2019.
7. Rayens E, Norris KA. Prevalence and healthcare burden of fungal infections in the United States, 2018. In: *Open Forum Infectious Diseases*. Oxford University Press US; 2022.
8. Gold JA, Adjei S, Gundlapalli AV, et al. Increased hospitalizations involving fungal infections during COVID-19 pandemic, United States, January 2020–December 2021. *Emerg Infect Dis*. 2023;29(7):1433. doi:10.3201/eid2907.221771
9. Kanj SS, Omrani AS, Al-Abdely HM, et al. Survival outcome of empirical antifungal therapy and the value of early initiation: a review of the last decade. *J Fungi*. 2022;8(11):1146. doi:10.3390/jof8111146
10. Zhang M-K, Rao Z-G, Ma T, et al. Appropriate empirical antifungal therapy is associated with a reduced mortality rate in intensive care unit patients with invasive fungal infection: a real-world retrospective study based on the MIMIC-IV database. *Front Med*. 2022;9:952611. doi:10.3389/fmed.2022.952611

11. Wu Y, Yan L, Wang H, et al. Clinical study on empirical and diagnostic-driven (pre-emptive) therapy of voriconazole in severe aplastic anaemia patients with invasive fungal disease after intensive immunosuppressive therapy. *Eur J Clin Microbiol Infect Dis*. 2021;40(5):949–954. doi:10.1007/s10096-020-04054-9
12. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of America. *Clin Infect Dis*. 2016;62(4):e1–50. doi:10.1093/cid/civ933
13. Keighley C, Cooley L, Morris AJ, et al. Consensus guidelines for the diagnosis and management of invasive candidiasis in haematology, oncology and intensive care settings, 2021. *Intern Med J*. 2021;51 Suppl 7:89–117. doi:10.1111/imj.15589
14. Jenks JD, Cornely OA, Chen SC-A, et al. Breakthrough invasive fungal infections: who is at risk? *Mycoses*. 2020;63(10):1021–1032. doi:10.1111/myc.13148
15. Muskett H, Shahin J, Eyres G, et al. Risk factors for invasive fungal disease in critically ill adult patients: a systematic review. *Crit Care*. 2011;15(6):1–15. doi:10.1186/cc10574
16. Hasseine L, Cassaing S, Robert-Gangneux F, et al. High negative predictive value diagnostic strategies for the reevaluation of early antifungal treatment: a multicenter prospective trial in patients at risk for invasive fungal infections. *J Infect*. 2015;71(2):258–265. doi:10.1016/j.jinf.2015.04.005
17. Bruyère R, Quenot J-P, Prin S, et al. Empirical antifungal therapy with an echinocandin in critically-ill patients: prospective evaluation of a pragmatic Candida score-based strategy in one medical ICU. *BMC Infect Dis*. 2014;14(1):1–9. doi:10.1186/1471-2334-14-385
18. Laine ME, Flannery AH, Moody B, et al. Need for expanded Candida Score for empiric antifungal use in medically critically ill patients? *Critical Care*. 2019;23(1):1–3. doi:10.1186/s13054-019-2525-3
19. Cortegiani A, Russotto V, Maggiore A, et al. Antifungal agents for preventing fungal infections in non-neutropenic critically ill patients. *Cochrane Database Syst Rev*. 2016;2016(1). doi:10.1002/14651858.CD004920.pub3.
20. Wang Y, Xie J, Xing Y, et al. Choosing optimal antifungal agents to prevent fungal infections in nonneutropenic critically ill patients: trial sequential analysis, network meta-analysis, and pharmacoeconomic analysis. *Antimicrob Agents Chemother*. 2017;61(12). doi:10.1128/AAC.00620-17
21. Russotto V, Cortegiani A, Raineri SM, et al. From bedside to bench: the missing brick for patients with fungal sepsis. *Crit Care*. 2016;20(1):1. doi:10.1186/s13054-016-1378-2
22. Cortegiani A, Russotto V, Raineri SM, et al. Untargeted antifungal treatment strategies for invasive candidiasis in non-neutropenic critically ill patients: current evidence and insights. *Curr Fungal Infection Rep*. 2017;11(3):84–91. doi:10.1007/s12281-017-0288-3
23. Timsit J-F, Azoulay E, Schwebel C, et al. Empirical micafungin treatment and survival without invasive fungal infection in adults with ICU-acquired sepsis, candida colonization, and multiple organ failure. *JAMA*. 2016;316(15):1555–1564. doi:10.1001/jama.2016.14655
24. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clinl Infect Dis*. 2006;43(1):25–31. doi:10.1086/504810
25. Santolaya ME, Alvarez AM, Acuña M, et al. Efficacy of pre-emptive versus empirical antifungal therapy in children with cancer and high-risk febrile neutropenia: a randomized clinical trial. *J Antimicrob Chemother*. 2018;73(10):2860–2866. doi:10.1093/jac/dky244
26. Wang J-L, Chang C-H, Young-Xu Y, et al. Systematic review and meta-analysis of the tolerability and hepatotoxicity of antifungals in empirical and definitive therapy for invasive fungal infection. *Antimicrob Agents Chemother*. 2010;54(6):2409–2419. doi:10.1128/AAC.01657-09
27. Brusselaers N, Lagergren J. The Charlson comorbidity index in registry-based research. *Meth Inform Med*. 2017;56(05):401–406. doi:10.3414/ME17-01-0051
28. Trifi A, Abdellatif S, Daly F, et al. Empiric antifungal and outcome in ICU patients. *Tunis Med*. 2019;97(4):579–587.
29. Chakrabarti A, Mohamed N, Capparella MR, et al. The role of diagnostics-driven antifungal stewardship in the management of invasive fungal infections: a systematic literature review. In: *Open Forum Infectious Diseases*. Oxford University Press; 2022.
30. Jacobs S, Price Evans DA, Tariq M, et al. Fluconazole improves survival in septic shock: a randomized double-blind prospective study. *Crit Care Med*. 2003;31(7):1938–1946. doi:10.1097/01.CCM.0000074724.71242.88
31. Hasan MJ, Neelotpol S, Rabbani R. Early empirical anidulafungin reduces the prevalence of invasive candidiasis in critically Ill patients: a case-control study. *J Crit Care Med*. 2022;8(2):89–99. doi:10.2478/jccm-2022-0006
32. Cui N, Wang H, Su L, et al. Initial therapeutic strategy of invasive candidiasis for intensive care unit patients: a retrospective analysis from the China-SCAN study. *BMC Infect Dis*. 2017;17(1):1–13. doi:10.1186/s12879-017-2207-1
33. Sun Y, Hu J, Huang H, et al. Fluconazole is as effective as other anti-mold agents in preventing early invasive fungal disease after allogeneic stem cell transplantation: assessment of antifungal therapy in haematological disease in China. *Transl Cancer Res*. 2020;9(11):6900. doi:10.21037/tcr-19-2887
34. Park S, Kim K, Jang JH, et al. Randomized trial of micafungin versus fluconazole as prophylaxis against invasive fungal infections in hematopoietic stem cell transplant recipients. *J Infect*. 2016;73(5):496–505. doi:10.1016/j.jinf.2016.06.011
35. Poissy J, Rouzé A, Cornu M, et al. The changing landscape of invasive fungal infections in ICUs: a need for risk stratification to better target antifungal drugs and the threat of resistance. *J Fungi*. 2022;8(9):946. doi:10.3390/jof8090946