

Evaluation of the In Vitro Activity of CD101, a Novel Echinocandin, and Comparators Against Recent Clinical Isolates of *Candida* spp.

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Abstract (Amended)

Background: CD101, a novel echinocandin with an extended half-life, is currently undergoing development for the treatment of candidemia and other forms of invasive candidiasis. To understand the in vitro activity profile of CD101, the MICs of CD101 and antifungal comparators were determined against 500 recent clinical isolates of *Candida* spp. including *C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, and *C. krusei*.

Methods: MICs were determined by broth microdilution in accordance with CLSI M27-A3, M27-S3, and M27-S4. The 500 test isolates (470 US isolates from 2012-2015; 30 non-US *C. krusei* from 2005-2006) included 100 recent clinical isolates of each *Candida* species. Relevant quality control strains were included during testing. Test agents included CD101, anidulafungin, micafungin, caspofungin, amphotericin B, fluconazole, and voriconazole.

Results: Activity is summarized in the table below.

Agent	MIC ₅₀ /MIC ₉₀ (µg/mL); %S				
	<i>C. albicans</i>	<i>C. tropicalis</i>	<i>C. parapsilosis</i>	<i>C. glabrata</i>	<i>C. krusei</i>
CD101	0.008/0.03; NA	0.008/0.03; NA	1/1; NA	0.03/0.03; NA	0.03/0.03; NA
Anidulafungin	0.004/0.008; 100%	0.004/0.015; 98.0%	0.5/2; 100%	0.03/0.03; 95.0%	0.03/0.03; 100%
Micafungin ¹	0.06/0.12; 100%	0.12/0.25; 100%	2/4; 84.0%	0.06/0.12; 98.0%	0.5/0.5; 100%
Caspofungin ¹	0.12/0.25; 99.0%	0.12/0.5; 100%	0.5/1; 100%	0.12/0.5; 98.0%	0.25/0.5; 100%
Amphotericin B	0.25/0.5; NA	0.5/1; NA	0.5/1; NA	0.5/0.5; NA	1/1; NA
Fluconazole	0.25/4; 88.0%	0.5/2; 90.0%	0.5/1; 96.0%	8/>32; NA	32/>32; NA
Voriconazole	0.008/0.5; 88.0%	0.03/0.12; 92.0%	0.015/0.03; 98.0%	0.5/>2; NA	0.25/0.5; 93.9%

¹CLSI M27-S3 interpretive criteria applied; water used as solvent
%S: % susceptible, NA: not applicable

CD101 had potent MICs similar to anidulafungin and lower than micafungin and caspofungin across the evaluated species. Echinocandin resistance was rarely encountered. CD101 MICs were elevated against the few echinocandin-resistant isolates (typically at 0.5 – 1 µg/mL). There was no impact of resistance to azoles on CD101 or comparator echinocandin activity.

Conclusions: CD101 was very active against the collection of recent clinical *Candida* spp. evaluated in this study, with potency similar to that of anidulafungin. CD101 activity was not impacted by resistance to azoles. As was the case with comparator echinocandins, CD101 MICs were elevated against the infrequently encountered echinocandin-resistant *Candida* isolates. These results demonstrate the potency of CD101 and the echinocandin class against recent clinical *Candida* spp.

Introduction

• CD101 is a novel echinocandin with a long half-life currently under development by Cidara Therapeutics, Inc. for the treatment of candidemia and other forms of invasive candidiasis.

• As part of the ongoing development of CD101, it is important to evaluate the *in vitro* activity of CD101 relative to comparators against large volumes of clinical isolates.

• In this study, the susceptibility of recent clinical isolates of prevalent *Candida* spp. (*C. albicans*, *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, and *C. krusei*) to CD101 and comparators, including the echinocandins anidulafungin, micafungin, and caspofungin, was evaluated by broth microdilution.

Objective

To establish the baseline *in vitro* activity profile of CD101 against target *Candida* spp. relative to other echinocandins and antifungals using a recent, representative population of isolates.

Methods

• Test isolates for MIC testing included clinical isolates from the Micromyx Repository (Kalamazoo, MI).

• A total of 100 each of *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* were tested.

• Of the tested isolates, 470 were isolated in the US from 2012-2015 and 30 were isolated outside of the US from 2005-2006.

• Tested isolates included standard quality control isolates from the American Type Culture Collection (ATCC; Manassas, VA).

• The susceptibility of test isolates to CD101 and comparators (anidulafungin, micafungin, caspofungin, amphotericin B, fluconazole, and voriconazole) was determined by broth microdilution in accordance with CLSI guidelines M27-A3¹ and M27-S3² in Roswell Park Memorial Institute (RPMI) media.

• MICs were reported based on 50% inhibition (MIC₅₀) for echinocandins and azoles and 100% inhibition (MIC₁₀₀) for amphotericin B. Echinocandins and amphotericin B were read after 24 hr incubation; azoles were read after 48 hr of incubation.

• With the exception of micafungin and caspofungin, which were dissolved in H₂O per M27-S3² as opposed to DMSO per M27-S4³, the reported susceptibility of isolates was based on the species-specific breakpoints in M27-S4³.

Results

C. albicans (Table 1, Figure 1; n=100)

• CD101 had an MIC₅₀/MIC₉₀ of 0.008/0.03 µg/mL, slightly higher than that of anidulafungin (0.004/0.008 µg/mL) and several-fold lower than micafungin (0.06/0.12 µg/mL) and caspofungin (0.12/0.25 µg/mL).

• *C. albicans* were highly susceptible (≥99% S) to the evaluated echinocandin comparators.

• Fluconazole and voriconazole had an MIC₅₀/MIC₉₀ of 0.25/4 and 0.008/0.5 µg/mL, respectively. Some resistance to azoles was noted (10% and 9%, respectively).

• 97% of isolates had amphotericin B MICs of 0.25 – 0.5 µg/mL.

Results

C. tropicalis (Table 1, Figure 2; n=100)

• CD101 had an MIC₅₀/MIC₉₀ of 0.008/0.03 µg/mL, similar to that of anidulafungin (0.004/0.015 µg/mL) and several-fold lower than micafungin (0.12/0.25 µg/mL) and caspofungin (0.12/0.5 µg/mL).

• *C. tropicalis* were highly susceptible (≥98% S) to the evaluated echinocandin comparators.

• Fluconazole and voriconazole had an MIC₅₀/MIC₉₀ of 0.5/2 and 0.03/0.12 µg/mL, respectively. Some resistance to azoles was noted (9% and 7%, respectively).

• 94% of isolates had amphotericin B MICs of 0.5 – 1 µg/mL.

C. parapsilosis (Table 1, Figure 3; n=100)

• CD101 had an MIC₅₀/MIC₉₀ of 1/1 µg/mL, similar to that of anidulafungin (0.5/2 µg/mL) and caspofungin (0.5/1 µg/mL), and lower than that observed with micafungin (2/4 µg/mL).

• *C. parapsilosis* were 100% susceptible to caspofungin and anidulafungin and 84% susceptible to micafungin. This disparity likely reflects a methodological issue as variation in susceptibility among echinocandins for *Candida* spp. is rare.³

• Fluconazole and voriconazole had an MIC₅₀/MIC₉₀ of 0.5/1 and 0.015/0.03 µg/mL, respectively, with little resistance observed (3% and 1%, respectively).

• 99% of isolates had amphotericin B MICs of 0.25 – 1 µg/mL.

C. glabrata (Table 1, Figure 4; n=100)

• CD101 had an MIC₅₀/MIC₉₀ of 0.03/0.03 µg/mL, identical to that of anidulafungin and lower than that observed with micafungin (0.06/0.12 µg/mL) and caspofungin (0.12/0.5 µg/mL).

• *C. glabrata* were highly susceptible (≥95% S) to the evaluated echinocandin comparators.

• For the rare echinocandin-resistant isolates (n=5), CD101 MICs were elevated (0.5 – 4 µg/mL) relative to echinocandin-susceptible isolates (0.008 – 0.06 µg/mL).

• Fluconazole and voriconazole had an MIC₅₀/MIC₉₀ of 8/>32 and 0.5/>2 µg/mL, respectively, with 18% resistant to fluconazole. Echinocandin activity was not impacted by fluconazole resistance.

• 90% of isolates had amphotericin B MICs of 0.25 – 0.5 µg/mL.

C. krusei (Table 1, Figure 5; n=100)

• CD101 had an MIC₅₀/MIC₉₀ of 0.03/0.03 µg/mL, identical to that of anidulafungin and 8- to 16-fold lower than micafungin (0.5/0.5 µg/mL) and caspofungin (0.25/0.5 µg/mL).

• *C. krusei* were 100% susceptible to the evaluated echinocandin comparators.

• Fluconazole and voriconazole had an MIC₅₀/MIC₉₀ of 32/>32 and 0.25/0.5 µg/mL, respectively, with 2% resistant to voriconazole.

• 98% of isolates had amphotericin B MICs of 0.5 – 1 µg/mL.

Table 1. Summary of Activity by MIC

Organism	Drug	MIC Range	MIC ₅₀	MIC ₉₀	%S	%R
<i>C. albicans</i>	CD101	0.002 - 0.5	0.008	0.03	NA	NA
	Anidulafungin	≤0.001 - 0.25	0.004	0.008	100	0.0
	Micafungin	0.008 - 2	0.06	0.12	100 ¹	NA
	Caspofungin	0.03 - 4	0.12	0.25	99.0 ¹	NA
	Amphotericin B	0.12 - 1	0.25	0.5	NA	NA
	Fluconazole	≤0.03 - >32	0.25	4	88.0	10.0
<i>C. tropicalis</i>	Voriconazole	≤0.002 - >2	0.008	0.5	88.0	9.0
	CD101	≤0.001 - 0.5	0.008	0.03	NA	NA
	Anidulafungin	≤0.001 - 0.5	0.004	0.015	98.0	98.0
	Micafungin	0.008 - 2	0.12	0.25	100 ¹	NA
	Caspofungin	0.03 - 2	0.12	0.5	100 ¹	NA
	Amphotericin B	0.25 - 1	0.5	1	NA	NA
<i>C. parapsilosis</i>	Fluconazole	0.06 - >32	0.5	2	90.0	9.0
	Voriconazole	≤0.002 - >2	0.03	0.12	92.0	7.0
	CD101	0.004 - 2	1	1	NA	NA
	Anidulafungin	0.004 - 2	0.5	2	100.0	100.0
	Micafungin	0.06 - 4	2	4	84.0 ¹	NA
	Caspofungin	0.06 - 2	0.5	1	100 ¹	NA
<i>C. glabrata</i>	Amphotericin B	0.12 - >16	0.5	1	NA	NA
	Fluconazole	0.25 - 16	0.5	1	96.0	3.0
	Voriconazole	≤0.002 - 1	0.015	0.03	98.0	1.0
	CD101	0.008 - 4	0.03	0.03	NA	NA
	Anidulafungin	0.004 - 2	0.03	0.03	95.0	5.0
	Micafungin	0.015 - 4	0.06	0.12	98.0 ¹	NA
<i>C. krusei</i>	Caspofungin	0.03 - >16	0.12	0.5	98.0 ¹	NA
	Amphotericin B	0.12 - 1	0.5	0.5	NA	NA
	Fluconazole	0.5 - >32	8	>32	NA	18.0
	Voriconazole	0.015 - >2	0.5	>2	NA	NA
	CD101	0.008 - 0.06	0.03	0.03	NA	NA
	Anidulafungin	0.004 - 0.06	0.03	0.03	100	100

¹ CLSI M27-S3² criteria applied; water used as solvent
² voriconazole tested against 99 *C. krusei* only
NA: not applicable

Figure 1. MIC Distribution of Echinocandins – *C. albicans*

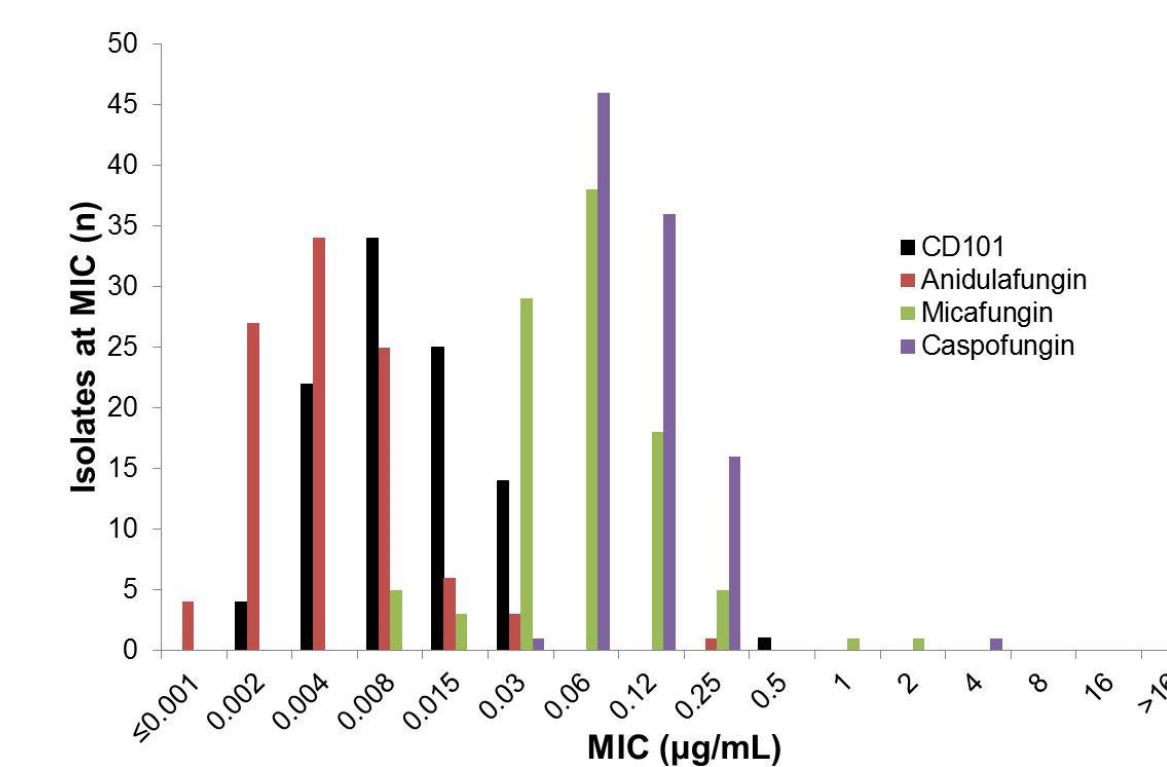


Figure 2. MIC Distribution of Echinocandins – *C. tropicalis*

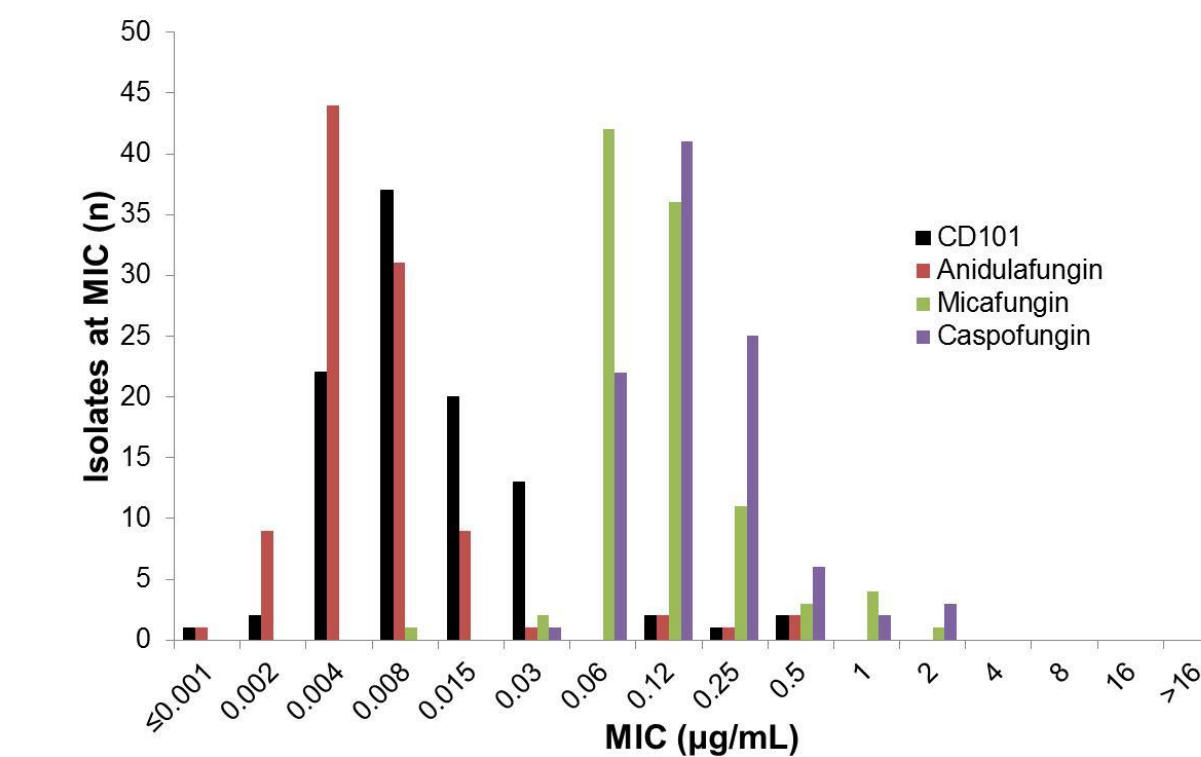


Figure 3. MIC Distribution of Echinocandins – *C. parapsilosis*

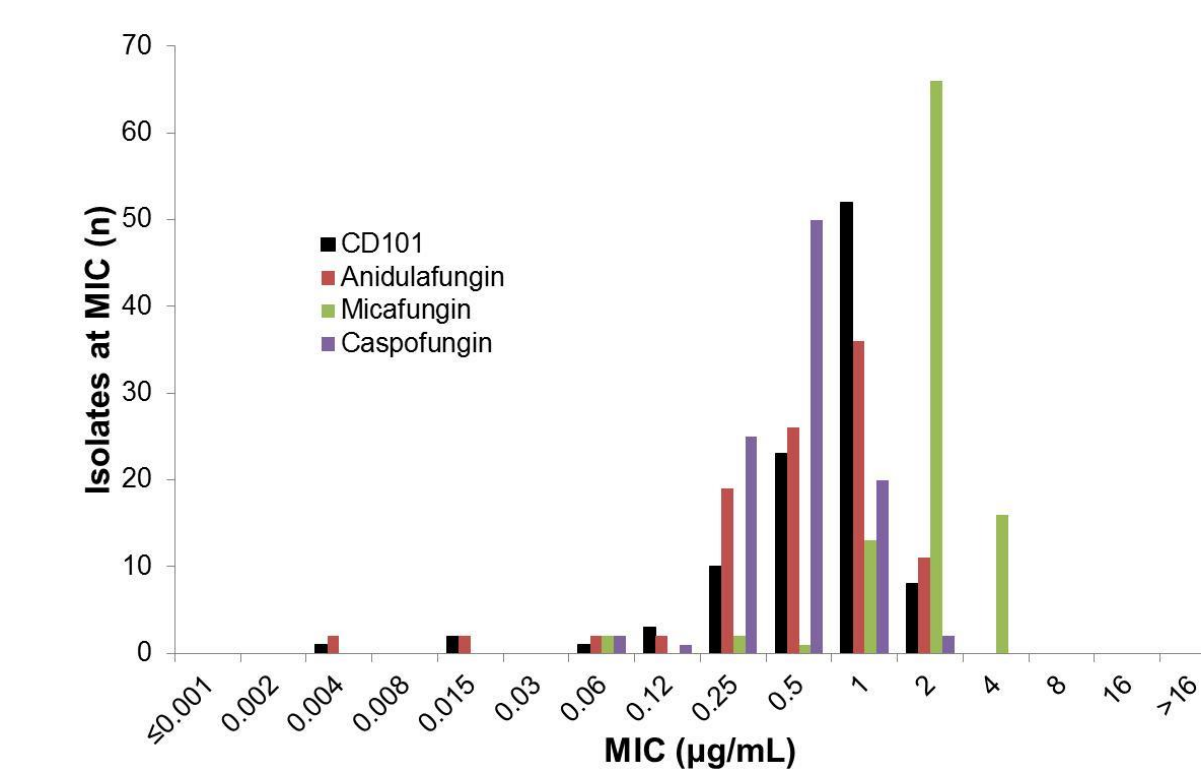


Figure 4. MIC Distribution of Echinocandins – *C. glabrata*

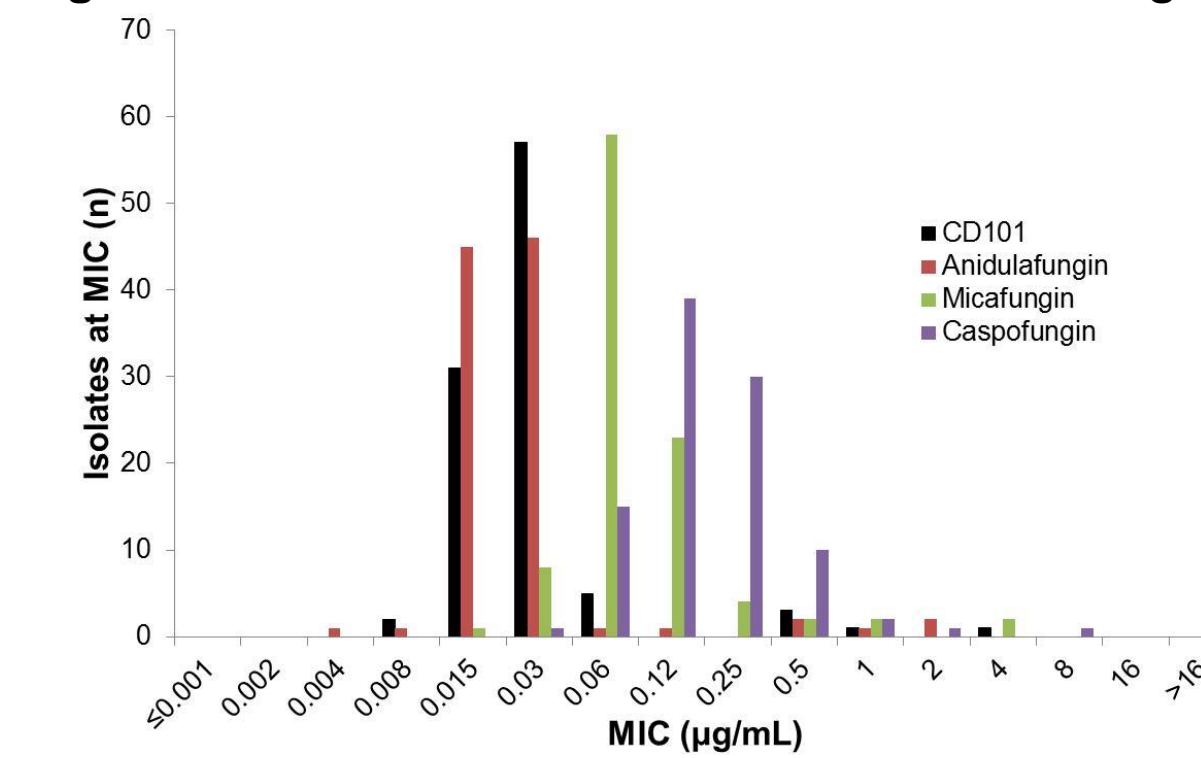
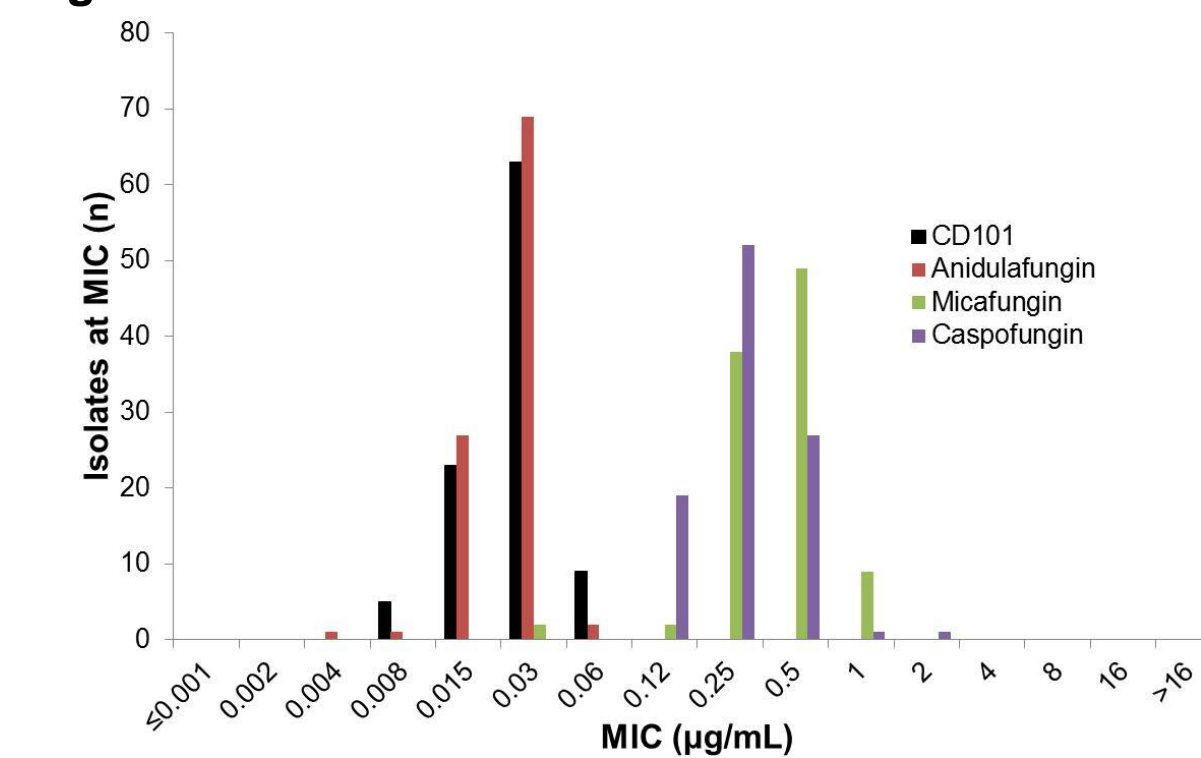


Figure 5. MIC Distribution of Echinocandins – *C. krusei*



Conclusions

• CD101 had potent activity against the evaluated *Candida* spp., with potency comparable to anidulafungin and greater than micafungin and caspofungin.

• It is important to note that variation in *in vitro* potency does not necessarily translate to variation in clinical efficacy with respect to echinocandins and *Candida* spp., and may reflect the use of water vs. DMSO as solvent for these agents.

• The evaluated isolates were highly susceptible to the members of the echinocandin class tested in this study.

• The activity of CD101 was not notably impacted by resistance to azoles.

• For the few echinocandin-resistant isolates, CD101 MICs were elevated relative to echinocandin-susceptible isolates.

• These results demonstrate the potency of CD101 and the echinocandin class against recent *Candida* spp. of US origin.

Acknowledgements

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References

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