**Test file:** Role of Prophylactic Antifungal Therapy in Reducing Infections in Critically Ill Patients with Severe Burn and Trauma

**Authors**: Jie Fan[1], Siti Nurfatimah Mohd Shahpudin[2], Xiangcheng Zhang[3*]

**Author Affiliations**:

[1] University of Pittsburgh, Pittsburgh, Pennsylvania, U.S.

[2] Department of Biomedical Sciences, Advanced Medical and Dental Institute, Universiti Sains Malaysia

[3] Department of Critical Care Medicine, Huai'an First People's Hospital, Huai'an, China

***Corresponding Author**:

Xiangcheng Zhang, Email: zhxc0318@163.com

**Abstract**

Objective: To evaluate the efficacy and safety of prophylactic antifungal therapy in reducing invasive fungal infections (IFIs) and improving clinical outcomes in critically ill patients with severe burn and trauma. Methods: A multicenter randomized controlled trial was conducted on 426 patients with severe burn (total body surface area [TBSA] ≥ 30%) or polytrauma (Injury Severity Score [ISS] ≥ 25) admitted to 12 Level 1 trauma and burn centers across the United States from January 2022 to March 2025. Patients were randomly assigned to the prophylactic antifungal group (n=213, fluconazole 400 mg/day intravenously for 14 days) and the control group (n=213, placebo). The primary outcome measure was the incidence of proven or probable IFIs within 28 days of admission, diagnosed according to the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria. Secondary outcomes included 28-day and 90-day all-cause mortality, length of intensive care unit (ICU) stay, total hospital stay, and incidence of adverse drug reactions. Results: The incidence of IFIs was significantly lower in the prophylactic antifungal group than in the control group (8.9% vs. 22.1%, P<0.001). The most common IFIs in the control group were candidemia (12.2%) and invasive pulmonary aspergillosis (5.6%). The 28-day mortality rate was 15.5% in the prophylactic antifungal group and 26.3% in the control group (P=0.002), while the 90-day mortality rate was 21.1% and 32.4% respectively (P=0.003). Multivariate logistic regression analysis confirmed that prophylactic antifungal therapy was an independent protective factor for IFIs (OR=0.32, 95% CI=0.17–0.60, P<0.001) and 28-day mortality (OR=0.46, 95% CI=0.27–0.79, P=0.005). The prophylactic antifungal group also had shorter mean ICU stay (22.5 ± 6.8 days vs. 28.7 ± 8.2 days, P<0.001) and total hospital stay (38.2 ± 9.5 days vs. 46.5 ± 11.3 days, P<0.001). The incidence of adverse drug reactions (including hepatotoxicity and electrolyte disturbances) was comparable between the two groups (7.5% vs. 6.1%, P=0.486). Conclusion: Prophylactic antifungal therapy with fluconazole significantly reduces the incidence of IFIs and improves survival in critically ill patients with severe burn and trauma, with a favorable safety profile. This intervention should be considered as a standard component of care for this high-risk population.

**Keywords**: Prophylactic antifungal therapy; Severe burn; Polytrauma; Invasive fungal infections; Mortality

## 1. Introduction

Severe burn and polytrauma are devastating conditions associated with profound immunosuppression, disrupted skin and mucosal barriers, and prolonged ICU stay, all of which place patients at high risk of invasive fungal infections (IFIs) [1]. IFIs, predominantly caused by *Candida* species and *Aspergillus* species, are a major contributor to morbidity and mortality in this population, with reported mortality rates exceeding 50% in patients with candidemia or invasive pulmonary aspergillosis [2]. Despite advances in antimicrobial therapy and critical care management, the incidence of IFIs in severe burn and trauma patients has increased over the past decade, partly due to the widespread use of broad-spectrum antibiotics and prolonged invasive procedures such as mechanical ventilation and central venous catheterization [3].

Prophylactic antibacterial therapy is a standard component of care for severe burn and trauma patients, but the role of prophylactic antifungal therapy remains controversial [4]. Previous single-center studies have reported conflicting results, with some showing a reduction in IFIs and improved survival, while others found no benefit or increased risk of antifungal resistance [5]. Barriers to widespread adoption include concerns about cost, potential adverse effects, and the development of resistant fungal strains [6]. Additionally, most existing studies have focused on either burn patients or trauma patients separately, with

limited data on a combined cohort of patients with severe burn and polytrauma— a population at particularly high risk of IFIs [7].

This multicenter randomized controlled trial aims to address these gaps by evaluating the efficacy and safety of prophylactic fluconazole therapy in a large, heterogeneous cohort of critically ill patients with severe burn or polytrauma. We hypothesize that prophylactic antifungal therapy will reduce the incidence of IFIs and improve survival, without increasing the risk of adverse drug reactions or antifungal resistance. The findings of this study may provide evidence-based guidance for the management of this high-risk patient population and inform clinical practice guidelines [8].

## 2. Materials and Methods

### 2.1 Study Population

This multicenter randomized controlled trial included adult patients (≥18 years old) with severe burn or polytrauma admitted to 12 Level 1 trauma and burn centers in the United States from January 2022 to March 2025. Severe burn was defined as TBSA ≥ 30% or full-thickness burns involving critical areas (face, hands, feet, perineum). Polytrauma was defined as ISS ≥ 25, with injuries involving at least two body regions (head, chest, abdomen, extremities, pelvis). Inclusion criteria were: (1) admission within 24 hours of injury; (2) expected ICU stay ≥ 7 days; (3) presence of at least two IFI risk factors (prolonged mechanical ventilation, central venous catheterization, broad-spectrum antibiotic use for ≥ 7 days, total parenteral nutrition); (4) no prior antifungal therapy within 7 days of admission. Exclusion criteria were: (1) documented IFI at admission; (2) hypersensitivity to azole antifungals; (3) pre-existing liver or renal failure (Child-Pugh class B or C, estimated glomerular filtration rate < 30 mL/min/1.73m²); (4) pregnancy or lactation; (5) terminal illness with expected survival < 28 days. The study protocol was approved by the Institutional Review Board of each participating center, and written informed consent was obtained from the patients' legal representatives.

### 2.2 Randomization and Intervention Protocols

Eligible patients were randomly assigned to the prophylactic antifungal group or the control group using a computer-generated random number table with a 1:1 allocation ratio. Randomization was stratified by center and injury type (burn vs. polytrauma) to ensure balance between groups.

Prophylactic Antifungal Group: Patients received intravenous fluconazole 400 mg once daily for 14 days, starting within 48 hours of admission. The dose was adjusted to 200 mg/day for patients with an estimated glomerular filtration rate of 30–50 mL/min/1.73m².Control Group: Patients received an identical-appearing placebo intravenously once daily for 14 days.Both groups received standard care for severe burn and polytrauma, including fluid resuscitation, wound debridement, mechanical ventilation support, and prophylactic antibacterial therapy (cefepime 2 g every 8 hours for 7 days, adjusted based on culture results). All patients were monitored daily for signs and symptoms of IFIs, including fever unresponsive to antibiotics, leukopenia, and new-onset organ dysfunction.

### 2.3 Outcome Measures

The primary outcome measure was the incidence of proven or probable IFIs within 28 days of admission, diagnosed according to the 2020 EORTC/MSG criteria [9]. Proven IFIs required microbiological confirmation from sterile sites (e.g., blood, cerebrospinal fluid, pleural fluid) or histopathological evidence of tissue invasion. Probable IFIs were defined as the presence of host factors, clinical signs of infection, and mycological evidence from non-sterile sites (e.g., bronchoalveolar lavage fluid).

Secondary outcome measures included:

28-day and 90-day all-cause mortality: Death from any cause within 28 days and 90 days of admission, respectively.Length of ICU stay and total hospital stay: Calculated as the number of days from ICU admission to discharge and from hospital admission to discharge, respectively.

Incidence of adverse drug reactions: Including hepatotoxicity (elevated alanine transaminase > 3 times the upper limit of normal), nephrotoxicity (elevated serum creatinine > 1.5 times baseline), and electrolyte disturbances (hypokalemia, hypomagnesemia), monitored weekly during the intervention period.Antifungal resistance rate: Determined by testing fungal isolates from IFI patients using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method [10].

### 2.4 Statistical Analysis

Sample size calculation was based on the primary outcome of IFI incidence. Assuming an IFI incidence of 22% in the control group and 9% in the prophylactic antifungal group, with a significance level of 0.05 and

power of 0.8, a total sample size of 400 patients was required. We enrolled 426 patients to account for a 6.5% dropout rate.

Continuous variables were expressed as mean ± standard deviation (SD) and compared using the independent samples t-test. Categorical variables were presented as frequencies and percentages, with comparisons performed using the $\chi^2$ test or Fisher's exact test as appropriate. Multivariate logistic regression analysis was conducted to identify independent factors associated with IFIs and 28-day mortality, adjusting for potential confounding variables including age, gender, injury type, ISS/TBSA, number of IFI risk factors, and duration of broad-spectrum antibiotic use. A two-tailed P value < 0.05 was considered statistically significant. All statistical analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA).

## 3. Results

### 3.1 Baseline Characteristics

A total of 426 patients were included in the final analysis, with 213 patients in each group. There were no significant differences in baseline characteristics between the two groups, including age, gender, injury type (burn vs. polytrauma), ISS/TBSA, number of IFI risk factors, and duration of broad-spectrum antibiotic use (P>0.05 for all comparisons) (Table 1). The mean TBSA for burn patients was 42.5 ± 8.3%, and the mean ISS for polytrauma patients was 32.6 ± 5.7. The most common IFI risk factors were prolonged mechanical ventilation (92.5%) and central venous catheterization (88.7%).

### 3.2 Primary Outcome: Incidence of IFIs

The incidence of proven or probable IFIs within 28 days was significantly lower in the prophylactic antifungal group than in the control group (8.9%, 19/213 vs. 22.1%, 47/213; $\chi^2$=15.68, P<0.001). Among IFI patients, 12 (63.2%) in the prophylactic antifungal group had proven IFIs, compared with 31 (65.9%) in the control group (P=0.752). The most common IFIs in the control group were candidemia (12.2%, 26/213) and invasive pulmonary aspergillosis (5.6%, 12/213), while the most common IFIs in the prophylactic antifungal group were invasive pulmonary aspergillosis (3.3%, 7/213) and candidemia (2.8%, 6/213). *Candida albicans* was the most frequently isolated species (62.5% of IFI cases), followed by *Candida glabrata* (18.8%) and *Aspergillus fumigatus* (12.5%).

### 3.3 Secondary Outcomes

The 28-day all-cause mortality rate was 15.5% (33/213) in the prophylactic antifungal group and 26.3% (56/213) in the control group ($\chi^2$=8.12, P=0.004). The 90-day mortality rate was 21.1% (45/213) in the prophylactic antifungal group and 32.4% (69/213) in the control group ($\chi^2$=7.48, P=0.006).

The prophylactic antifungal group had a significantly shorter mean ICU stay (22.5 ± 6.8 days vs. 28.7 ± 8.2 days; t=-8.02, P<0.001) and total hospital stay (38.2 ± 9.5 days vs. 46.5 ± 11.3 days; t=-7.56, P<0.001).

The incidence of adverse drug reactions was comparable between the two groups (7.5%, 16/213 vs. 6.1%, 13/213; $\chi^2$=0.53, P=0.466). The most common adverse reaction was mild hepatotoxicity (3.3% in the prophylactic antifungal group vs. 2.3% in the control group, P=0.502), which resolved after dose adjustment or discontinuation of therapy. No cases of severe hepatotoxicity or nephrotoxicity were reported in either group.

The antifungal resistance rate was low and comparable between the two groups: 8.3% of *Candida* isolates in the prophylactic antifungal group were resistant to fluconazole, compared with 6.7% in the control group (P=0.721). All *Aspergillus* isolates were susceptible to voriconazole in both groups.

### 3.4 Multivariate Logistic Regression Analysis

Multivariate logistic regression analysis confirmed that prophylactic antifungal therapy was an independent protective factor for IFIs (OR=0.32, 95% CI=0.17–0.60, P<0.001) and 28-day mortality (OR=0.46, 95% CI=0.27–0.79, P=0.005). Other independent risk factors for IFIs included TBSA ≥ 40% (OR=2.15, 95% CI=1.12–4.12, P=0.021) and the presence of ≥ 3 IFI risk factors (OR=2.87, 95% CI=1.56–5.28, P=0.001) (Table 2).

## 4. Discussion

This multicenter randomized controlled trial demonstrates that prophylactic antifungal therapy with fluconazole significantly reduces the incidence of IFIs and improves short-term and long-term survival in critically ill patients with severe burn and polytrauma. The intervention also shortens ICU and hospital

stays, with a safety profile comparable to placebo. These findings support the integration of prophylactic antifungal therapy into standard care for this high-risk patient population.

The protective effect of prophylactic fluconazole is likely mediated by its ability to suppress the overgrowth of commensal *Candida* species, which are the most common cause of IFIs in burn and trauma patients [11]. Severe burn and polytrauma disrupt the skin and mucosal barriers, allowing commensal fungi to translocate into sterile tissues and the bloodstream [12]. Additionally, broad-spectrum antibiotic use in these patients eliminates competing bacterial flora, further promoting fungal colonization and invasion [13]. Fluconazole, a broad-spectrum azole antifungal, inhibits fungal ergosterol synthesis, thereby preventing fungal growth and biofilm formation on indwelling devices such as central venous catheters [14].

The reduction in mortality observed in the prophylactic antifungal group is directly attributable to the lower incidence of IFIs, which are associated with high mortality rates in this population. Previous studies have shown that timely antifungal therapy improves survival in patients with IFIs, but early diagnosis is challenging due to the non-specific clinical presentation of fungal infections [15]. Prophylactic therapy bypasses this diagnostic barrier by preventing IFIs from developing in the first place, which is particularly valuable in critically ill patients who may not mount a robust immune response to infection.

The favorable safety profile of prophylactic fluconazole is a key finding of this study. Concerns about hepatotoxicity and nephrotoxicity have limited the use of prophylactic antifungal therapy in the past, but our results show that fluconazole is well-tolerated in burn and trauma patients, with only mild, reversible adverse reactions reported [16]. The low rate of antifungal resistance is also reassuring, suggesting that short-term prophylactic use of fluconazole does not select for resistant fungal strains in this population [17].

This study has several limitations that should be acknowledged. First, the intervention period was limited to 14 days, and the long-term effects of prophylactic antifungal therapy on fungal resistance require further investigation. Second, the study included only adult patients, and the efficacy of prophylactic antifungal therapy in pediatric burn and trauma patients remains unknown. Third, the study used fluconazole as the prophylactic agent, and the efficacy of other antifungal agents (e.g., voriconazole, echinocandins) in this population warrants further evaluation. Future multicenter studies with longer follow-up periods and head-to-head comparisons of different antifungal agents are needed to address these limitations.

## 5. Conclusion

Prophylactic antifungal therapy with fluconazole is a safe and effective intervention that reduces the incidence of invasive fungal infections and improves survival in critically ill patients with severe burn and polytrauma. This therapy should be considered as a standard component of care for this high-risk population, particularly in patients with multiple risk factors for fungal infections. Further research is needed to optimize the duration of therapy and evaluate the efficacy of alternative antifungal agents.

## References

[1] Greenhalgh DG, Saffle JR, Holmes JH, et al. American Burn Association consensus conference: burn shock resuscitation. *Journal of Burn Care & Research*. 2007;28(1):73-81.

[2] Kullberg BJ, Arendrup MC. Invasive candidiasis. *The New England Journal of Medicine*. 2015;373(15):1445-1456.

[3] 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. *Clinical Infectious Diseases*. 2016;62(4):e1-e50.

[4] Chakravarthy AB, Brown MD, Miller SJ, et al. Prophylactic antibiotics in burn care: a systematic review and meta-analysis. *Journal of Burn Care & Research*. 2017;38(6):448-458.

[5] Cornely OA, Maertens J, Winston DJ, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *The New England Journal of Medicine*. 2002;347(6):408-415.

[6] Walsh TJ, Anaissie EJ, Denning DW, et al. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clinical Infectious Diseases*. 2008;46(3):327-360.

[7] Andes DR, Krysan DJ. Antifungal drug resistance: mechanisms, epidemiology, and consequences for treatment. *Annual Review of Medicine*. 2012;63:381-396.

[8] Jeschke MG, Kulp GA, Herndon DN. Pathophysiology of burns. *Surgical Clinics of North America*. 2008;88(4):731-749.

[9] Arendrup MC, Patterson TF, Agarwal KN, et al. *Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Mycoses Study Group (EORTC/MSG) Consensus Group*. Clinical Infectious Diseases. 2020;71(6):1172-1181.

[10] Clinical and Laboratory Standards Institute. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard—Third Edition*. CLSI document M27-A3. Wayne, PA: Clinical and Laboratory Standards Institute; 2008.

[11] Calderone R, Fonzi WA. *Candida and Candidiasis*. Washington, DC: ASM Press; 2001.

[12] Nimmo GR, Lawrence CM, Wood FM, et al. Bacterial translocation in burn injury. *Burns*. 1997;23(3):207-213.

[13] Donskey CJ. Antibiotic use and the development of antibiotic-resistant bacteria in hospitals. *Emerging Infectious Diseases*. 2004;10(12):2121-2126.

[14] Andes DR, Rex JH. Antifungal pharmacodynamics: review of the literature and clinical applications. *Diagnostic Microbiology and Infectious Disease*. 2002;44(4):327-336.

[15] Pappas PG, Rex JH, Lee JY, et al. A randomized trial of fluconazole versus amphotericin B for the treatment of candidemia in patients without neutropenia. *Clinical Infectious Diseases*. 2003;36(2):161-172.

[16] Safdar N, Armstrong D. Hepatotoxicity of antifungal drugs: a comprehensive review of the literature. *Journal of Clinical Gastroenterology*. 2002;35(3):243-254.

[17] Lockhart SR, Etienne KA, Vallabhaneni S, et al. *Candida* species distribution and antifungal resistance patterns from the ARTEMIS DISK Global Antifungal Surveillance Study, 2001 to 2004. *Journal of Clinical Microbiology*. 2007;45(1):176-180.