



## Echinocandins

Updated: July 5, 2017.

### OVERVIEW

#### Introduction

The echinocandins include anidulafungin, caspofungin, and micafungin and are a relatively new class of antifungal agents that are administered parenterally and are used in therapy or prevention of serious, invasive aspergillosis and candidal infections. All three agents can cause transient and asymptomatic serum aminotransferase elevations, and individual instances of acute liver injury have been observed during therapy with these agents, but none has been definitely shown to cause clinically apparent acute drug induced liver injury.

#### Background

The echinocandins are a relatively new class of antifungal agents, whose activity is due to inhibition of glucan synthetase, the enzyme that is responsible for synthesis of  $\beta$ -1, 3-D-glucan, an essential component of the cell wall of filamentous fungi, such as *Aspergillus* and *Candida* species. This enzyme inhibition results in alteration in the fungal membrane integrity, followed by cell ballooning and, for *Candida* cells, lysis. Three echinocandins are available for use: caspofungin (kas" poe fun' jin), micafungin (mye" ka fun' jin) and anidulafungin (ay nid" ue la fun' jin). Caspofungin was approved for use in the United States in 2001, micafungin in 2005 and anidulafungin in 2006. All three are given intravenously and currently approved for therapy of esophageal candidiasis and for severe, disseminated or invasive candidiasis. Caspofungin is also approved for use as a secondary therapy of invasive aspergillosis and as empirical therapy for presumed fungal infection in febrile, neutropenic patients. Micafungin is also approved for prophylaxis against candidiasis in hematopoietic stem cell transplant recipients. Caspofungin is available under the brand name Cancidas in a formulation for intravenous use, the recommended dose in adults being 70 mg on the first day of treatment followed by 50 or 100 mg daily. Micafungin is available under the brand name of Mycamine in an intravenous formulation, the recommended dosage being 50 mg daily for prophylaxis and 100 to 150 mg daily for therapy of candidemia. Anidulafungin is available under the brand name of Eraxis in intravenous formulations and the recommended dosage for disseminated candidal infection is 200 mg on day 1 followed by 100 mg daily. The echinocandins are administered intravenously in a slow infusion over one hour (to decrease the risk of acute infusion reactions). Common side effects include phlebitis and the histamine-like reaction marked by rash, urticaria, flushing, bronchospasm, hypotension and facial swelling.

#### Hepatotoxicity

Transient elevations in liver enzymes have occurred in 2% to 15% of patients treated with the echinocandins, typically returning to baseline after withdrawal of therapy. Clinically apparent hepatotoxicity has occurred in

isolated cases; however, a causal relationship to the antifungal agent is often difficult to prove, as these agents are typically used in persons who are critically ill and have other conditions that are associated with liver injury. The largest experience has been with caspofungin, which may have a higher rate of serum enzyme elevations than with micafungin or anidulafungin and has more frequently been linked to cases of acute, symptomatic liver injury. Nevertheless, the product label for all three echinocandins mentions adverse events of serum enzyme elevations, hepatitis and acute liver failure.

Likelihood score: D (possible cause of clinically apparent liver injury).

## Mechanism of Injury

The cause of serum aminotransferase elevations during echinocandin therapy is unknown. In preclinical studies in animals, highest drug concentrations are found in the liver and a direct toxic effect or production of a toxic intermediate may be the cause of the abnormalities.

## Outcome and Management

The liver injury seen with caspofungin, micafungin and anidulafungin rarely progresses beyond mild serum enzyme elevations. Caution should be taken in patients with preexisting hepatic insufficiency in whom the likelihood of severe acute liver injury appears to be greatest. Product labels for the echinocandins recommend monitoring of liver tests during therapy, particularly in patients with underlying liver disease. The effects of rechallenge and cross reactivity to hepatic injury among the echinocandins has not been evaluated.

Drug Class: [Antifungal Agents](#)

## PRODUCT INFORMATION

### REPRESENTATIVE TRADE NAMES

Anidulafungin – Eraxis®

Caspofungin – Cancidas®

Micafungin – Mycamine®

### DRUG CLASS

Antifungal Agents

### COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

## CHEMICAL FORMULAS AND STRUCTURES

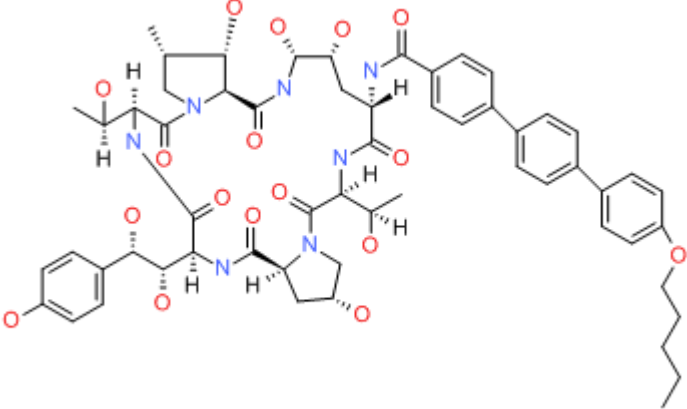
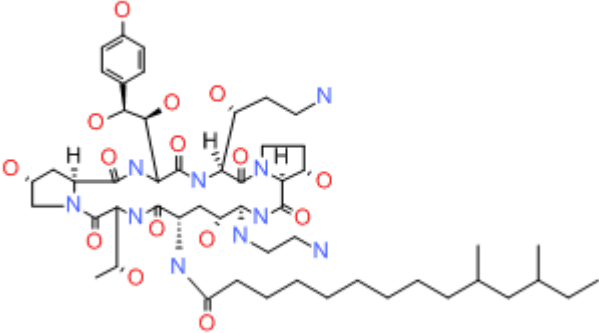
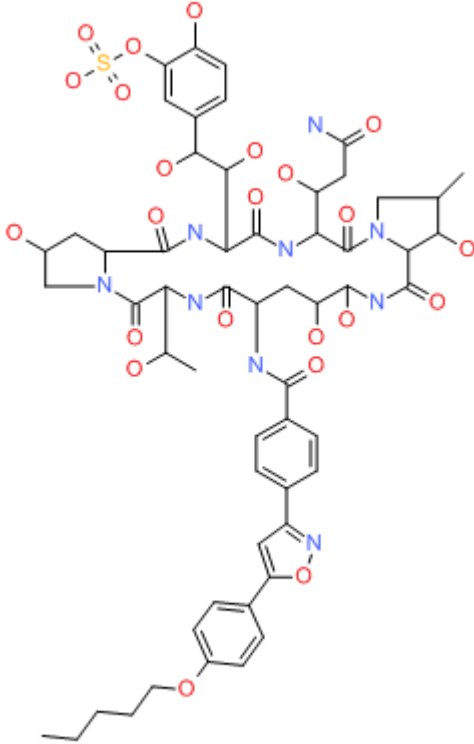
DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Anidulafungin	166663-25-8	C <sub>58</sub> -H <sub>73</sub> -N <sub>7</sub> -O <sub>17</sub>	 <p>The chemical structure of Anidulafungin is a complex polycyclic molecule. It features a central bicyclic core with multiple nitrogen atoms (blue) and carbonyl groups (red). The structure is highly branched and includes several aromatic rings, including a piperidine ring, a benzimidazole ring, and a phenyl ring. A long, flexible side chain is attached to the structure, consisting of a benzene ring, a piperidine ring, and a terminal piperidine ring with a long alkyl chain. The overall structure is highly complex and contains many stereocenters.</p>
Caspofungin	162808-62-0	C <sub>52</sub> -H <sub>88</sub> -N <sub>10</sub> -O <sub>15</sub>	 <p>The chemical structure of Caspofungin is a complex polycyclic molecule. It features a central bicyclic core with multiple nitrogen atoms (blue) and carbonyl groups (red). The structure is highly branched and includes several aromatic rings, including a piperidine ring, a benzimidazole ring, and a phenyl ring. A long, flexible side chain is attached to the structure, consisting of a benzene ring, a piperidine ring, and a terminal piperidine ring with a long alkyl chain. The overall structure is highly complex and contains many stereocenters.</p>

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DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Micafungin	235114-32-6	C <sub>56</sub> H <sub>71</sub> N <sub>9</sub> O <sub>23</sub> S	

## ANNOTATED BIBLIOGRAPHY

References updated: 05 July 2017

Zimmerman HJ. Antifungal agents. Hepatic injury from antimicrobial agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 609-11.

*(Expert review of hepatotoxicity of antifungal agents published in 1999 before availability of the echinocandins).*

Moseley RH. Antifungal agents. Hepatotoxicity of antimicrobials and antifungal agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 470-3.

*(Review of hepatotoxicity of antifungal agents; caspofungin was the first of a new class of parenterally administered antifungal agents; mentions that elevations in ALT levels occur in 2-4% of patients during caspofungin therapy and that adverse reactions are less frequent with micafungin and anidulafungin).*

Bennett JE. Antifungal agents. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1571-93.

*(Textbook of pharmacology and therapeutics; the echinocandins have activity against fungal organisms acting to inhibit glucan synthesis; the 3 agents in clinical use have similar mechanism of action, but different pharmacological properties).*

Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, Lupinacci R, et al.; Caspofungin Invasive Candidiasis Study Group. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med* 2002; 347: 2020-9. PubMed PMID: 12490683.

*(Controlled trial comparing caspofungin and amphotericin B in 224 adults with invasive candidiasis; similar efficacy but lower rate of side effects with caspofungin vs amphotericin: elevated ALT levels in 3.7% vs 8.1%, Alk P 8.3% vs 15.6%, bilirubin 2.8% vs 8.9%, but no serious hepatic adverse events attributed to either).*

Villanueva A, Gotuzzo E, Arathoon EG, Noriega LM, Kartsonis NA, Lupinacci RJ, Smietana JM, et al. A randomized double-blind study of caspofungin versus fluconazole for the treatment of esophageal candidiasis. *Am J Med* 2002; 113: 294-9. PubMed PMID: 12361815.

*(Among 177 patients with esophageal candidiasis treated with either caspofungin or fluconazole for 14-42 days, serum ALT and Alk P elevations were more frequent with fluconazole [12% and 12%] than anidulafungin [5% and 9%], but no patient developed clinically apparent liver injury).*

Marr KA, Hachem R, Papanicolaou G, Somani J, Arduino JM, Lipka CJ, Ngai AL, et al. Retrospective study of the hepatic safety profile of patients concomitantly treated with caspofungin and cyclosporin A. *Transpl Infect Dis* 2004; 6: 110-6. PubMed PMID: 15569226.

*(Retrospective study of 40 patients who received both caspofungin and cyclosporin A from 4 medical centers; 24 [60%] had at least one serum enzyme elevation and 4 [10%] stopped therapy because of hepatotoxicity; nevertheless, it was difficult to attribute the hepatic injury to caspofungin and "no severe hepatic adverse events were noted").*

Maertens J, Raad I, Petrikos G, Boogaerts M, Selleslag D, Petersen FB, Sable CA, et al.; Caspofungin Salvage Aspergillosis Study Group. Efficacy and safety of Caspofungin for treatment of invasive aspergillosis in patients refractory to or intolerant of conventional antifungal therapy. *Clin Infect Dis* 2004; 39: 1563-71. PubMed PMID: 15578352.

*(Experience in treating 83 patients with invasive aspergillosis with caspofungin for an average of 28 days; ALT elevations occurred in only one patient and no serious drug related hepatic adverse events were reported).*

Wagner C, Graninger W, Presterl E, Joukhadar C. The echinocandins: comparison of their pharmacokinetics, pharmacodynamics and clinical applications. *Pharmacology* 2006; 78: 161-77. PubMed PMID: 7047411.

*(Review of structure, pharmacology, clinical efficacy and safety of the echinocandins; elevations in ALT levels occur in up to 10% of patients treated with caspofungin, may be less with micafungin and anidulafungin).*

Bennett JE. Echinocandins for candidemia in adults without neutropenia. *N Engl J Med* 2006; 355: 1154-9. PubMed PMID: 16971721.

*(Concise review on use of echinocandins in invasive fungal infections; ALT elevations occur in 11% of patients receiving caspofungin; isolated cases of clinically significant hepatic injury have occurred, "although it is not clear whether they were drug-related").*

Reboli AC, Rotstein C, Pappas PG, Chapman SW, Kett DH, Kumar D, Betts R, et al.; Anidulafungin Study Group. Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med* 2007; 356: 2472-82. PubMed PMID: 17568028.

*(Among 245 patients with invasive candidiasis treated with either caspofungin or fluconazole for 14-42 days, serum enzyme elevations were more frequent with fluconazole [7%] than anidulafungin [1.5%]).*

Cappelletty D, Eiselstein-McKittrick K. The echinocandins. *Pharmacotherapy* 2007; 27: 369-88. PubMed PMID: 17316149.

*(Review of structure, pharmacokinetics, activity, clinical efficacy and side effects of the echinocandins; ALT elevations occur in 1-15% with caspofungin, 1-8% with micafungin, and 3-5% with anidulafungin).*

- Anttila VJ, Salonen J, Ylipalosaari P, Koivula I, Riikonen P, Nikoskelainen J. A retrospective nationwide case study on the use of a new antifungal agent: patients treated with caspofungin during 2001-2004 in Finland. *Clin Microbiol Infect* 2007; 13: 606-12. PubMed PMID: 17378926.
- (Retrospective analysis of 78 patients treated with caspofungin in Finland; 2 had severe hepatic toxicity, but the role of medication was uncertain as other factors were present, one patient died of acute liver failure after stopping caspofungin).*
- Chalasanani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. *Gastroenterology* 2008; 135: 1924-34. PubMed PMID: 18955056.
- (Among 300 cases of drug induced liver disease in the US collected between 2004 and 2008, 8 were attributed to antifungal agents, including 4 to terbinafine, 2 to fluconazole, 1 each to ketaconazole and itraconazole but none to the echinocandins).*
- Fortún J, Martín-Dávila P, Montejo M, Muñoz P, Cisneros JM, Ramos A, Aragón C, et al.; GESITRA Study Group. Prophylaxis with caspofungin for invasive fungal infections in high-risk liver transplant recipients. *Transplantation* 2009; 87: 424-35. PubMed PMID: 19202450.
- (Experience in using caspofungin for 21-90 days as prophylaxis against invasive fungal infections in 71 high risk liver transplant recipients; ALT elevations were frequent, but difficult to relate to drug because of the underlying condition).*
- Zaoutis TE, Jafri HS, Huang LM, Locatelli F, Barzilai A, Ebell W, Steinbach WJ, et al. A prospective, multicenter study of caspofungin for the treatment of documented *Candida* or *Aspergillus* infections in pediatric patients. *Pediatrics* 2009; 123: 877-84. PubMed PMID: 19255017.
- (Open label study of caspofungin for 2 to 87 days in 49 children with invasive fungal infections; ALT elevations occurred in 14.6%, all resolved despite continuation of therapy and none were clinically apparent).*
- Antifungal drugs. *Treat Guidel Med Lett* 2009; 7: 95-102. PubMed PMID: 19940816.
- (Concise summary of therapy of fungal infections with recommendations on agents, dosage and duration of treatment and safety; mentions that the echinocandins all have mild hepatic toxicities).*
- Menichetti F. Anidulafungin, a new echinocandin: effectiveness and tolerability. *Drugs* 2009; 69 Suppl 1: 95-7. PubMed PMID: 19877741.
- (Review of efficacy and safety of anidulafungin mentions that adverse events are uncommon, but include increases in GGT, ALT and AST levels).*
- King KY, Edwards MS, Word BM. Hepatitis associated with micafungin use in a preterm infant. *J Perinatol* 2009; 29: 320-2. PubMed PMID: 19325554.
- (Female premature newborn [HCV- and HIV-exposed] developed elevation in liver tests starting on day 2 of micafungin therapy, with peak on day 16 [bilirubin 16.3 mg/dL, ALT 860 U/L], liver tests improved gradually following discontinuation of drug).*
- Wang JL, Chang CH, Young-Xu Y, Chan KA. 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: 2409-19. PubMed PMID: 20308378.
- (Systematic review of 39 controlled trials in more than 8000 patients, found liver enzyme elevations in 14.5% of patients on amphotericin (pooled estimate); 19.7% on voriconazole; 18.9% itraconazole; 10% fluconazole; 2.8% anidulafungin; 7.2% caspofungin; and 5.7% micafungin).*
- Arrieta AC, Maddison P, Groll AH. Safety of micafungin in pediatric clinical trials. *Pediatr Infect Dis J* 2011; 30: e97-e102. PubMed PMID: 21378595.

*(Review of 6 clinical trials of micafungin in pediatric patients found 3% of 296 children developed “treatment related” ALT elevations, but no mention was made of clinically apparent liver injury).*

Cornely OA, Pappas PG, Young JA, Maddison P, Ullmann AJ. Accumulated safety data of micafungin in therapy and prophylaxis in fungal diseases. *Expert Opin Drug Saf* 2011; 10: 171-83. PubMed PMID: 21306282.

*(Review of pooled adverse event data from 17 clinical studies of micafungin in 3028 patients found 8.6% had treatment related hepatic adverse events, 2% had ALT elevations, 1% hyperbilirubinemia, 0.5% required treatment discontinuation, and 0.1% had hepatic failure, but no specifics given).*

Valerio M, Muñoz P, Bouza E. [Liver toxicity of micafungin. Is this drug safe?]. *Enferm Infecc Microbiol Clin* 2011; 29 Suppl 2: 29-32. Spanish. PubMed PMID: 21420574.

*(Review of safety of micafungin, mentions that ALT elevations occur in 7% of patients treated with caspofungin, 3% with micafungin and 2% with anidulafungin).*

Doria C, Bodzin AS, Vaccino S, Daskalakis C, Krawitz S, Ramirez CB. A retrospective analysis of the use of caspofungin in recipients of liver transplant with a modified high index of suspicion for fungal infection. A critical review of mortality, acute cellular rejection, infections, and changes in the liver function tests while on caspofungin. *Clin Transplant* 2011; 25: 569-75. PubMed PMID: 20662881.

*(Among 82 liver transplant recipients, 16 received caspofungin in the early posttransplant period for suspected invasive fungal infection, 3 [13%] of whom had transient rise in ALT or AST, but none of whom required dose modification).*

Yamaguchi M, Kurokawa T, Ishiyama K, Aoki G, Ueda M, Matano S, Takami A, et al. Efficacy and safety of micafungin as an empirical therapy for invasive fungal infections in patients with hematologic disorders: a multicenter, prospective study. *Ann Hematol* 2011; 90: 1209-17. PubMed PMID: 21695388.

*(Among 121 adults with hematologic disorders treated with micafungin for either febrile neutropenia or suspected invasive fungal infection, 4 [3.3%] developed ALT elevations and one developed jaundice).*

Goto N, Hara T, Tsurumi H, Ogawa K, Kitagawa J, Kanemura N, Kasahara S, et al. Efficacy and safety of micafungin for treating febrile neutropenia in hematological malignancies. *Am J Hematol* 2010; 85: 872-6. PubMed PMID: 20882524.

*(Among 53 patients with febrile neutropenia treated with micafungin, 6 developed AST elevations, but all were transient, mild [ $<3$  times ULN], and asymptomatic).*

Wang LL, Zhuge X, Xiao GH, Zhang Y. Hepatic safety of caspofungin during treatment of invasive fungal diseases in elderly patients. *Chin Med J (Engl)* 2012; 125: 2240. PubMed PMID: 22884162.

*(Among 50 patients above 80 years of age treated with caspofungin for invasive fungal disease, 21 had abnormal liver tests before treatment, of whom 3 [14%] worsened on therapy [1 mild and 2 severe] compared to 2 of 29 with normal liver tests initially, of whom 2 worsened [7%], but both were mild).*

León-Gil C, Ubeda-Iglesias A, Loza-Vázquez A, de la Torre MV, Raurich-Puigdevall JM, Alvarez-Sánchez B, Ortiz-Leyva C, et al; ProCAS Study Group. Efficacy and safety of caspofungin in critically ill patients. ProCAS Study. *Rev Esp Quimioter* 2012; 25: 274-82. PubMed PMID: 23303260.

*(Among 98 critically ill patients with severe fungal infections treated with caspofungin for 9-21 days, there were no significant changes in serum bilirubin, ALT or Alk P levels and no liver related serious adverse events).*

Ruhnke M, Paiva JA, Meersseman W, Pacht J, Grigoras I, Sganga G, Menichetti F, et al. Anidulafungin for the treatment of candidaemia/invasive candidiasis in selected critically ill patients. *Clin Microbiol Infect* 2012; 18: 680-7. PubMed PMID: 22404732.

*(Among 216 critically ill patients with invasive fungal infections treated with anidulafungin for 10 to 42 days, 3 [1.7%] developed AST elevations above 5 times ULN, but there were no liver related serious adverse events).*

Kohno S, Izumikawa K, Yoshida M, Takesue Y, Oka S, Kamei K, Miyazaki Y, et al. A double-blind comparative study of the safety and efficacy of caspofungin versus micafungin in the treatment of candidiasis and aspergillosis. *Eur J Clin Microbiol Infect Dis* 2013; 32: 387-97. PubMed PMID: 23052987.

*(Among 121 patients with invasive fungal infections randomized to receive either micafungin or caspofungin, ALT elevations occurred in 8.3% of caspofungin vs 6.7% of micafungin treated patients and were above 5 times ULN in 0% vs 3%, but no patient developed clinically apparent liver injury with jaundice).*

Kobayashi R, Suzuki N, Yoshida M, Iizuka S, Suzuki D, Sano H, Kudoh T. Efficacy and safety of micafungin for febrile neutropenia in pediatric patients with hematological malignancies: a multicenter prospective study. *J Pediatr Hematol Oncol* 2013; 35: e276-9. PubMed PMID: 23743960.

*(Among 25 children with 30 episodes of febrile neutropenia after cancer chemotherapy who were treated with micafungin for 6 to 47 days, ALT elevations occurred in 2, but were transient and mild, not requiring dose modification).*

Yamazaki S, Nakamura F, Yoshimi A, Ichikawa M, Nannya Y, Kurokawa M. Safety of high-dose micafungin for patients with hematological diseases. *Leuk Lymphoma* 2014 Mar 7. [Epub ahead of print] PubMed PMID: 24460099.

*(Retrospective analysis of safety of two doses of micafungin for invasive fungal infections, found any elevation in ALT in 26% of 58 recipients of standard dose [150 mg/day; n=58] vs 27% of 26 recipients of high dose [300 mg/day], and elevations above 5 times ULN in only 1 patient in each group).*

Chalasan N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. *Gastroenterology* 2015; 148: 1340-52. PubMed PMID: 25754159.

*(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to an echinocandin).*

Jung DS, Tverdek FP, Jiang Y, Kontoyiannis DP. Switching to anidulafungin from caspofungin in cancer patients in the setting of liver dysfunction is associated with improvement of liver function tests. *J Antimicrob Chemother* 2015; 70: 3100-6. PubMed PMID: 26311837.

*(In a retrospective study of 61 patients who developed abnormal liver tests during treatment with caspofungin and were then switched to anidulafungin, values improved overall, mean ALT falling from 132 to 71 U/L and bilirubin from 2.5 to 2.2 mg/dL, suggesting that anidulafungin is less hepatotoxic than caspofungin).*

Kyriakidis I, Tragiannidis A, Munchen S, Groll AH. Clinical hepatotoxicity associated with antifungal agents. *Expert Opin Drug Saf* 2017; 16: 149-65. PubMed PMID: 27927037.

*(Review of the hepatotoxicity of antifungal agents discusses the frequency of serum enzyme elevations during anidulafungin, caspofungin and micafungin therapy but not clinically apparent liver injury).*