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Blake S. Sanford

Wayne State University, bsanford@med.wayne.edu

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Anidulafungin: a noninferior alternative to fluconazole for treatment of esophageal candidiasis

BLAKE S. SANFORD, Wayne State University School of Medicine, bsanford@med.wayne.edu

ABSTRACT A critical appraisal and clinical application of Krause DS, Simjee AE, van Rensburg C, et al. A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. *Clin Infect Dis*. 2004;39(6):770-775. doi: [10.1086/423378](https://doi.org/10.1086/423378).

Keywords: *esophageal candidiasis, anidulafungin, echinocandin, fluconazole, HIV, QTc*

Clinical Context

Our patient is a 78-year-old African American man with a medical history of HIV managed with antiretroviral therapy, hepatitis C infection undergoing treatment with glecaprevir/pibrentasvir, and hepatocellular carcinoma status post laproscopic right hepatectomy and microwave ablation. He initially presented to the Emergency Department with primary concerns of fatigue and shortness of breath and was admitted to the hospital for further workup and management. During hospitalization, he revealed that he had been experiencing maroon-colored stools for the past two weeks and mild dysphagia for one week. While blood in his stool and difficulty swallowing were not his primary concerns on presentation, he became more concerned about his condition and wanted to know what was causing his symptoms. He underwent endoscopy for gastrointestinal bleeding. No source of bleeding was identified but he was incidentally found to have esophageal candidiasis. Laboratory studies revealed a CD4 count >500 and undetectable HIV RNA. An electrocardiogram acquired during his hospitalization showed Type I heart block with premature ventricular contractions and a prolonged QTc at 520. While fluconazole is the first line therapy for esophageal candidiasis in HIV positive patients¹ there was concern about the use of fluconazole in a patient with a prolonged QTc, as azole antifungals are QTc prolonging agents and can induce torsades de pointes.² The infectious disease service was consulted, which recommended intravenous anidulafungin for treatment of the patient's esophageal candidiasis. Anidulafungin is a member echinocandin class of antifungals and has not been shown to prolong QTc.³ The patient said he was amenable to whichever treatment was necessary and that his insurance would be able to cover most the costs associated with his hospitalization.

Clinical Question

Is anidulafungin an effective alternative to fluconazole for the treatment of esophageal candidiasis?

BLAKE S. SANFORD is an M.D./M.P.H. student at Wayne State University School of Medicine.



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Research Article

Krause DS, Simjee AE, van Rensburg C, et al. A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. *Clin Infect Dis.* 2004;39(6):770-775. doi: [10.1086/423378](https://doi.org/10.1086/423378)

Related Literature

A literature search was performed using Pubmed using the search term “anidulafungin esophageal candidiasis.” The search generated 32 results. 28 articles were excluded based on title and abstract not being relevant to the clinical question. Four articles were selected for further review.⁴⁻⁷

One of the articles was a systematic review by Vazquez on the management of oropharyngeal and esophageal candidiasis in HIV positive patients.⁴ While this article provided a useful overview of different treatments for oral and esophageal candidal infections in patients with HIV, the scope of the review was broader than the clinical question. Furthermore, the goal of this appraisal is to assess primary literature, not systematic reviews.

Another article by Vazquez, et al. was a phase-2 clinical trial on the efficacy of anidulafungin forazole refractory mucosal-candidiasis.⁵ The study supports the use of anidulafungin as a safe and effective therapy for the treatment of esophageal candidiasis. However, the study was not randomized, did not compare anidulafungin to standard therapy, and had a small sample size with only 19 patients. Furthermore, our patient had a contraindication toazole therapy, not refractory esophageal candidiasis, making this article less relevant to the care of our patient.

The literature search also included an article by Cross and Scott that reviewed the uses of micofungin for the treatment of invasive and esophageal candidiasis.⁶ While the findings of this review article suggest that micofungin is noninferior to fluconazole or caspofungin for the treatment of esophageal candidiasis, the clinical question was to evaluate whether anidulafungin specifically is an effective alternative to fluconazole.

Ultimately, a study by Krause, et al. that compared anidulafungin to fluconazole in the treatment of esophageal candidiasis was selected because it was a large, multicenter, double-blinded, randomized trial that compared anidulafungin to standard therapy and did not go beyond the scope of the clinical question.⁷ Additionally, it was the only article referenced in the systematic review by Vazquez that studied anidulafungin specifically.⁴

Critical Appraisal

This study was a multicenter, double-blinded, double-dummy, randomized trial with the goal of comparing the efficacy and safety of anidulafungin to fluconazole for the treatment of esophageal candidiasis.⁷ Adult patients ages 18-65 with esophageal candidiasis, as diagnosed by upper endoscopic findings, clinical symptoms, and biopsy, were recruited for the study. Major exclusion criteria included evidence of systemic fungal infection, ulcerative esophagitis, or known allergy to echinocandin medication. A total of 601 patients from South Africa, Thailand, Argentina, and the United States were enrolled. Patients were randomized into one of two treatment groups. 300 patients were given intravenous anidulafungin, 100mg loading dose followed by 50mg daily and an oral placebo daily. 301 patients were given oral fluconazole, 200mg loading dose followed by 100mg daily and an intravenous placebo given daily. Both treatment groups received treatment until seven days after resolution of symptoms for a minimum of 14 days and a maximum of 21 days. The primary outcome was endoscopic appearance. Secondary outcomes were clinical response, as defined by improvement in odontophagia, dysphagia, and retrosternal chest pain symptoms, and mycological improvement, as defined by eradication of candida species found at baseline.

A total of 504 patients complied with the study protocol and were eligible for efficacy analyses at the end of therapy. For the primary outcome of endoscopic appearance, 97.2% of patients receiving anidulafungin therapy experienced cure or improvement compared to 98.8% of those receiving fluconazole therapy (95% CI, -4.8% to 0.8%). Anidulafungin was considered to be noninferior to fluconazole for successful treatment of esophageal candidiasis because the lower bound of the 95% confidence interval was less than the predetermined limit of -10%. An intent-to-treat analysis revealed similar results with 86.7% of those treated with anidulafungin achieving treatment success compared to 88% of those treated with fluconazole (95% CI, -6.7% to 3.9%).



Both treatment groups also experienced similarly high success rates for secondary outcomes with 98.8% of the anidulafungin group experiencing symptomatic clinical success compared to 99.6% of the fluconazole group and 86.7% of the anidulafungin group experiencing mycological success, compared to 90.9% of the fluconazole group. Additionally, the adverse effect profiles were similar between the two treatments. Safety analysis performed on the intention to treat population showed similar rates of adverse effects in both treatment groups, with 9.3% of the anidulafungin group experiencing adverse effects and 12% of the fluconazole group.

Overall, this study appears to be a well-organized randomized trial. According to the Oxford Center for Evidence Based Medicine, this study meets criteria for Level 1b evidence as it is a randomized trial with a narrow confidence interval.⁸ The randomization of treatment groups reduced selection bias and the double blinded nature of the study helped to decrease potential observer bias. The double dummy model, in which the anidulafungin group received an oral placebo and the fluconazole group received an intravenous placebo, reduced potential bias from the placebo effect. 504/601 patients completed the study protocol, with a loss to follow up rate of 16.1%. While any loss to follow up may affect study results, the loss to follow up in this study was <20%, which is often regarded as acceptable.⁹ The study also used both efficacy analyses and an intent-to-treat analysis, which had similar outcomes, suggesting that differences in loss to follow up between groups did not affect study results.

With at least 300 patients in each study group, the study had an adequate sample size to reach a significant conclusion. The primary and secondary outcomes appear to be appropriate to address the stated goal of the study, and the exclusion of patients with fungal infection or ulcerative esophagitis reduced confounding. Randomization was successfully based on similar demographics between the two treatment groups and the use of a -10% difference between treatment groups as the efficacy margin for the noninferiority analysis was reasonable.¹⁰

The patient population of this study was similar to our patient because all study patients had esophageal candidiasis and most were HIV positive. Our patient did not meet any of the exclusion criteria. However, our patient failed to meet two of the inclusion criteria. He did not have AIDS or an active immunocompromising condition, and at 78-years-old, he was older than the age range of the study. Additionally, the majority of patients enrolled in this study were from South Africa and were not taking antiretroviral therapy, while our patient was African American and on antiretroviral therapy. Such differences may affect the applicability of the study results to our patient.

A shortcoming of this study is the criteria by which treatment success was defined. Treatment was considered successful if the patient experienced cure, defined as absence of esophageal lesions on endoscopy, or improvement in endoscopic appearance. When comparing cure rates alone, 88% of patients receiving anidulafungin experienced cure after treatment compared to 93.3% of patients receiving fluconazole. A confidence interval was not calculated. Thus, it cannot be concluded that anidulafungin is noninferior to fluconazole for cure of esophageal candidiasis, only for cure or improvement. Additionally, the study did not report the confidence intervals for the differences between the secondary outcomes. While the results of the secondary outcomes appear similar between the fluconazole and anidulafungin treatment groups, it is uncertain whether they are statistically significant.

Clinical Application

The findings of this study suggest that anidulafungin would be an effective alternative to fluconazole for the treatment of esophageal candidiasis in patients with contraindications to fluconazole therapy. The results demonstrate that anidulafungin is effective and noninferior to fluconazole in curing or improving endoscopic appearance, improving clinical symptoms, and achieving mycological success. The rates of adverse effects between the two treatments were also found to be similar. While anidulafungin therapy may be less effective than fluconazole in achieving complete cure of esophageal candidiasis, anidulafungin therapy still had a high cure rate at 88%. Of note, anidulafungin is significantly more expensive than fluconazole so anidulafungin treatment should be reserved for those unable to tolerate azole therapy.^{11,12}

Ultimately, it was decided to treat our patient with a 100mg loading-dose of intravenous anidulafungin followed by 50mg intravenous daily for seven days during his hospitalization. Though our patient did not match the demographics of the study population exactly, we still considered the study results to be robust and generalizable enough to apply to our patient. Within two days after the initiation of treatment, he said he was able to swallow food more easily. His melena resolved spontaneously and his hemoglobin and vital signs remained stable. Prior to

discharge, a repeat ECG revealed a QTc interval within normal limits at 416, so it was deemed safe to discontinue anidulafungin and complete treatment at home with oral fluconazole 200mg daily for 7 days. He agreed with the treatment plan and was discharged home.

Take Home points:

1. Anidulafungin is a safe and effective alternative to fluconazole for the treatment of esophageal candidiasis.
2. Treatment should include an intravenous loading-dose of anidulafungin followed by intravenous treatment daily for a minimum of 14 days.
3. Due to higher costs, anidulafungin should be reserved for patients unable to tolerate azole therapy.

References

1. 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-e50. doi: [10.1093/cid/civ933](https://doi.org/10.1093/cid/civ933)
2. Owens RC, Jr., Nolin TD. Antimicrobial-associated QT interval prolongation: points of interest. *Clin Infect Dis.* 2006;43(12):1603-1611. doi: [10.1086/508873](https://doi.org/10.1086/508873)
3. US Food and Drug Administration. *Highlights of Prescribing Information. ERAXIS™ (anidulafungin) For injection, for intravenous use Initial U.S. Approval: 2006.* https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021632s011lbl.pdf. Accessed April 16, 2018
4. Vazquez JA. Optimal management of oropharyngeal and esophageal candidiasis in patients living with HIV infection. *HIV/AIDS (Auckland, NZ).* 2010;2:89-101. doi: [10.2147/hiv.s6660](https://doi.org/10.2147/hiv.s6660)
5. Vazquez JA, Schranz JA, Clark K, Goldstein BP, Reboli A, Fichtenbaum C. A phase 2, open-label study of the safety and efficacy of intravenous anidulafungin as a treatment for azole-refractory mucosal candidiasis. *Journal of acquired immune deficiency syndromes.* 2008;48(3):304-309. doi: [10.1097/qai.0b013e31817af47a](https://doi.org/10.1097/qai.0b013e31817af47a)
6. Cross SA, Scott LJ. Micafungin: a review of its use in adults for the treatment of invasive and oesophageal candidiasis, and as prophylaxis against Candida infections. *Drugs.* 2008;68(15):2225-2255. doi: [10.2165/00003495-200868150-00010](https://doi.org/10.2165/00003495-200868150-00010)
7. Krause DS, Simjee AE, van Rensburg C, et al. A randomized, double-blind trial of anidulafungin versus fluconazole for the treatment of esophageal candidiasis. *Clin Infect Dis.* 2004;39(6):770-775. doi: [10.1086/423378](https://doi.org/10.1086/423378)
8. Oxford Center for Evidence Based Medicine. *Levels of Evidence.* <https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/>. Updated March 2009. Accessed April 16, 2018
9. Dettori JR. Loss to follow-up. *Evidence-based spine-care journal.* 2011;2(1):7-10. doi: [10.1055/s-0030-1267080](https://doi.org/10.1055/s-0030-1267080)
10. Althunian TA, de Boer A, Groenwold RHH, Klungel OH. Defining the noninferiority margin and analysing noninferiority: An overview. *British Journal of Clinical Pharmacology.* 2017;83(8):1636-1642. doi: [10.1111/bcp.13280](https://doi.org/10.1111/bcp.13280)
11. Good Rx. *Prices and coupons for 14 vials of Eraxis 50mg.* <https://www.goodrx.com/anidulafungin>. Updated 2018. Accessed August 12, 2018
12. Good Rx. *Prices and coupons for 1 tablet of fluconazole 150mg.* <https://www.goodrx.com/fluconazole?drug-name=fluconazole>. Updated 2018. Accessed August 12, 2018