

# Histoplasmosis in patients with cell-mediated immunodeficiency: HIV infection, organ transplantation, or TNF- $\alpha$ inhibition

Keith Lockett M.D., Lora Thomas M.D., Geraldine Miller M.D., Sydney Hester M.D., Steve Dummer M.D.

## Background:

Histoplasmosis is known to cause severe disease in patients with defects of cell-mediated immunity who live in an endemic area. It is not known whether disease presentation or outcome varies related to the type of immunodeficiency.

## Methods:

All cases of active histoplasmosis at Vanderbilt University Medical Center occurring in patients with HIV infection, a history of transplantation, or TNF- $\alpha$  inhibitor use from July 1999 to June 2012 were retrospectively reviewed. These groups were compared for differences in clinical presentation and outcomes.

## Results:

Table 1: Demographics

	HIV N=56	Transplant N=23	P value: HIV vs. Transplant	TNF- $\alpha$ inhibitor N=11	P value: HIV vs. TNF- $\alpha$ inhibitor
Male	46 (82%)	8 (35%)	<0.001	7 (64%)	0.2
Age (years)	42 (26-74)	49 (20-67)	0.08	43 (23-65)	0.7
Rural Environment	13 (27%)	14 (61%)	0.003	5 (45%)	0.16
Race (W/B/H)	26/26/4	17/5/0	0.02	10/1/0	0.03

Table 2: Presentation

	HIV N=56	Transplant N=23	P value: HIV vs. Transplant	TNF- $\alpha$ inhibitor N=11	P value: HIV vs. TNF- $\alpha$ inhibitor
Presented to hospital	49 (88%)	18 (78%)	0.3	2 (18%)	<0.001
Severity of illness:					
Mild (outpatient)	2%	4%	0.54	27%	0.014
Moderate (inpatient)	70%	61%		45%	
Severe (ICU)	29%	35%		27%	
Days to Diagnosis	5	6	0.08	18	0.0004

Table 3: Laboratory data and Imaging

	HIV N=56	Transplant N=23	P value: HIV vs. Transplant	TNF- $\alpha$ inhibitor N=11	P value: HIV vs. TNF- $\alpha$ inhibitor
WBC (thousand/mL)	3.15 (0.7-8.9)	4.3 (1.6-10.8)	0.008	5.3 (3.8-14.2)	0.0004
Hematocrit (%)	31 (14-47)	31 (23-39)	NS	40 (31-44)	0.0003
Platelet count (thousand/mL)	127 (14-451)	191 (51-538)	0.04	262 (93-489)	0.014
Creatinine (mg/dL)	0.9 (0.4-1.2)	2 (0.9-6.2)	<0.0001	0.9 (0.7-2.2)	NS
Positive blood cultures	18/35 (51%)	4/15 (27%)	0.095	0/5 (0%)	0.04
Positive urine histoplasma Ag	43/49 (88%)	21/22 (95%)	NS	10/11 (91%)	NS
CT Adenopathy	70%	29%	0.02	22%	0.02
CT Miliary pattern	7%	7%	NS	44%	0.02
Median histoplasma urine antigen (ng/mL)	19.6	14.6	NS	6.9	0.02
Initial Therapy with Amphotericin	32 (57%)	5 (22%)	0.006	6 (55%)	NS

- 114 cases were identified, 90 (79%) in immunocompromised patients.
- There was no significant difference in presenting symptoms (fever, headache, weight loss, cough).
- All HIV patients had CD4 counts <200 cells/mL; median 31 cells/mL and only 5 on ART and adherent (9%).
- The median time since transplant was 36 months and the majority of patients (70%) had kidney transplants. No stem cell transplant patients developed histoplasmosis.
- The median time since initiation of TNF- $\alpha$  inhibitor was 26 months; 55% for IBD, 18% for RA and 18% for psoriasis.
- Adalimumab was used in 64% and Infliximab in 36%. No one on Etanercept developed histoplasmosis. 73% had received a second agent as well.

Figure 1: Antigen level vs. severity of disease

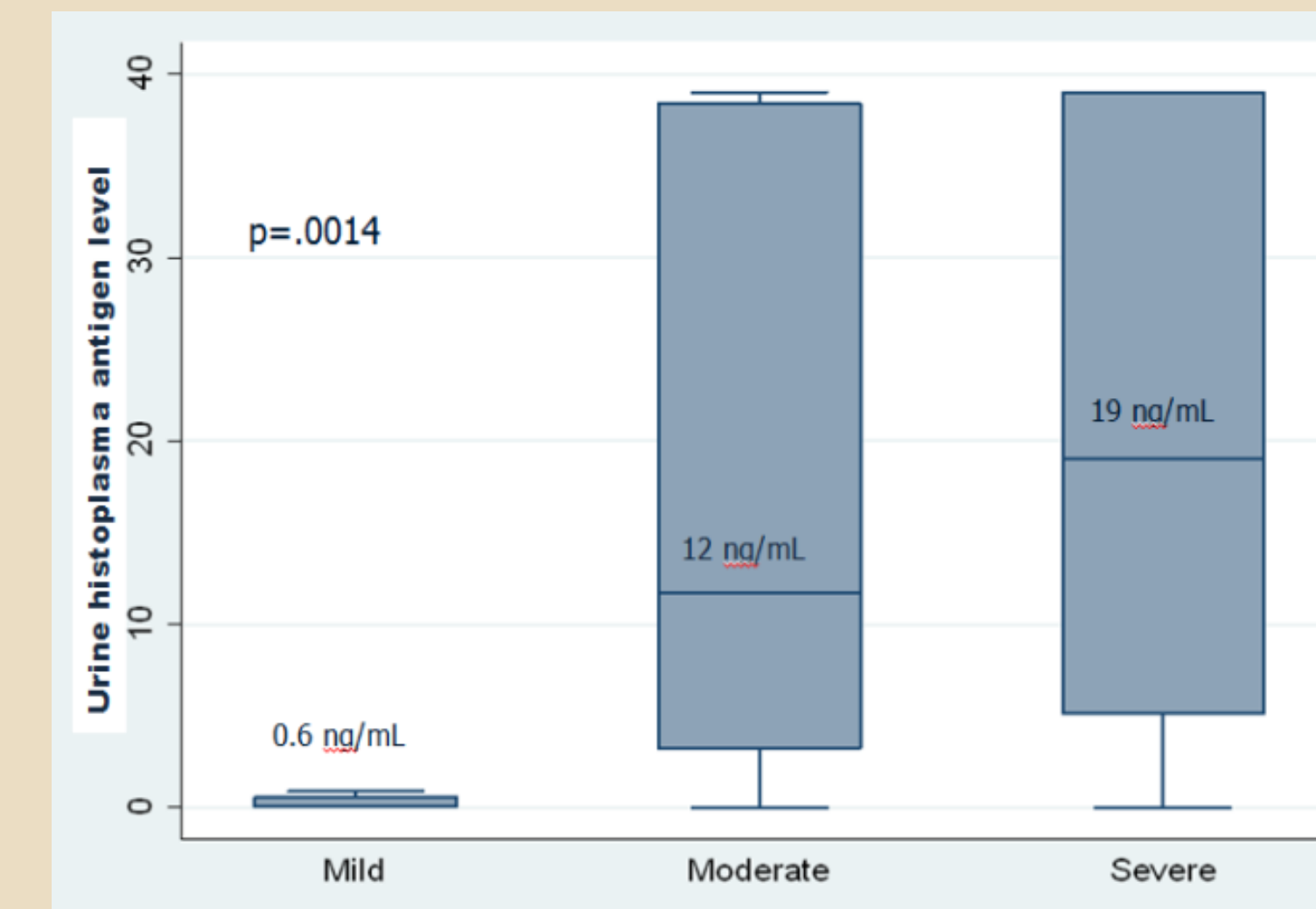
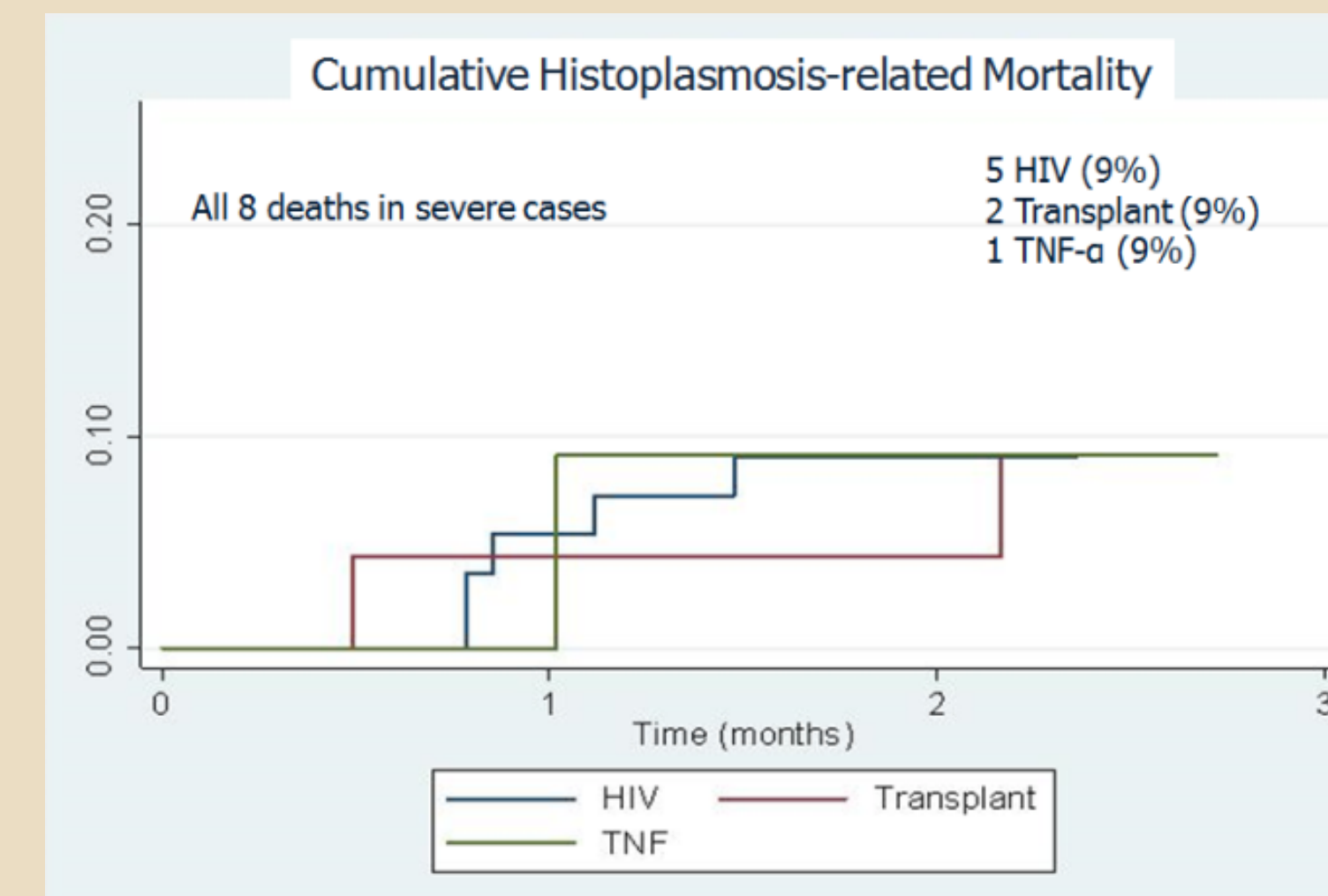


Figure 2: Ninety day mortality



- There was no difference in 90 day mortality based on type of immunodeficiency or initial therapy.
- There were only 8 failures with initial azole therapy; 4 HIV, 4 transplant.
- Patients who failed azole therapy had significantly higher urine antigen levels.
- All azole failures had severe disease.
- The median duration of treatment was significantly shorter in the TNF- $\alpha$  group; 8 months vs. 19 months in HIV and 14 months in transplant ( $p=0.0007$ ).
- Median follow up for all patients was 18 months
- Sixteen patients were lost to follow up but had a median of 16 months of care before being lost.

Figure 3: Mortality by initial therapy

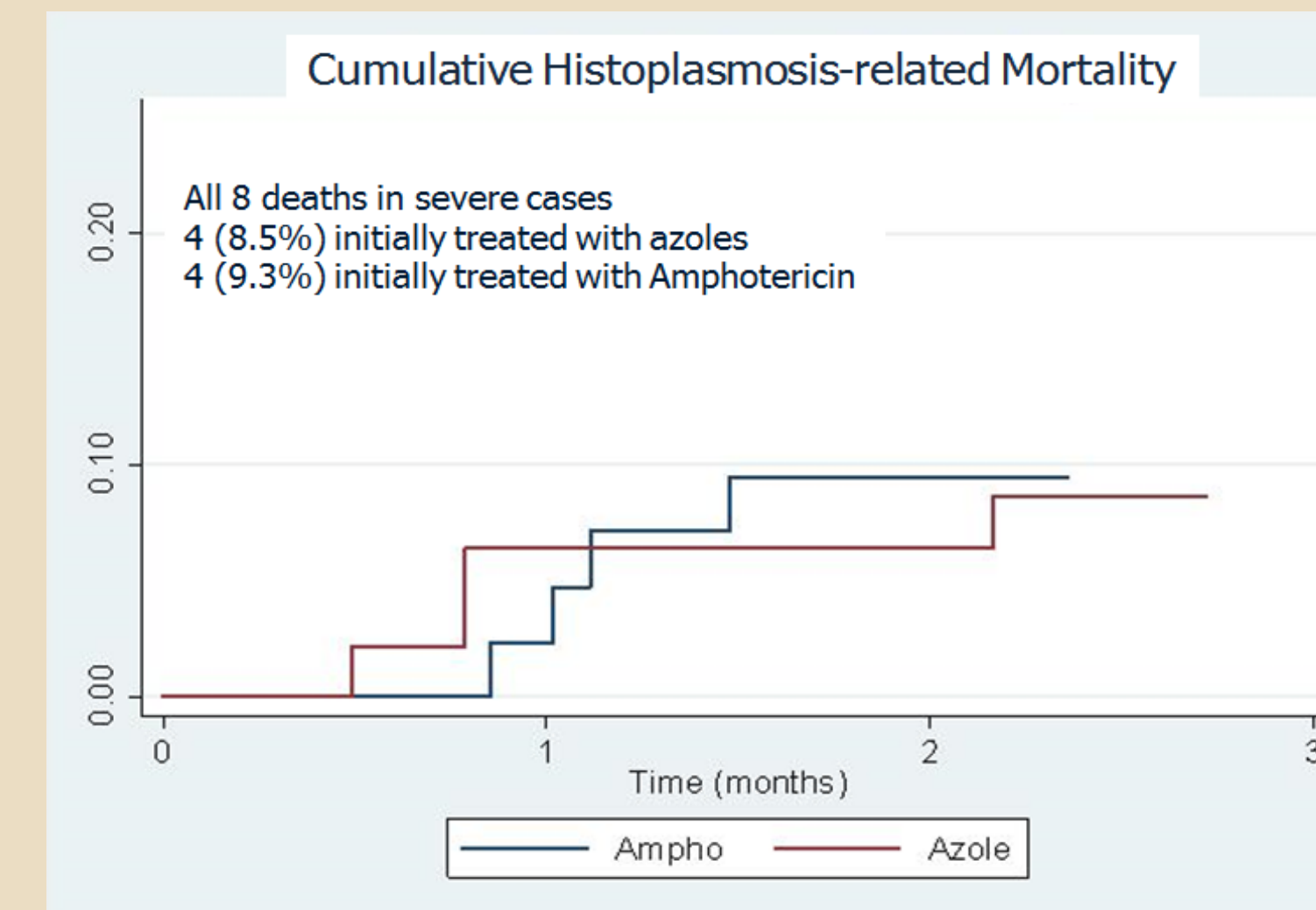
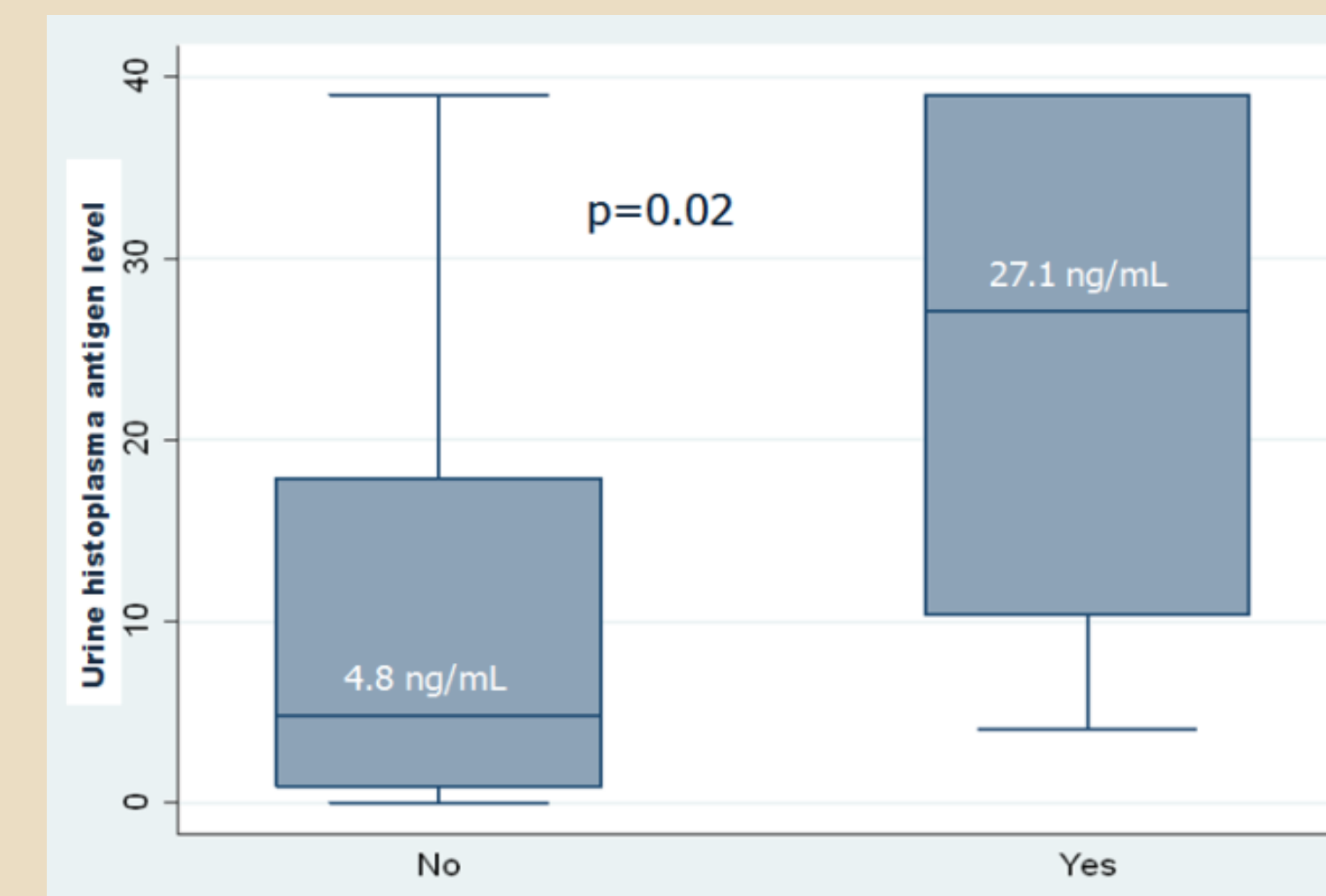


Figure 4: Antigen level and azole failure



## Conclusions:

Histoplasmosis caused milder disease in patients receiving TNF- $\alpha$  inhibitors than patients with HIV or solid organ transplantation. HIV patients had more bone marrow suppression and fungemia. The presence of *Histoplasma* antigenuria was high in all three groups, but antigen levels were lower in TNF- $\alpha$  patients. The majority of transplant recipients were successfully managed without the use of amphotericin, but azole failures correlated with higher urine antigen levels. Ninety day mortality did not differ among the groups and was less than 10%.