OPEN ACCESS

Saudi Journal of Medical and Pharmaceutical Sciences
Abbreviated Key Title: Saudi J Med Pharm Sci
ISSN 2413-4929 (Print) | ISSN 2413-4910 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article **Medicine**

Hepatotoxicity Patterns of Anidulafungin and Fluconazole in the Management of Candida Infections: A Comparative Study among Hospitalized Patients

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DOI: 10.36348/sjmps.2024.v10i07.001 | **Received:** 27.05.2024 | **Accepted:** 01.07.2024 | **Published:** 04.07.2024

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Abstract

Hepatotoxicity can potentially arise in hospitalized patients with Candida infections due to antifungal medications. Ongoing research has focused on the hepatotoxicity profiles of fluconazole and anidulafungin. Nevertheless, a limited number of studies have directly compared the hepatotoxicity of these two antifungals. This study compares the hepatotoxic effects of anidulafungin and fluconazole in patients hospitalized with Candida infections. This retrospective study was conducted at the Prince Mohamed Bin Abdelaziz Hospital in Saudi Arabia to compare the hepatotoxicity of fluconazole and anidulafungin in patients with Candida infection. The liver function test results were analyzed using linear mixed models, with adjustments made for confounding factors. The investigation comprised 202 cases, of which 85 (42%) were treated with fluconazole and 117 (58%) was treated with anidulafungin—mortality and prevalence of candidemia and septic shock in the Anidulafungin group (p 0.001). There was no significant difference between the two groups regarding age, gender, duration of treatment, or concomitant use of hepatotoxic drugs. Analyses utilizing Linear Mixed-Effects Models revealed higher alanine aminotransferase (ALT) (p = 0.001) and aspartate aminotransferase (AST) (p = 0.001) levels in the Anidulafungin group initially; however, after adjusting for covariates, these differences were no longer statistically significant. The levels of alkaline phosphatase (ALP) and gamma-glutamyl transferase (GTT) did not differ significantly between groups after controlling for confounding variables. However, the Anidulafungin group had substantially higher bilirubin levels than the Fluconazole group, and this difference remained significant after adjusting for potential confounding variables (p = 0.022). In summary, this study contributes to understanding the relative hepatotoxicity of anidulafungin and fluconazole. After controlling for confounding variables, it was found that there were no significant differences in liver enzyme levels between the two groups. When assessing the hepatotoxicity of these antifungal agents, it is imperative to consider the individual patient characteristics, underlying health conditions, and concurrent administration of other hepatotoxic medications.

Keywords: Hepatotoxicity, Anidulafungin, Fluconazole, Candida Infection, Retrospective Study, Antifungal Therapy.

INTRODUCTION

Candida is a common fungal infection among hospitalized patients, especially those with compromised immune systems [1]. (Magill SS, NEJM2014) These infections can cause considerable morbidity and mortality [2]. (Pappas PG, CID2016) [3] (Pappas PG CID2003) Candida infections are usually treated with antifungal drugs, with echinocandins and azoles constituting the most common classes. Anidulafungin and fluconazole are frequently prescribed medications within these classes and are extensively used to treat invasive candidiasis [4] (Andes DR, CID2012) [2] (Pappas PG, CID2016).

According to numerous studies, the incidence of hepatotoxicity associated with fluconazole use ranges from 2% to 11%, which can manifest as a mild elevation in liver enzymes or progress to more severe cases that lead to acute liver failure and the possibility of death

([5]des Sousa), ([6]zahou), ([7]gadour). On the other hand, the exact rate of liver injury attributed to anidulafungin is unknown, although some reports indicate it is less than 2% ([8] Reboli NEJM 2007). Additional studies are required to understand better and compare the hepatotoxicity profiles of fluconazole and anidulafungin and establish their respective risk-benefit profiles in clinical practice.

Anidulafungin is a broad-spectrum antifungal medication prescribed for treating more resistant Candida infections ([9] Vazquez CID2006) It is often prescribed as an alternative to fluconazole in cases where liver toxicity is a concern. ([2]-Pappas CID2016) (However, there is limited research explicitly comparing the incidence of hepatotoxicity between anidulafungin and fluconazole, and the results of the existing studies are inconsistent. ([8], Roboli N Engl J 2007] ([10] Damle,Chemother, March 2009). ([6] Zhou *et al.*, (2022).

The study comparing the hepatotoxicity of fluconazole and anidulafungin has implications for clinical decision-making and patient safety. Understanding the relative hepatotoxicity of these antifungal medications can guide treatment decisions, reduce liver-related adverse events, and prevent the unnecessary prescription of anidulafungin.

METHODS

Study Design: This retrospective observational investigation was conducted at the Prince Mohamed Bin Abdelaziz Hospital in Madinah, Saudi Arabia.

Population Studied: Hospitalized adult patients who received antifungal therapy for candida infection between 1 January 2017 and 30 June 2022. Excluded from the analysis were cases younger than 14, without liver function measured at least twice during therapy, and those receiving two or more antifungal medicines within 60 days. Patients who received antifungal treatment for candida infection during the study period were identified from pharmacy records. Data acquisition from electronic medical records followed standardized procedures to reduce information bias. The sample size was not predetermined. To ensure a thorough evaluation of hepatotoxicity profiles, we include all eligible patients during the study period.

Exposure and Outcome Variables

Fluconazole and anidulafungin were the primary exposure variables. The primary outcome measure was the change in liver function test results, including ALT, AST, ALP, bilirubin levels, and coagulation parameters (PT and aPTT). Laboratory measurements were performed utilizing standardized procedures in the hospital's clinical laboratory. Several variables were evaluated as potential confounders and effect modifiers, including age, pre-existing liver disease, comorbidities, shock, and concurrent use of hepatotoxic medications. These variables were assessed and accounted for in the analysis to minimize confounding effects.

Ethical Considerations: The investigation adhered to the Helsinki Declaration's ethical guidelines. Institutional Review Board (IRB) approval was obtained to assure patient confidentiality, data privacy, and adherence to ethical standards throughout the study.

Data Analysis

Descriptive statistics summarized the demographic and clinical characteristics of the research population. Considering sample size and data distribution, the association between antifungal medication and abnormal liver function test results was evaluated using appropriate statistical analyses, such as chi-square or Fisher's exact tests. Adjusted analysis was conducted using linear mixed models to correct for confounding, considering the correlation between repeated measurements within the same patient. Multiple imputation and complete case analyses were utilized to account for missing data. The statistical software STATA 13 was used for data analysis.

RESULTS

Initially, we evaluated 500 cases of candida infection treated with antifungal therapy. After excluding patients that received antifungal medications other than anidulafungin and fluconazole and two or more antifungal medications within 60 days, we excluded cases where liver function test data was missing. The analysis included 202 patients, of which 85 (42%) received fluconazole and 117 (58%) received anidulafungin [Table 1]. Compares the variables between the two groups.

The median age was 73 years, and there was no significant difference in age between the fluconazole and anidulafungin groups ($p = 0.474$). 116 (57%) of the study population were male, with 44 (52%) in the fluconazole group and 72 (62%) in the anidulafungin group ($p = 0.195$). Mortality was markedly higher in the anidulafungin group than in the fluconazole group at 30 days of antifungal therapy ($p = 0.001$). Similarly, candidemia, septic shock, and acute kidney injury (AKI) were significantly more prevalent in the group receiving anidulafungin ($p = 0.002$, $p = 0.001$, and $p = 0.001$, respectively). The median duration of antifungal treatment was eight days in both groups, and there was no significant difference in the proportion of patients receiving hepatotoxic drugs between the fluconazole and anidulafungin groups.

Table 1: Comparison of Demographic and Clinical Characteristics in Patients Treated with Fluconazole and Anidulafungin for Candida Infections

Variables	All 202	Fluconazole 85(42%)	Anidulafungin 117(58%)	P value
Age (median)	73(63-82)	72(60-82)	73(64-81)	0.474
Male	116(57)	44(52)	72(62)	0.195
Body Mass Index	28(23-32)	26(21-30)	28(25-33)	0.0034
Length of hospitalization (days)	27(17-44)	25(12-41)	29(19-46)	0.061
Days in intensive care (days)	10(0-25)	0(0-7)	20(10-34)	0.001
Mortality at 30 days	92(46)	14(16)	78(67)	0.001
Candidemia	28(14)	4(8)	24(21)	0.002
Antifungal duration (days)		8(5-14)	8(5-13)	0.999
Septicshock	107(53)	11(13)	96(82)	0.001
Acute kidney injury	113(56)	28(33)	85(73)	0.001
Mild liver disease	10(5)	4(5)	6(5)	1.000
Moderate to sever liver disease	5(2)	2(2)	3(3)	1.000
One hepatotoxic drug	47(23)	22(26)	25(21)	0.502
Two hepatotoxic drugs	58(29)	27(32)	31(27)	0.434
Three hepatotoxic drugs	37(18)	14(16)	23(20)	0.587
Four hepatotoxic drugs	29(14)	10(12)	19(16)	0.421
Alanine Aminotransferase	26(17-49)	20(11-31)	36(19-52)	0.001
Aspartate Aminotransferase	31(20-55)	23(17-33)	38(25-69)	0.001
Alkaline Phosphatase	116(85-198)	119(85-206)	114(88-195)	0.801
Gamma-Glutamyl Transferase	210(108-294)	199(105-271)	228(111-308)	0.634
Total Bilirubin	14(8-27)	8(6-14)	17(11-39)	0.001
Albumin	27(24-31)	27(24-30)	27(24-31)	0.894
Partial Thromboplastin Time	32(28-41)	28(26-31)	36(30-46)	0.001
Prothrombin Time	14(13-18)	14(12-15)	15(13-21)	0.001
International Normalized Ratio	1.2(1.08-1.56)	1.13(1.07-1.29)	1.3(1.09-1.76)	0.012

Median values (interquartile range) are reported for continuous variables, while number and percentage values are reported for categorical variables. All labs value at the start of antifungal therapy.

Liver Enzyme and Bilirubin Levels and Antifungals Treatment

ALT (Alanine Aminotransferase) levels in patients receiving Fluconazole or Anidulafungin were analyzed in Figure 1, and multiple measurement days revealed statistically significant differences between the two groups. Throughout the investigation, the Fluconazole group had consistently lower median ALT levels than the Anidulafungin group. This distinction was statistically substantial on Day 1, Day 5, Day 10, and Day 15. On Days 20, 25, 30, and 60, however, no significant differences in ALT levels were observed between groups.

Aspartate Aminotransferase (AST) levels in patients receiving Fluconazole or Anidulafungin are depicted in Figure 2, and multiple measurement days revealed statistically significant differences in AST levels between the two groups. The results determined that the Fluconazole group had consistently lower median AST levels than the Anidulafungin group. This distinction was statistically significant on Day 1, Day 5, Day 10, and Day 15. No statistically significant differences were observed on Days 20, 25, 30, and 60.

On all measurement days, including Days 1, 5, 10, 15, 20, 25, 30, and 60, there were no significant differences between the median Alkaline Phosphatase (ALP) and GGT (Gamma-Glutamyl Transferase) levels of the Fluconazole and Anidulafungin groups. [Figure 3, 4]. In addition, the results showed that patients treated with Anidulafungin consistently had significantly higher bilirubin levels than those treated with Fluconazole at multiple time points.

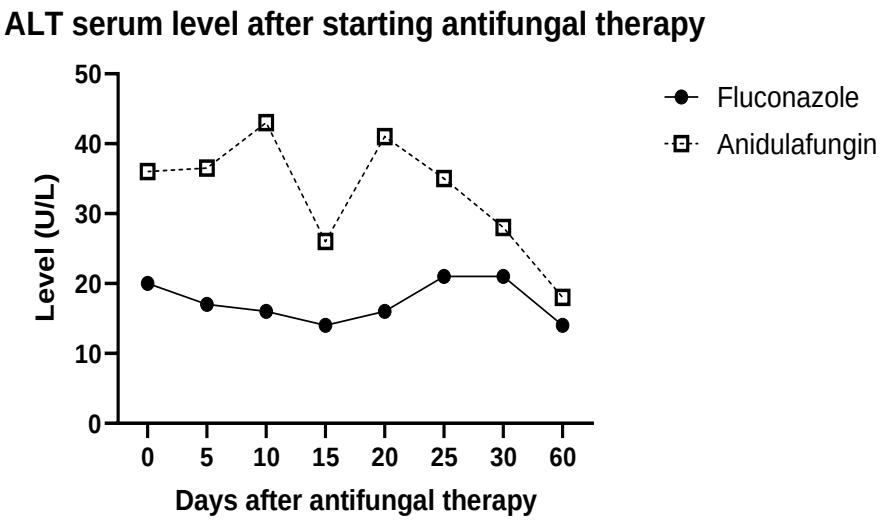

Figure 1: ALT (Alanine Aminotransferase) levels in patients receiving Fluconazole or Anidulafungin

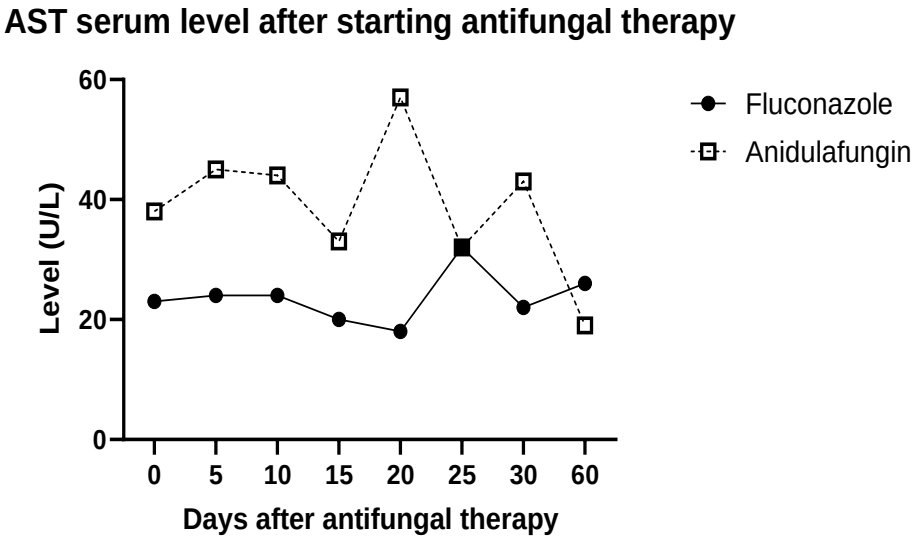

Figure 2: Aspartate Aminotransferase (AST) levels in patients receiving Fluconazole or Anidulafungin

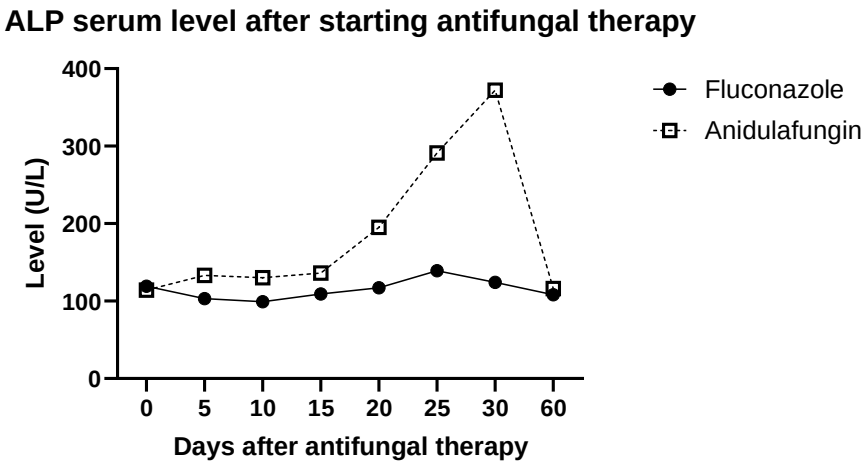

Figure 3: Alkaline Phosphatase (ALP)levels in patients receiving Fluconazole or Anidulafungin

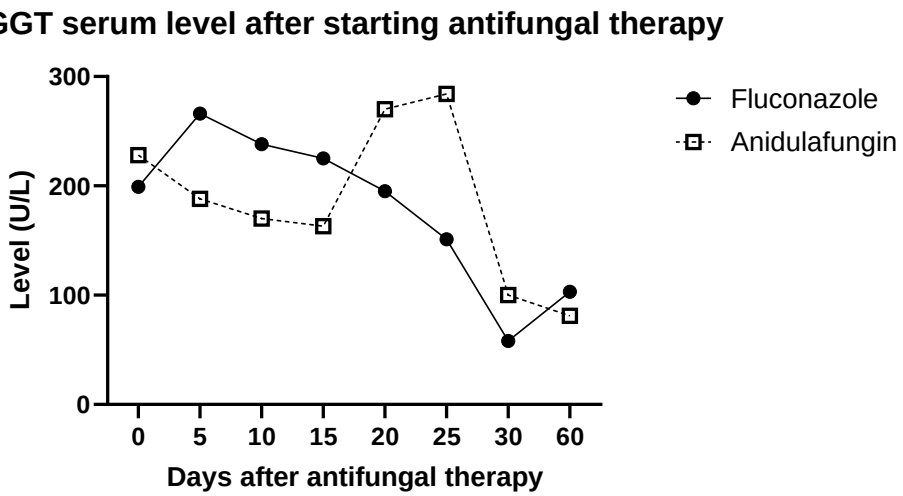

Figure 4: Gamma-Glutamyl Transferase (GGT) levels in patients receiving Fluconazole or Anidulafungin

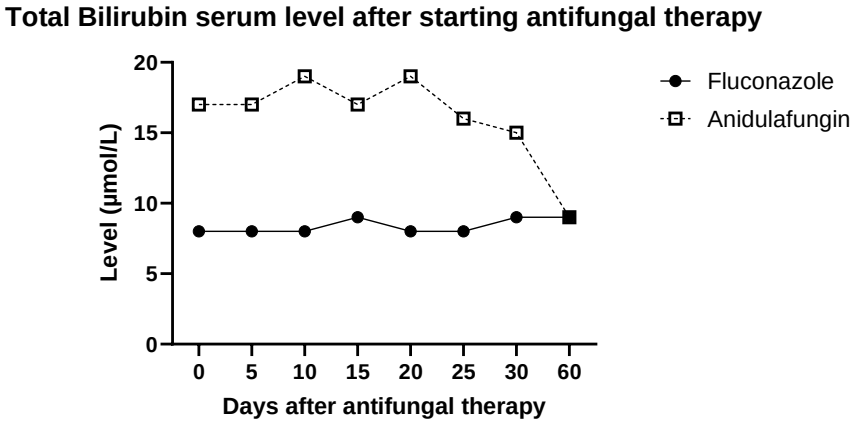

Figure 5: Bilirubin levels in patients receiving Fluconazole or Anidulafungin

Assessing Liver Enzymes Using Linear Mixed-Effects Models

The Linear Mixed-Effects Model analysis revealed statistically significant differences in the levels of liver enzymes between the Fluconazole and Anidulafungin groups. Initially, the Anidulafungin group had higher levels of ALT (The estimated coefficients (β)= 80.6, The standard errors SE = 23.8, p = 0.001) and AST (β = 86.6, SE = 24.1, p = 0.001) than the Fluconazole group. After controlling for potential confounders, such as septic shock and preexisting liver disease, the differences in ALT (β = 42.1, SE = 35, p = 0.238) and AST (β = 37.6, SE = 41.8, p = 0.238) levels between the groups became statistically insignificant, suggesting that these confounding factors may have influenced the initial associations.

In addition, patients in the Anidulafungin group had significantly higher baseline ALP levels than those in the Fluconazole group (β = 83.9%, SE = 30.9%, p = 0.007). Nonetheless, after adjusting for septic shock and preexisting liver disease, the difference in ALP levels between the groups became statistically insignificant (β = 55.5, SE = 49.7, p = 0.265). Similarly, for GTT levels, there was no significant difference between the Fluconazole and Anidulafungin groups (β = 68.2, SE = 45.3, p = 0.158). These findings indicate that septic shock and preexisting liver disease may have affected the initial associations between drug treatments and ALP levels.

In contrast, the bilirubin levels of patients in the Anidulafungin group were significantly higher than those in the Fluconazole group (β = 35, SE = 11.9, p = 0.003). Importantly, this difference remained significant even after controlling for septic shock and preexisting liver disease (β = 38.8, SE = 15.7, p = 0.022), indicating that the impact of Anidulafungin on bilirubin levels is independent of these confounding variables.

DISCUSSION

The findings of this study provide important insights into the comparative hepatotoxicity profiles of anidulafungin and fluconazole. While the study showed no significant differences in ALT, AST, and ALP levels between the two groups after controlling for confounding factors, it is crucial to note the significantly

higher total bilirubin levels observed in the anidulafungin group.

When comparing the hepatotoxicity of anidulafungin and fluconazole, it is essential to consider patients' variations in metabolism, underlying health conditions, severity of infection, and the concomitant use of other hepatotoxic medications. Shock and pre-existing chronic liver disease affect liver function independently of the antifungal treatment. ([11]Spernovasilis J Fungi).Shock can lead to hepatic ischemia and impaired liver function, while chronic liver disease can cause alterations in liver enzyme levels and bilirubin metabolism. Therefore, it is plausible that the differences in liver parameters observed between the treatment groups at the onset of therapy were driven by these confounding factors.

The comparative hepatotoxicity of fluconazole and anidulafungin has been the subject of ongoing research and debate. Few studies directly compared anidulafungin and fluconazole hepatotoxicity. In line with our results, some studies found that anidulafungin and fluconazole cause comparable hepatic injury. ([12]Krause CID 2004)([13] Winston, Am J Transplant. 2014). Another study found that both medication cause hepatic injury but ranked anidulafungin higher than fluconazole. ([6], ZhouFront Pharmacol. 2022 Apr). In contrast, other studies found fluconazole more hepatotoxic than anidulafungin.[8],Roboli N Engl J Med. 2007] ([10] Damle, Chemother. 2009 Mar). Hepatotoxicity risks and safety profiles of anidulafungin and fluconazole in these studies should be interpreted with caution due to differences in designs, patient populations, and potential limitations of the studies. Continued research and monitoring are necessary to understand further these antifungal agents' hepatotoxicity risks and long-term safety profiles.

Notably, the incidence of fluconazole-induced hepatotoxicity is very low [8, 10]. Most cases return to normal liver enzyme levels shortly after discontinuing fluconazole, with rare cases of severe liver injury reported. ([14] Lawson, Canadian Journal of Hospital Pharmacy, 1998 May). It is important to emphasize that some studies have not found patients who developed acute hepatic failure from either medication. ([14]Lawson, Canadian Journal of Hospital Pharmacy, 1998 May; [15]Vena, Infectious Diseases and Therapy, 2020 Mar) .However, the risk of hepatotoxicity can vary depending on various factors such as genetics, underlying health conditions, and the simultaneous use of other hepatotoxic medications, which may increase susceptibility. ([16]LEE, N Engl J Med, 2003 Jul).

The limitations of this study should be acknowledged. Firstly, the retrospective design introduces inherent limitations in establishing causality. Although we tried to adjust for potential confounders, residual confounding may still exist, so randomized controlled trials would provide more robust evidence. Secondly, we conducted this study at a single hospital, which may limit the generalizability of the findings to broader populations. Thirdly, the sample size of 202 patients, although adequate for the scope of the study, may still be relatively small in evaluating rare adverse events such as hepatotoxicity. Furthermore, the study relied on data collected from electronic medical records, which may be subject to documentation bias or incomplete information.

Despite these limitations, the study provides valuable data regarding the comparative hepatotoxicity profiles of these antifungal agents. Further research is needed to delve deeper into the hepatotoxicity profiles of fluconazole and anidulafungin, exploring dose-dependent effects, drug interactions, biomarkers for early detection, impact on treatment outcomes, and conducting comprehensive risk-benefit analyses. Collectively, these investigations will contribute to developing evidence-based guidelines for the optimal use of antifungal agents in patients with candida infections, ensuring patient safety and treatment efficacy.

In conclusion, based on the available evidence, there is no clear evidence that fluconazole is more hepatotoxic than anidulafungin. The comparative hepatotoxicity of these antifungal agents may vary depending on individual patient characteristics and other factors. From an antifungal stewardship perspective, fluconazole offers several advantages, including targeted therapy based on susceptibility testing, a favorable side effect profile, outpatient management potential, efficient resource allocation, adherence to clinical guidelines, and promoting education and awareness. By incorporating fluconazole into antifungal stewardship programs, healthcare providers can achieve optimal treatment outcomes while minimizing the risk of resistance and ensuring responsible antifungal use.

Funding: The authors declare that no funds, grants, or other support were received during manuscript preparation.

Competing Interests: The authors have no relevant financial or non-financial competing interests to disclose.

Contributions of Authors

All authors contributed equally to the conception and design of the investigation. Data collection and analysis were carried out by [full name], [full name], and [full name] in collaboration. The initial iteration of the manuscript was co-written by [full name], [full name], and [full name], and all authors provided insightful feedback and reviewed the document. All authors have viewed and approved the final manuscript version.

Data Availability: The datasets generated and/or analyzed during the current study are available upon reasonable request from the corresponding author.

Ethical Approval

This investigation was conducted in accordance with the principles of the Helsinki Declaration. The King Abdullah Research Center's Ethics Committee granted approval (27/6/2022 Approval No NRM22M/008/02). As this was a retrospective observational study, participant consent was not required.

Consent to Publish: The authors certify that no personal information of any kind, including names, images, or videos, was included in this manuscript. Therefore, no permission to publish was required.

ACKNOWLEDGMENT

The authors wish to express their sincere appreciation to Dr. Abdalrhaman Al Shahir for his invaluable contributions and support throughout this study.

REFERENCES

1. Magill, S. S., Edwards, J. R., Bamberg, W., Beldavs, Z. G., Dumyati, G., Kainer, M. A., Lynfield, R., Maloney, M., McAllister-Hollod, L., Nadle, J., Ray, S. M., Thompson, D. L., Wilson, L. E., & Fridkin, S. K. (2014). Emerging Infections Program Healthcare-Associated Infections and Antimicrobial Use Prevalence Survey Team. Multistate point-prevalence survey of health care-associated infections. *N Engl J Med*, *370*(13), 1198-208. doi: 10.1056/NEJMoa1306801. Erratum in: N Engl J Med. 2022 Jun 16;386(24):2348. PMID: 24670166; PMCID: PMC4648343.
2. Pappas, P. G., Kauffman, C. A., Andes, D. R., Clancy, C. J., Marr, K. A., Ostrosky-Zeichner, L., ... & Sobel, J. D. (2016). Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clinical infectious diseases*, *62*(4), e1-e50. doi: 10.1093/cid/civ933. PMID: 26679628; PMCID: PMC4725385.
3. Pappas, P. G., Rex, J. H., Lee, J., Hamill, R. J., Larsen, R. A., Powderly, W., ... & Dismukes, W. E. (2003). NIAID Mycoses Study Group: A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. *Clin Infect Dis*, *37*(5), 634-643. doi: 10.1086/376906. Epub 2003 Aug 14. PMID: 12942393.
4. Andes, D. R., Safdar, N., Baddley, J. W., Playford, G., Reboli, A. C., Rex, J. H., ... & Kullberg, B. J. (2012). Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. *Clinical infectious diseases*, *54*(8), 1110-1122. doi: 10.1093/cid/cis021. Epub 2012 Mar 12. PMID: 22412055.
5. de Souza, M. C. P., Santos, A. G. D., & Reis, A. M. M. (2016). Adverse drug reactions in patients receiving systemic antifungal therapy at a high-complexity Hospital. *The Journal of Clinical Pharmacology*, *56*(12), 1507-1515. doi:10.1002/jcph.772
6. Zhou, Z. X., Yin, X. D., Zhang, Y., Shao, Q. H., Mao, X. Y., Hu, W. J., ... & Li, Z. L. (2022). Antifungal drugs and drug-induced liver injury: a real-world study leveraging the FDA adverse event reporting system database. *Frontiers in Pharmacology*, *13*, 891336. doi:10.3389/fphar.2022.891336
7. Gadour, E., & Kotb, A. (2021). Systematic Review of Antifungal-Induced Acute Liver Failure. *Cureus*, *13*(7), e16461. doi:10.7759/cureus.18940
8. Reboli, A. C., Rotstein, C., Pappas, P. G., Chapman, S. W., Kett, D. H., Kumar, D., ... & Walsh, T. J. (2007). Anidulafungin versus fluconazole for invasive candidiasis. *New England Journal of Medicine*, *356*(24), 2472-2482. doi:10.1056/NEJMoa066906
9. Vazquez, J. A., & Sobel, J. D. (2006). Anidulafungin: a novel echinocandin. *Clinical infectious diseases*, *43*(2), 215-222. doi: 10.1086/505204. Epub 2006 Jun 9. PMID: 16779750.
10. Damle, B. D., Dowell, J. A., Walsky, R. L., Weber, G. L., Stogniew, M., & Inskeep, P. B. (2009). In vitro and in vivo studies to characterize the clearance mechanism and potential cytochrome P450 interactions of anidulafungin. *Antimicrobial agents and chemotherapy*, *53*(3), 1149-1156. doi:10.1128/AAC.01279-08
11. Spernovasilis, N., & Kofteridis, D. P. (2018). Pre-Existing Liver Disease and Toxicity of Antifungals. *J Fungi (Basel)*, *4*(4), 133. doi: 10.3390/jof4040133. PMID: 30544724; PMCID: PMC6309049.
12. Krause, D. S., Simjee, A. E., Van Rensburg, C., Viljoen, J., Walsh, T. J., Goldstein, B. P., ... & Henkel, T. (2004). A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. *Clinical infectious diseases*, *39*(6), 770-775. doi: 10.1086/423378. Epub 2004 Aug 27. PMID: 15472806.
13. Winston, D. J., Limaye, A. P., Pelletier, S., Safdar, N., Morris, M. I., Meneses, K., ... & Singh, N. (2014). Randomized, double-blind trial of anidulafungin versus fluconazole for prophylaxis of invasive fungal infections in high-risk liver transplant recipients. *American journal of transplantation*, *14*(12), 2758-2764. doi:10.1111/ajt.12963
14. Lawson, C. A., Karlowsky, J. A., & Zhanel, G. G. (1998). Fluconazole-induced hepatotoxicity: review of published case reports. *Canadian Journal of Hospital Pharmacy*, *51*(2), 111-116.

15. Vena, A., Bouza, E., Bassetti, M., Menichetti, F., Merelli, M., Grau, S., ... & Muñoz, P. (2020). Comparison of the Safety and Tolerance Profile of Micafungin with that of Other Echinocandins and Azoles in Patients with Pre-existing Child–Pugh B or C Liver Disease: A Case–Control Retrospective Study. *Infectious Diseases and Therapy*, *9*, 151-163.
16. Lee, W. M. (2003). Drug-induced hepatotoxicity. *N Engl J Med.*, *349*(5), 474-485. doi:10.1056/NEJMra021844