Development and Evaluation of an Experimental Model of Invasive Candidiasis caused by *Candida auris*

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BACKGROUND & OBJECTIVE

- *Candida auris* is an emerging cause of invasive candidiasis, primarily observed in immunocompromised individuals with multiple co-morbidities
- High rates of antifungal resistance, including multi-drug resistance isolates, have been reported
- High mortality rates have been reported, and treatment options may be limited
- Animal models of invasive disease are needed to evaluate novel therapeutic strategies
- Our objective was to develop and evaluate a murine model of invasive candidiasis due to *C. auris*. This model must be amendable to evaluating responses to treatment with antifungals, including investigational agents.

MATERIALS & METHODS

- Immunocompetent and neutropenic ICR mice were used
- Mice were rendered neutropenic by 5-fluorouracil (150 mg/kg IV x1) 1 day prior to inoculation via the lateral tail vein
- The virulence of two clinical bloodstream isolates of *C. auris* (UTHSCSA DI17-46 and DI17-47) was assessed over a range of inocula.
- To assess response to therapy, neutropenic mice infected with DI17-46 were treated with oral fluconazole (10 & 20 mg/kg QD; 20 mg/kg BID; MIC >64 mg/L) or intraperitoneal caspofungin (1, 5, & 10 mg/kg QD; MIC 0.25 mg/L)
- Therapy was initiated 1 day post-inoculation
- Outcome measures included survival and changes in kidney and brain tissue fungal burden
- Multiple experiments were conducted to evaluate the reproducibility of the results

RESULTS

- Immunocompetent mice were relatively resistant to *C. auris.*
  - Survival was 100% at day 14 post-challenge at inocula ranging between 5 x 10^4 to 4.5 x 10^6 cells/mouse
- In neutropenic mice, virulence differed between the two isolates.
  - In mice infected with DI17-47, mortality range between 40% to 70% over an inocula range of 2.6 x 10^6 to 2.5 x 10^7 cells/mouse.
  - In mice infected with DI17-46, mortality was rapid (median survival 2-3 days) and approached 100% with higher inocula (4.1-8.6 x 10^7 cells/mouse)
- Kidney fungal burden was significantly reduced in mice treated with caspofungin (mean range 3.35 – 4.23 $\log_{10}$ CFU/g) compared to controls after 7 days of therapy (mean range 6.69 – 7.1 $\log_{10}$ CFU/g; p < 0.001) but not with fluconazole (mean range 5.0 - 7.71 $\log_{10}$ CFU/g)

ISOLATES

Table 1. Clinical *C. auris* Isolates used murine model experiments.

Isolate	Source	Fluconazole	Voriconazole	Caspofungin	Micafungin
DI17-46	Blood	>64	1	0.25	0.25
DI17-47	---	>64	2	0.5	0.25

CONCLUSIONS

- Immunocompetent mice were relatively resistant to infection
- *C. auris* was able to cause lethal disease in neutropenic mice, and standard doses of fluconazole were ineffective
- Treatment with caspofungin did improve outcomes, but this was inoculum dependent
- This neutropenic model may be useful in evaluating new treatment strategies against this emerging pathogen.

Figure 1. Survival & fungal burden in immunocompetent & neutropenic mice.

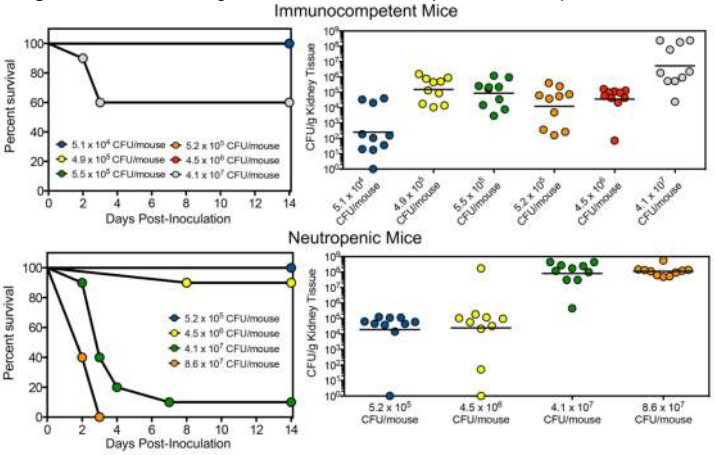


Figure 2. Survival in neutropenic mice infected with DI17-46 vs. DI17-47.

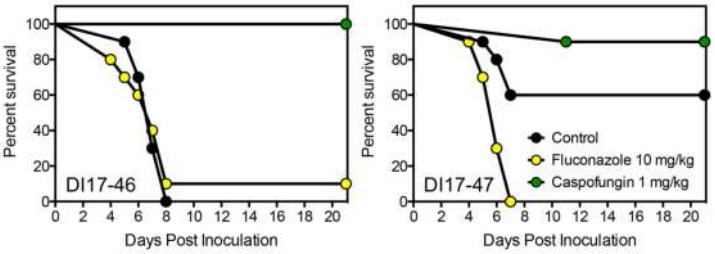
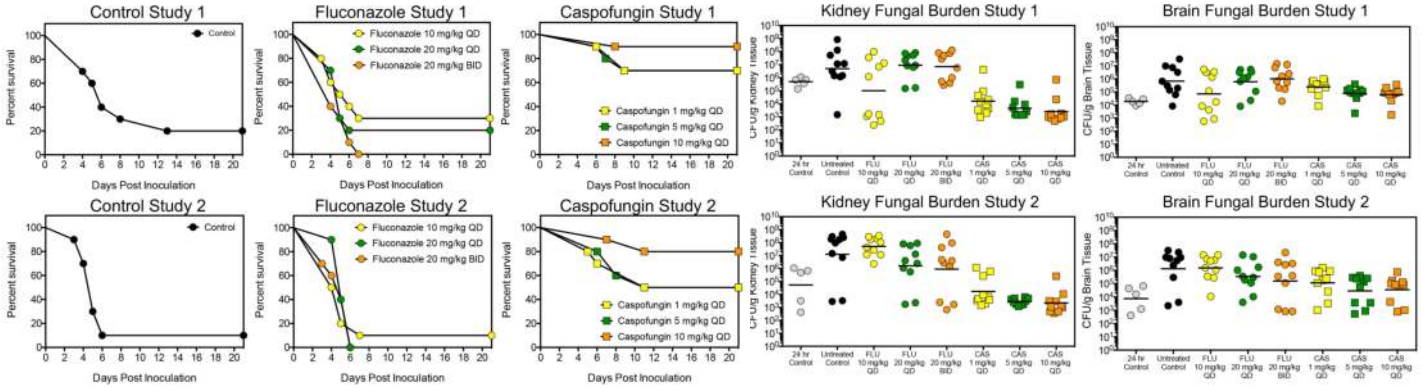


Figure 3. Survival and fungal burden (kidneys & brains) in neutropenic mice infected with DI17-46 and treated with fluconazole (FLU) or caspofungin (CAS) for 7 days.



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