Breakpoints and ECVs - Use and limitations

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Thanks to Dr. Ota & Dr. Potula

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Case

- 77 y.o. male with a history of Hep C and heart failure, presenting to ED with inability to walk. Patient states he cannot walk secondary to back pain and weakness in his legs starting 3 months ago. His son also reports decline and weight loss over the past several months.

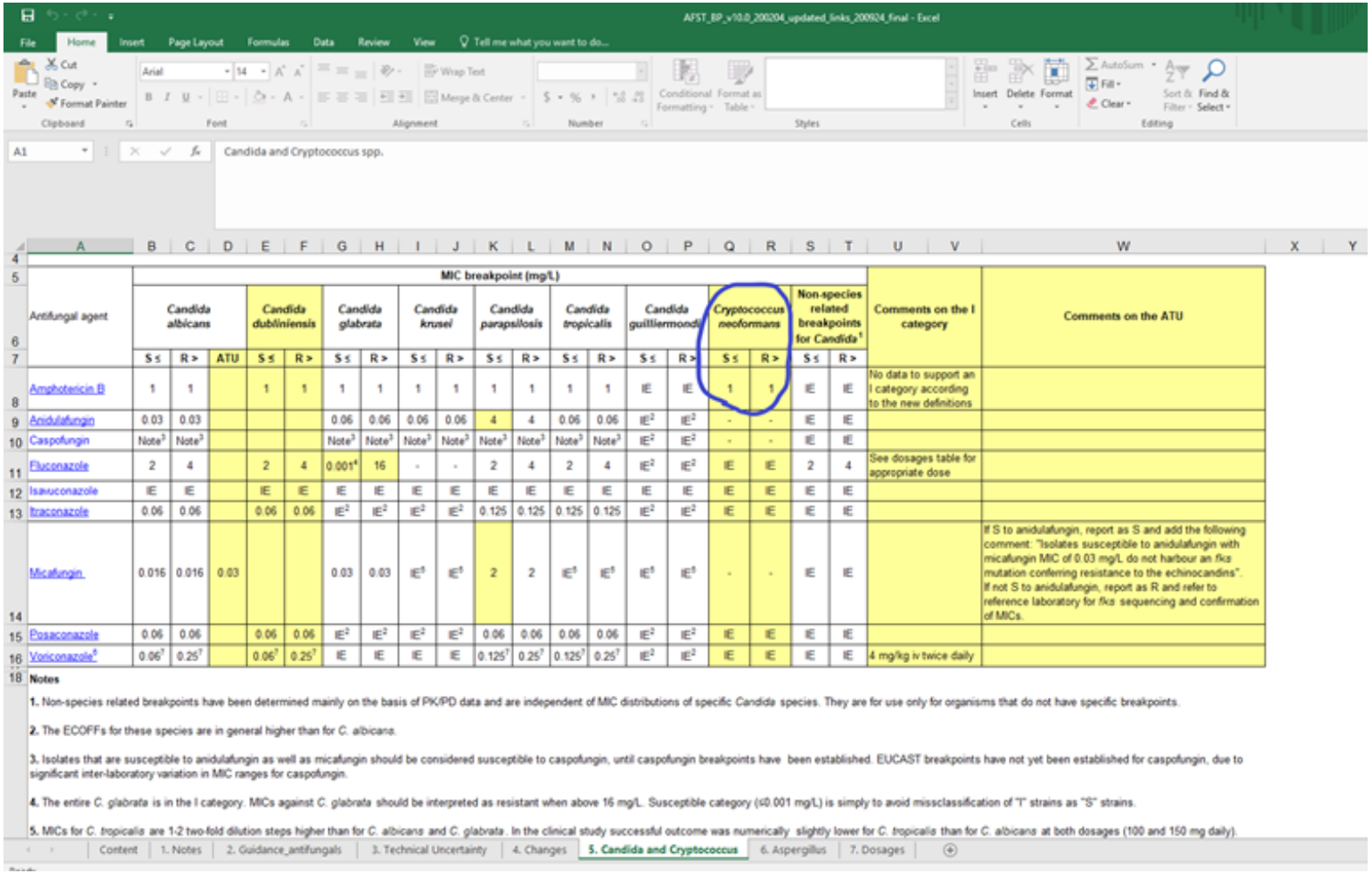
- Blood culture was positive for a budding yeast, and cryptococcal antigen returned strongly positive.
- The diagnosis of cryptococcal meningitis was made and he was started on Amphotericin B and Flucytosine.

Organism identified by client.
There are no established interpretive guidelines for agents reported without interpretations.
Organism: CRYPTOCOCCUS NEOFORMANS species complex
Antibiotic MIC (mcg/mL) Interpretation
Anidulafungin >8
Amphotericin B 1
Caspofungin >8
Fluconazole 4
5-flucytosine 4
Itraconazole 0.12
Micafungin >8
Posaconazole 0.12
Voriconazole 0.03
Amphotericin B: This MIC is consistent with the Epidemiological Cutoff Value (ECV) observed in isolates WITH acquired resistance; however, correlation with treatment outcome is unknown.
Fluconazole: This MIC is consistent with the Epidemiological Cutoff Value (E V) observed in isolates WITHOUT acquired resistance; ho ver, correlation with treatment outcome is unknown.
5-flucytosine: Flucytosine shoul [illegible] monotherapy due to the potential of existing or emerging resistance. This MIC is consistent with the Epidemiological Cutoff Value (ECV) observed in isolates WITHOUT acquired resistance; however, correlation with treatment outcome is unknown.
Itraconazole: This MIC is consistent with the Epidemiological Cutoff Value (ECV) observed in isolates WITHOUT acquired resistance; however, correlation with treatment outcome is unknown.
Posaconazole: This MIC is consistent with the Epidemiological Cutoff Value (ECV) observed in isolates WITHOUT acquired resistance; however, correlation with treatment outcome is unknown.
Voriconazole: This MIC is consistent with the Epidemiological Cutoff Value (ECV) observed in isolates

Table 2. Epidemiological Cutoff Values for *In Vitro* Susceptibility Testing of Various *Cryptococcus* spp. With No Breakpoints[*1-5]

Antifungal Agent	Species (Genotype)	ECV, µg/mL[†,‡]
Amphotericin B	*C. neoformans* (VNI)	0.5
	C. gattii (VGI)	0.5
	C. gattii (VGII)	1
Fluconazole	*C. neoformans* (VNI)	8
	C. gattii (VGI)	16
	C. gattii (VGII)	32
Flucytosine	*C. neoformans* (VNI)	8
	C. gattii (VGI)	4
	C. gattii (VGII)	32
Itraconazole	*C. neoformans* (VNI)	0.25
	C. gattii (VGI)	0.5
	C. gattii (VGII)	1
Posaconazole	*C. neoformans* (VNI)	0.25
Voriconazole	*C. neoformans* (VNI)	0.25
	C. gattii (VGI)	0.5
	C. gattii (VGII)	0.5

[*] ECVs were adopted by the Subcommittee on Antifungal Susceptibility Tests during a Web conference in May 2016. The ECVs for *Cryptococcus* were established against the distinct molecular types. The phylogeny for *Cryptococcus* is currently in transition. VGI and VGII are molecular genotypes of *C. gattii* that can be recognized only by molecular typing of isolates by polymerase chain reaction or DNA sequencing–based methods including multilocus sequence typing and amplified



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A1 | Candida and Cryptococcus spp.

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S	T	U	V	W	X	Y
4																									
5		MIC breakpoint (mg/L)																							
6	Antifungal agent	*Candida albicans*			*Candida dubliniensis*		*Candida glabrata*		*Candida krusei*		*Candida parapsilosis*		*Candida tropicalis*		*Candida guilliermondi*		*Cryptococcus neoformans*		Non-species related breakpoints for *Candida*[1]		Comments on the I category		Comments on the ATU		
7		S ≤	R >	ATU	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >	S ≤	R >					
8	Amphotericin B	1	1		1	1	1	1	1	1	1	1	1	1	IE	IE	1	1	IE	IE	No data to support an I category according to the new definitions				
9	Anidulafungin	0.03	0.03				0.06	0.06	0.06	0.06	4	4	0.06	0.06	IE[2]	IE[2]	-	-	IE	IE					
10	Caspofungin	Note[3]	Note[3]				Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	Note[3]	IE[2]	IE[2]	-	-	IE	IE					
11	Fluconazole	2	4		2	4	0.001[4]	16	-	-	2	4	2	4	IE[2]	IE[2]	IE	IE	2	4	See dosages table for appropriate dose				
12	Isavuconazole	IE	IE		IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE	IE					
13	Itraconazole	0.06	0.06		0.06	0.06	IE[2]	IE[2]	IE[2]	IE[2]	0.125	0.125	0.125	0.125	IE[2]	IE[2]	IE	IE	IE	IE					
14	Micafungin	0.016	0.016	0.03			0.03	0.03	IE[5]	IE[5]	2	2	IE[5]	IE[5]	IE[5]	IE[5]	-	-	IE	IE			If S to anidulafungin, report as S and add the following comment: "Isolates susceptible to anidulafungin with micafungin MIC of 0.03 mg/L do not harbour an *fks* mutation conferring resistance to the echinocandins". If not S to anidulafungin, report as R and refer to reference laboratory for *fks* sequencing and confirmation of MICs.		
15	Posaconazole	0.06	0.06		0.06	0.06	IE[2]	IE[2]	IE[2]	IE[2]	0.06	0.06	0.06	0.06	IE[2]	IE[2]	IE	IE	IE	IE					
16	Voriconazole[6]	0.06[7]	0.25[7]		0.06[7]	0.25[7]	IE	IE	IE	IE	0.125[7]	0.25[7]	0.125[7]	0.25[7]	IE[2]	IE[2]	IE	IE	IE	IE	4 mg/kg iv twice daily				
18	**Notes**																								

1. Non-species related breakpoints have been determined mainly on the basis of PK/PD data and are independent of MIC distributions of specific *Candida* species. They are for use only for organisms that do not have specific breakpoints.

2. The ECOFFs for these species are in general higher than for *C. albicans*.

3. Isolates that are susceptible to anidulafungin as well as micafungin should be considered susceptible to caspofungin, until caspofungin breakpoints have been established. EUCAST breakpoints have not yet been established for caspofungin, due to significant inter-laboratory variation in MIC ranges for caspofungin.

4. The entire *C. glabrata* is in the I category. MICs against *C. glabrata* should be interpreted as resistant when above 16 mg/L. Susceptible category (≤0.001 mg/L) is simply to avoid missclassification of "I" strains as "S" strains.

5. MICs for *C. tropicalis* are 1-2 two-fold dilution steps higher than for *C. albicans* and *C. glabrata*. In the clinical study successful outcome was numerically slightly lower for *C. tropicalis* than for *C. albicans* at both dosages (100 and 150 mg daily).

Content | 1. Notes | 2. Guidance_antifungals | 3. Technical Uncertainty | 4. Changes | 5. Candida and Cryptococcus | 6. Aspergillus | 7. Dosages

MIC

- Lowest concentration of an antimicrobial that will prevent the growth of an organism in vitro.

Breakpoint

- The value that is used for determining whether or not a microorganism is likely to respond in vivo to an antimicrobial.

ECV

- The value that separates a population into isolates with and those without mutational resistance. (Wild type or non-wild type).

How is a breakpoint generated?

- ECV values
- Pharmacokinetics/dynamic studies
- Data from clinical trials

Drawbacks:

- Difficult and expensive
- For fungi, there are not enough cases available to perform a clinical trial.

Usefulness of ECVs

- No breakpoints
- Predicts if an isolate has possible resistance to an antifungal agent
- Must always be interpreted in conjunction with treatment

Should the patient switch medications?

- Patient was responding to Amphotericin B and antigen titers were dropping
- ECV implies that he has an isolate possibly resistant to Amphotericin B
- Next step? - Continue the same treatment regimen

Thank you