

## CASPOFUNGIN (CSP): WHAT MEASURES RESISTANCE?

Hernandez S, Najvar L, Lopez-Ribot J, McCarthy D, Bocanegra R, Graybill JR, UT Health Sciences Center, San Antonio, United States

**BACKGROUND:** There are no clear in vitro standards which predict clinical response to CSP. Resistant isolates are few and tend to be laboratory mutants which are avirulent in mice. We present a patient with rising MIC to CSP and clinical failure. We evaluated 3 sequential isolates of *C. albicans* in mice to determine whether this model could predict in vivo failure.

**METHODS:** A patient with HIV associated *C. albicans* esophagitis sequentially failed multiple antifungals, including fluconazole (FLU) and other triazoles. He then responded to 4 weeks with CSP at 50 mg/day. Later he relapsed, and then failed second course of CSP. Isolate 1 was pre-CSP; isolate 2 followed a successful 4 week CSP treatment; isolate 3 was post CSP failure. MIC values were done by NCCLS M27-A methods. Groups of 8-10 mice were infected intravenously with *C. albicans* and treated with water (controls) PO, FLU at 5 mg/kg PO BID or increasing doses of CSP intraperitoneally. Mann Whitney test was used to compare kidney counts. \*= $p < 0.05$  treatment versus control (0 drug). Values are  $\mu\text{g/ml}$  for MIC at 48hrs and median  $\log_{10}$  CFU/kidney/mouse.

RESULTS:	MIC	INCREASING DOSE OF CSP in mg/kg						
		FLU	5	0	0.0625	0.125	0.250	0.50
Isolate 1	0.25	5.9	5.8	5.1*	4.0*	3.8*	2.6*	3.0*
Isolate 2	0.25	6.0						
		5.6	4.8	2.5*	2.2*	1.9*	1.8*	
Isolate 3 (pulled studies)		<64	5.5	5.4	5.2	5.3	5.3	
	5.0	4.5*						

Mice infected with isolate 3, (clinical failure and CSP MIC of  $<64 \mu\text{g/ml}$ ) required a much higher dose of CSP to reduce kidney counts.

**CONCLUSIONS:** In this patient, a high MIC to CSP was associated with clinical failure. The resistant isolate 3 was virulent in mice (unlike prior lab mutants) and required 1 mg/kg CSP to reduce kidney counts. Thus, the in vitro and animal studies are consistent with the clinical course. The fact that 1 mg/kg CSP did reduce kidney counts suggested that higher doses of CSP may be effective in treatment of more resistant isolates.