Case Presentation

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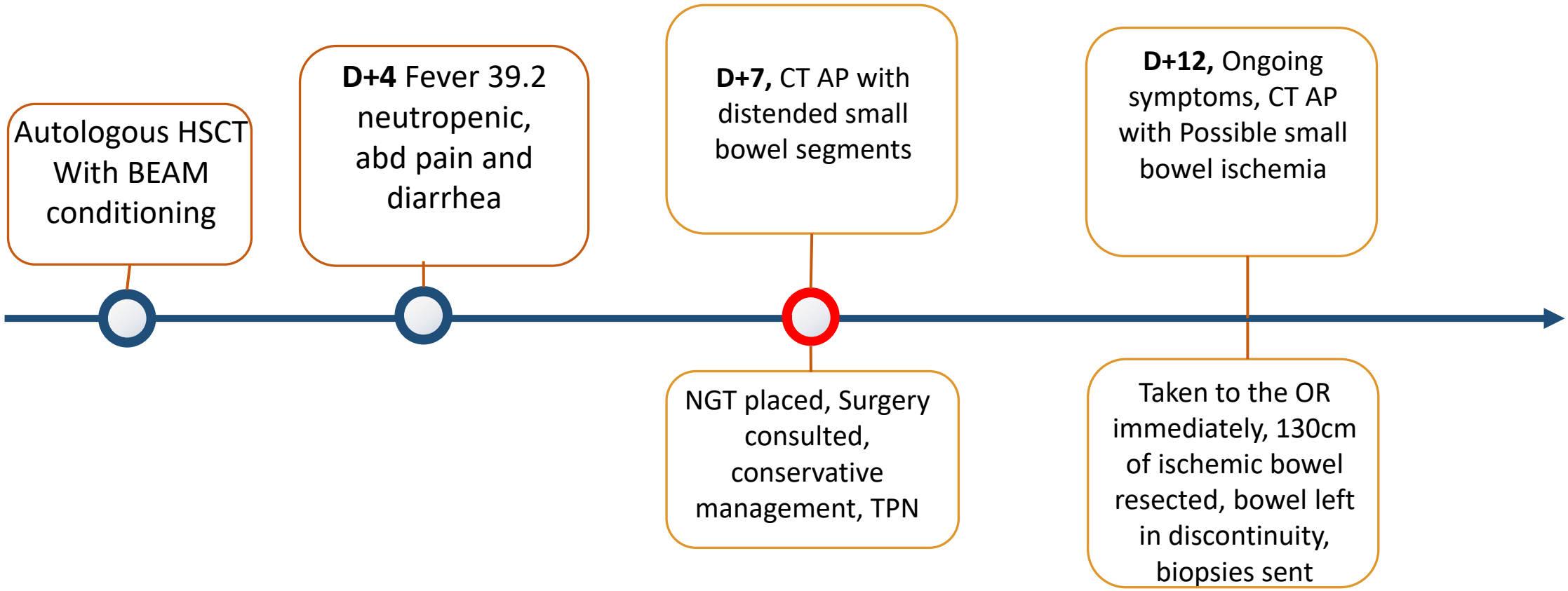
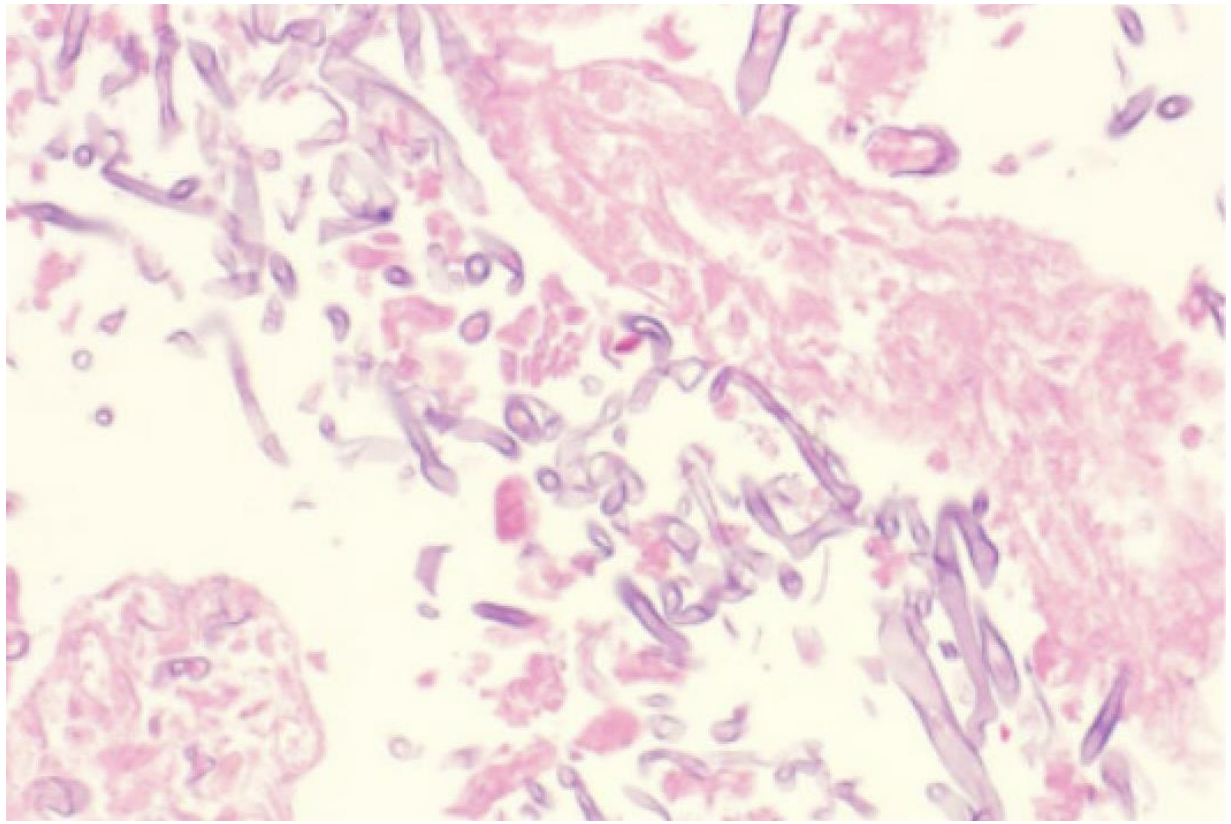
[redacted] yr old [redacted] with h/o DLBCL

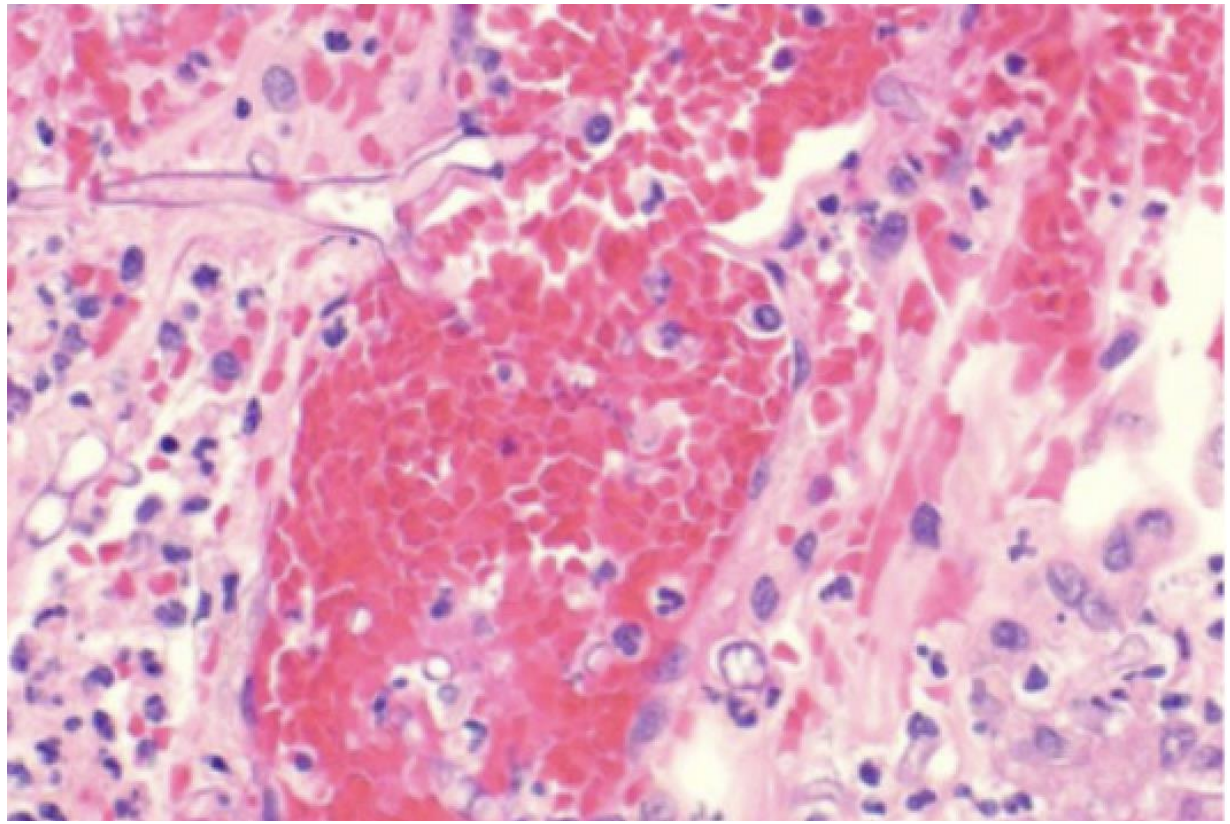
- Admitted for autologous HSCT
- Prior chemo: R-CHOP x 6 cycles and S/P Brentuximab-Nivolumab x3 cycles
- Prophylaxis: ACV, Fluconazole and levofloxacin during neutropenia

[redacted] yr old [redacted] with h/o DLBCL



Surgical Pathology from Small intestine





Gastrointestinal mucormycosis

- Broad pauci-septate hyphae, ribboning, branching at 90 degrees

- Transmural necrosis and angioinvasion

ID is consulted for further management. Which antifungal(s) would you recommend for treatment?

1) Liposomal amphotericin B

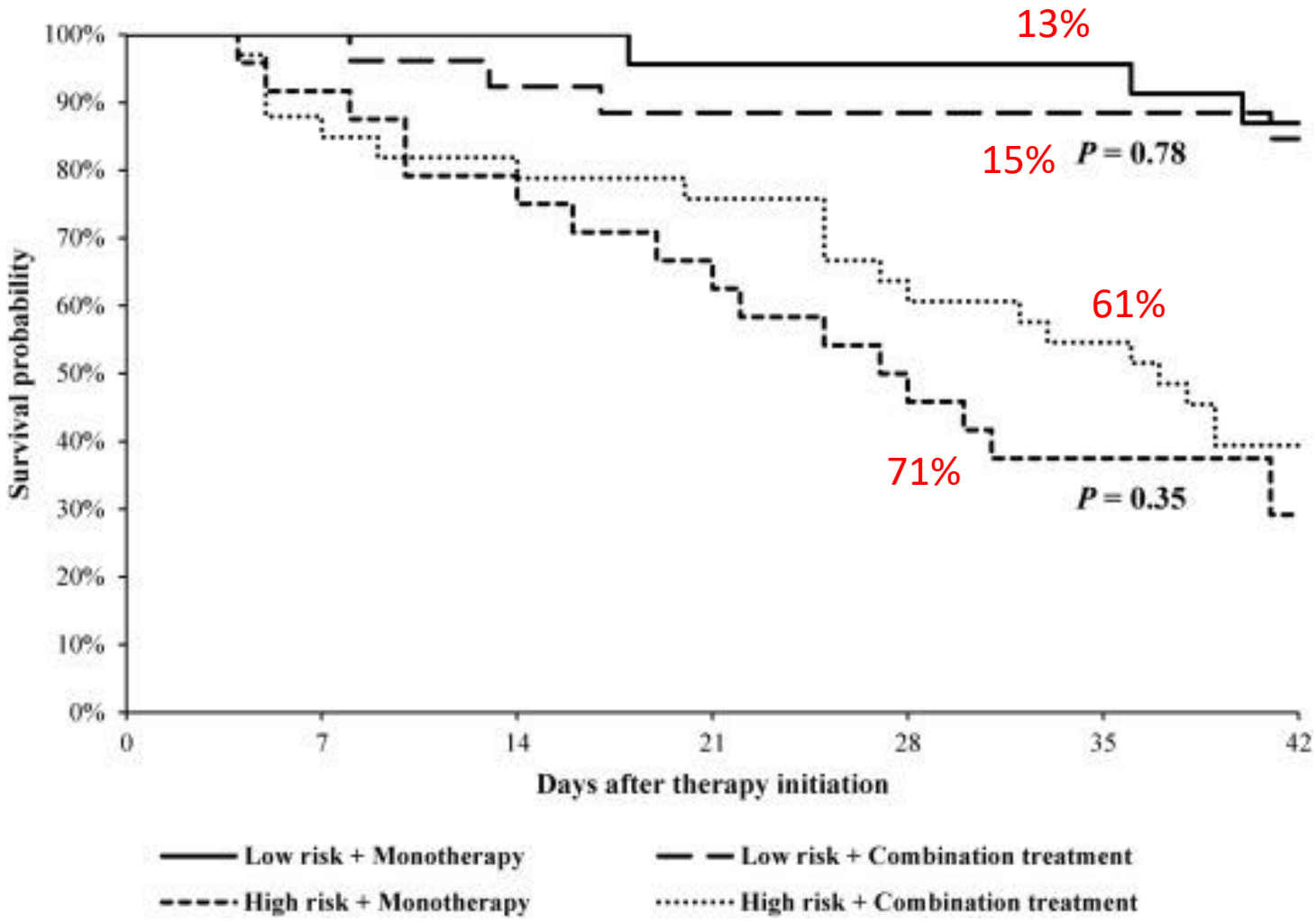
2) Liposomal amphotericin B + Micafungin + Isavuconazole

2) Liposomal amphotericin B + Micafungin

3) Liposomal amphotericin B + Micafungin + Posaconazole

Role of combination antifungal therapy for mucormycosis

- Retrospective review from 1994-2014
- 106 pts with hematologic malignancies
- 44% Monotherapy, 56% combo therapy (amb + echinocandin/posa)



Kyvernitakis et al. Clin Microbiol Infect. 2016

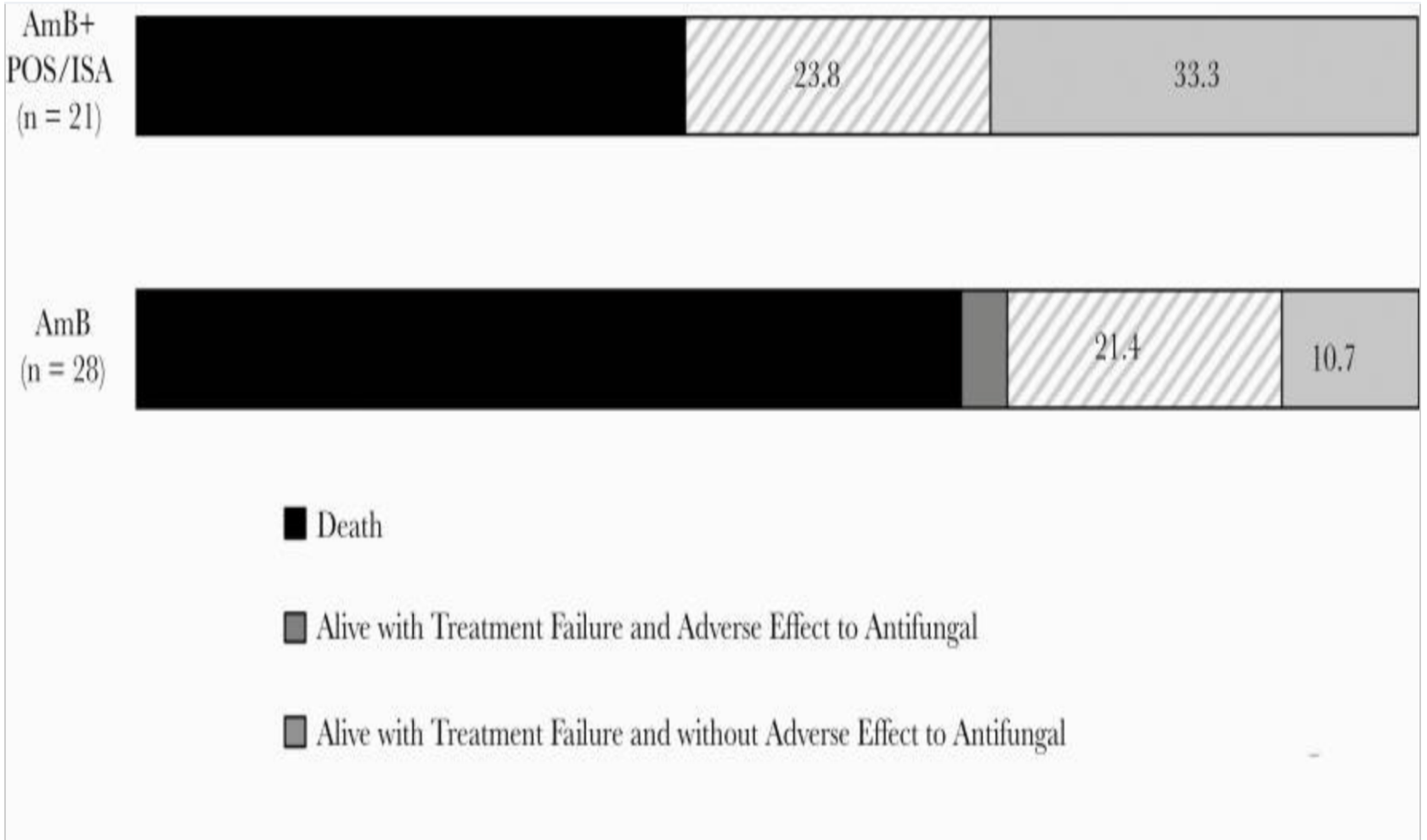
Retrospective multicenter study from 10 centers in North America,
patients with invasive mucormycosis
in hematologic malignancies/HSCT (2007-17)

30 d and 1 yr all cause mortality

- AmB monotherapy: 43% and 68%
- Amb + azole combo therapy: 28% and 57%
- Surgical debridement: 16% and 17%

Trend towards lower mortality in combination group but not statistically significant (p > 0.1)

DOOR Analysis



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Started on ambisome and micafungin + IP ambisome lavage

D+ 18 Went to the OR, excision of bowel, murky ascites found

D+19 and D+23: Further I and D, involving subcutaneous tissue, cx growing Mold

D + 25 Posaconazole started

D+30 Large GI bleed, requiring pressors, no further surgical interventions possible

D + 31 Transition to comfort care after family discussion. Discharged to home hospice

The mold is identified as *Rhizopus microsporus*. Primary team asks if there are any oral options to send the patient to home with. Which one would you recommend ?

- 1) Itraconazole
- 2) Posaconazole
- 3) Isavuconazole

Susceptibility testing of 854 clinical isolates of Mucorales spp at UT San Antonio Health 2015-20

MIC ranges, MIC_{50}s, MIC_{90}s, modal MICs, and GM MICs to antifungals

Species (no. tested)	Antifungal	MIC (µg/ml)				
		Range	50%	90%	Modal	GM
Cunninghamella spp. (all isolates, 16)	Amphotericin B	0.5 to 2	2	2	2	1.35
	Isavuconazole	4 to >16	>16	>16	>16	>16
	Posaconazole	0.25 to 1	0.5	1	0.25	0.420
Cunninghamella bertholletiae (11)	Amphotericin B	0.5 to 2	2	2	2	1.37
	Isavuconazole	4 to >16	>16	>16	>16	16
	Posaconazole	0.25 to 1	0.5	1	0.25	0.441
Lichtheimia spp. (all isolates, 40)	Amphotericin B	≤0.03 to 1	0.125	0.5	0.06	0.134
	Isavuconazole	0.125 to 4	1	4	1	1.17
	Posaconazole	≤0.03 to 1	0.25	0.5	0.5	0.220
Lichtheimia corymbifera (16)	Amphotericin B	0.06 to 0.5	0.5	0.5	0.5	0.249
	Isavuconazole	1 to 4	2	4	2	2.29
	Posaconazole	0.125 to 0.5	0.5	0.5	0.5	0.310
Lichtheimia ramosa (22)	Amphotericin B	≤0.03 to 1	0.06	0.25	0.06	0.095
	Isavuconazole	0.125 to 2	1	2	1	0.802
	Posaconazole	0.06 to 1	0.125	1	0.06	0.186
Mucor spp. (all isolates, 106)	Amphotericin B	≤0.03 to 8	0.125	0.5	0.06	0.124
	Isavuconazole	2 to >16	8	>16	8	8.27
	Posaconazole	0.125 to 8	1	2	1	1.03

Badali H et al. *J Clin Microbiol*. 2021

-Of the azoles tested, posaconazole was most active (GM MIC range, 0.157 to 1µg/ml)

-Isavuconazole (GM MIC range, 1.13 to 16µg/ml)

-The activity of isavuconazole was markedly lower against *Cunninghamella*, *Mucor spp*

Mucor circinelloides (67)	Amphotericin B	≤0.03 to 8	0.06	0.5	0.06	0.110
	Isavuconazole	2 to >16	8	16	8	8.87
	Posaconazole	0.125 to 8	1	2	1	1.17
Mucor velutinosus (24)	Amphotericin B	≤0.03 to 0.5	0.125	0.5	0.03	0.103
	Isavuconazole	2 to >16	4	8	4	3.77
	Posaconazole	0.25 to 2	1	2	1	0.728
Rhizomucor pusillus (32)	Amphotericin B	≤0.03 to 0.5	0.125	0.5	0.06	0.131
	Isavuconazole	0.06 to 2	2	2	2	1.07
	Posaconazole	≤0.03 to 0.5	0.25	0.5	0.25	0.157
Rhizopus spp. (all isolates, 304)	Amphotericin B	≤0.03 to 2	0.25	0.5	0.25	0.181
	Isavuconazole	0.125 to >16	1	8	1	1.23
	Posaconazole	≤0.03 to >16	0.25	1	0.25	0.257
Rhizopus arrhizus (114)	Amphotericin B	≤0.03 to 1	0.125	0.5	0.06	0.136
	Isavuconazole	0.125 to 4	1	2	1	0.907
	Posaconazole	≤0.03 to 1	0.25	0.5	0.25	0.189
Rhizopus delemar (67)	Amphotericin B	≤0.03 to 2	0.25	0.5	0.5	0.195
	Isavuconazole	1 to 16	4	16	2	4.34
	Posaconazole	0.125 to >16	0.5	1	0.5	0.621
Rhizopus microsporus (121)	Amphotericin B	≤0.03 to 1	0.25	1	0.25	0.227
	Isavuconazole	0.125 to >16	1	2	1	0.823
	Posaconazole	≤0.03 to 4	0.25	0.5	0.25	0.213

Badali H et al. *J Clin Microbiol*. 2021

VITAL study

- Single arm open label trial in 34 centers to assess the safety and efficacy of isavuconazole to treat mucormycosis
- 37 pts with mucormycosis received isavuconazole for median of 84 days

- By D 42, 4(11%) had partial
  6 (43%) had stable invasive fungal disease
  1 (3%) had disease progression
  13(35%) died

- All cause mortality at D42 was similar between isavuconazole and amphotericin B matched controls (weighted all-cause mortality: 33% *vs* 41%; p=0·595)

Marty et al. *The Lancet Infect Dis*. 2016

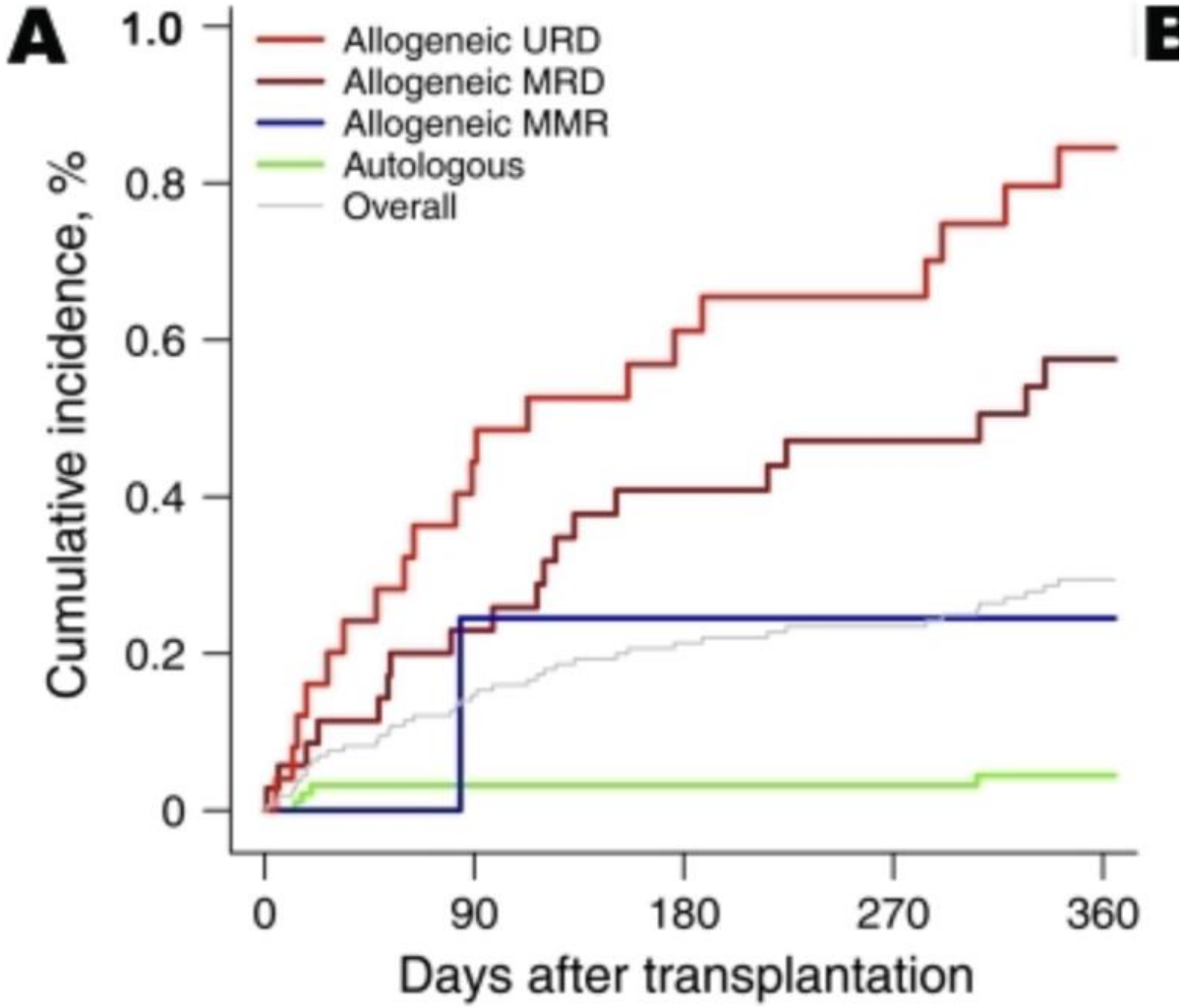
RESULTS OF ANTIFUNGAL SUSCEPTIBILITY TESTING:

DRUGS:	RESULTS: mcg/ml	INTERPRETATION:
Amphotericin B (AMB)	0.25	No Established Breakpoints
Posaconazole (POS)	0.06	No Established Breakpoints
Isavuconazole (ISA)	0.5	No Established Breakpoints
Terbinafine (TERB)	0.06	No Established Breakpoints

Performed at UT Health San Antonio

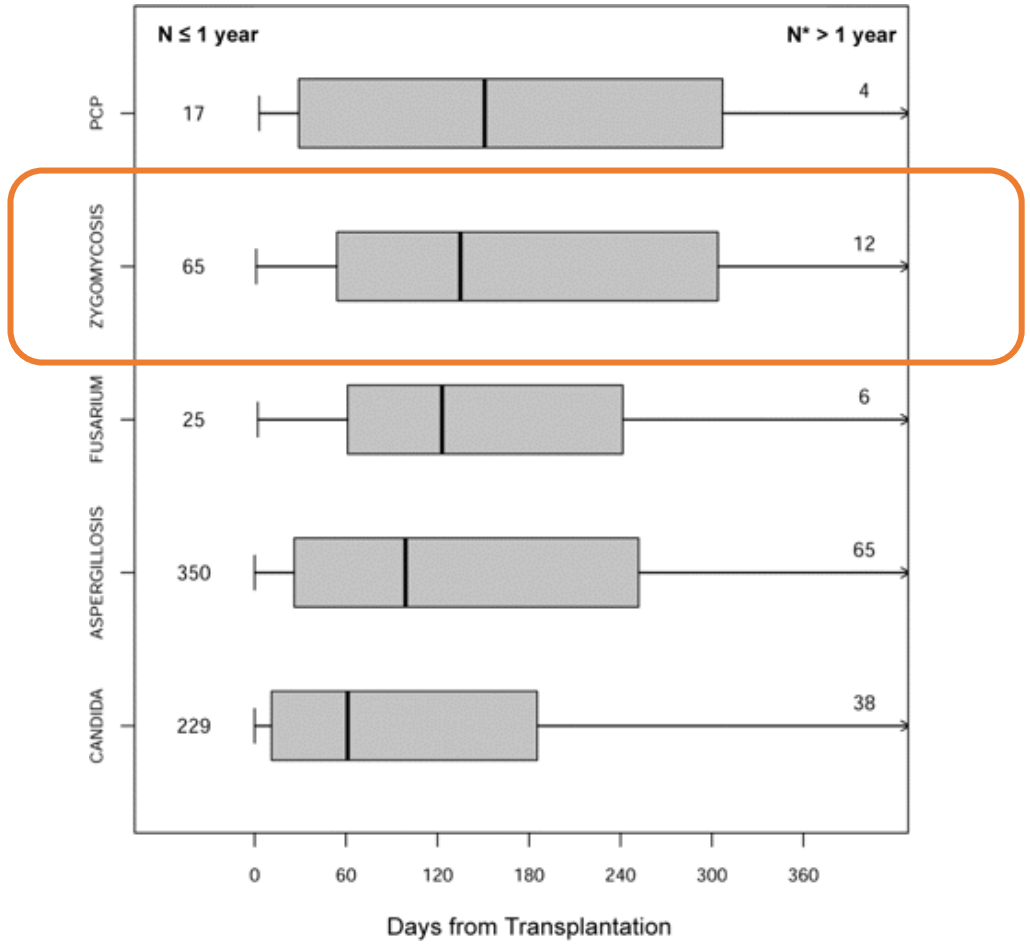
Invasive Mucormycosis in HSCT and hematologic malignancies

Twelve-month cumulative incidence of mucormycosis for hematopoietic stem-cell transplant (HSCT) recipients



Park et al. Emerg Infect Dis. 2011

Figure 1. Distribution of time to invasive fungal infection (IFI) stratified by infection type (all IFI cases in ...



Clin Infect Dis, Volume 50, Issue 8, 15 April 2010, Pages 1091–1100, https://doi.org/10.1086/651263

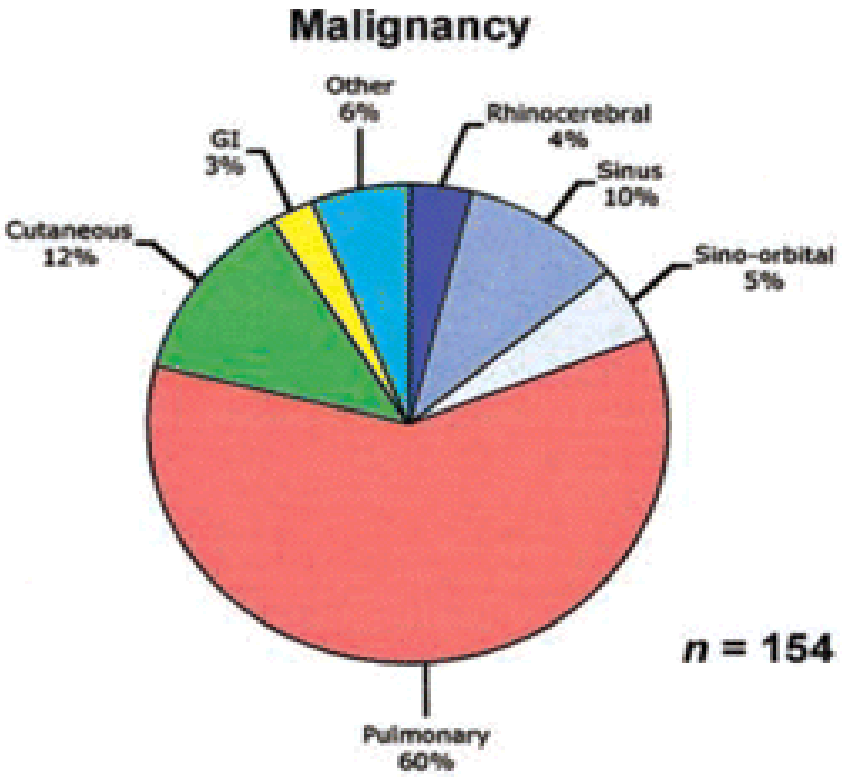
Risk factors associated with non-*Aspergillus* invasive mold infection in 20 patients who received allogeneic hematopoietic stem cell transplants at Fred Hutchinson Cancer Research Center (Seattle, WA), 1998–2002.

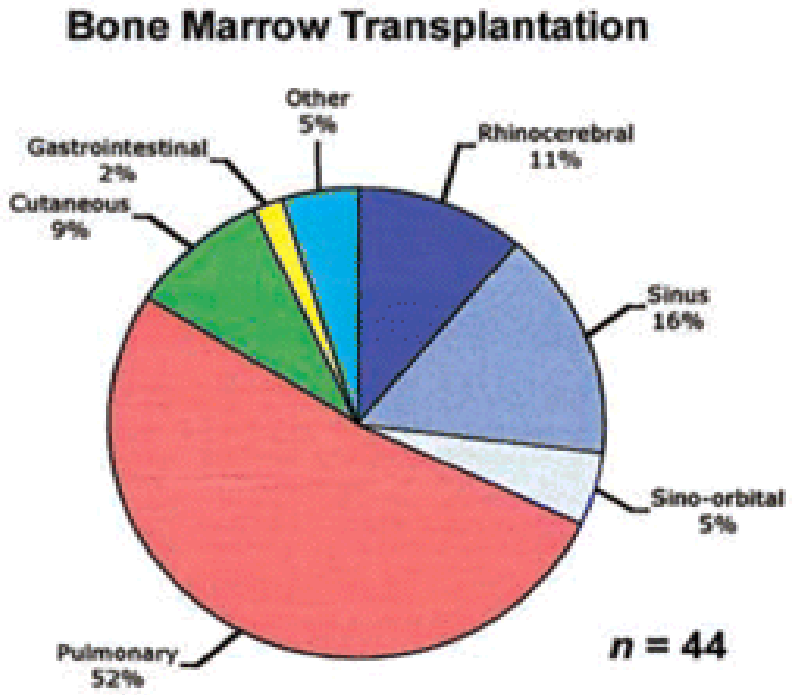
Variable	Unadjusted HR (95% CI)	P
Nonmyeloablative conditioning	2.7 (1.1–6.8)	.03
High dose TBI in conditioning	3.1 (1.1–8.9)	.04
Neutropenia	4.1 (1.4–12.3)	.01
Ferritin level >2000 ng/mL	5.8 (1.0–34.7)	.05
Bone marrow iron level increased	3.5 (0.9–13.6)	.06
Transfusions, per 1 U increase	3.2 (1.2–8.9)	.02
Acute GVHD, grade ≥3	5.1 (2.1–12.5)	<.01
Chronic GVHD, clinically extensive	6.2 (1.5–25.3)	.01
Corticosteroid dosage 2.0–2.9 mg/kg/day	5.5 (1.1–28.5)	.04

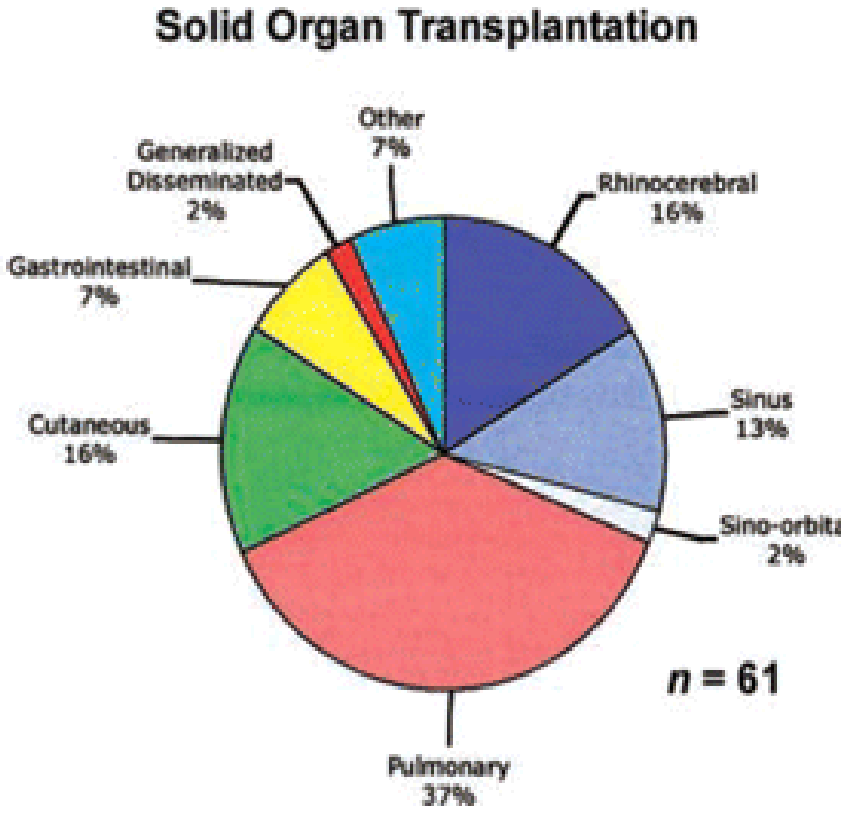
Other risk factors from small retrospective studies: DM, Malnutrition, Voriconazole prophylaxis

Garcia-Vidal et al. Clin Infect Dis.2008
Xhaard et al. Clinical Microbiology and infection.2012
Kontoyiannis et al. The Journal of Infectious Diseases.2005

Review of 929 cases of
Zygomycosis
Site of involvement

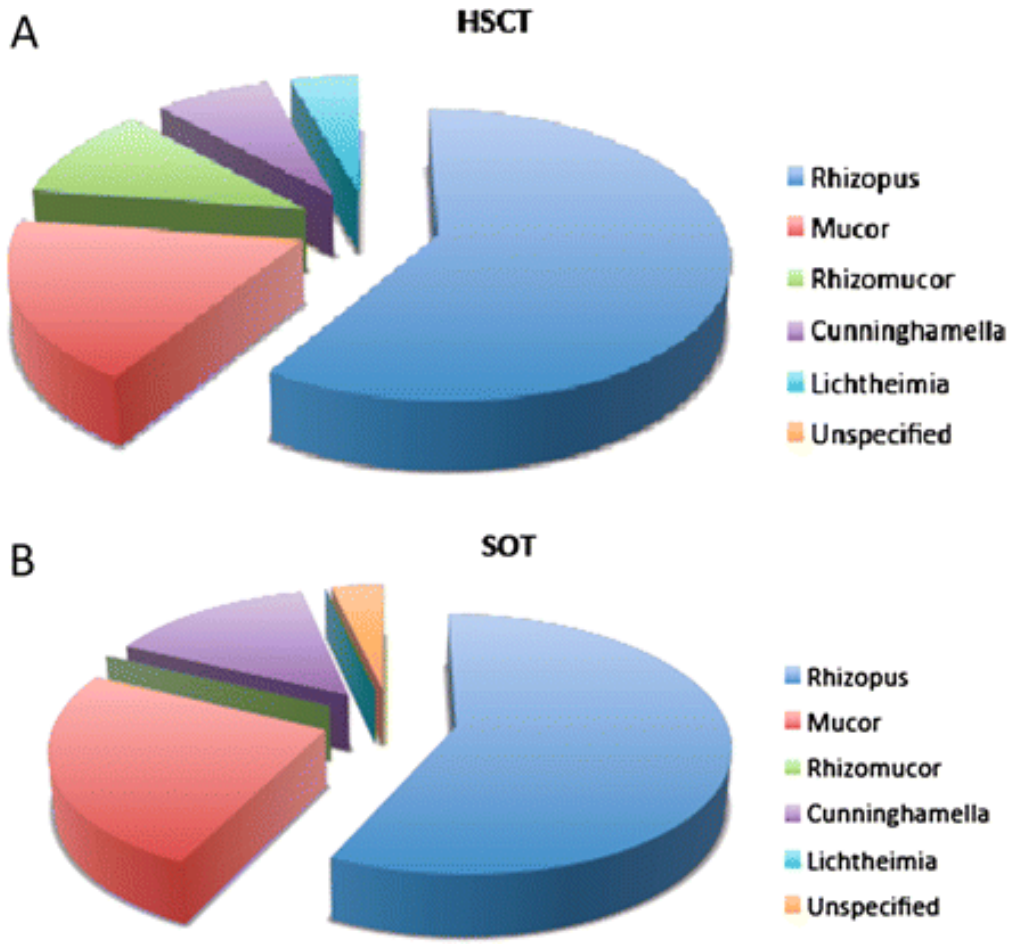






Roden et al. Clinical Infect Dis. 2005

Figure 4. Distribution of Mucorales species among hematopoietic stem-cell transplant (HSCT; A) and solid-organ transplant (SOT; B) in TRANS-NET study from 2001-06



Clin Infect Dis, Volume 54, Issue 11, 1 June 2012, Pages 1–8, https://doi.org/10.1093/cid/cis195

Review of 31 cases of GI Mucormycosis

- Gastric mucormycosis more common in SOT (11/13)
- Intestinal mucormycosis more common in hematologic malignancies (12/16)

- Commonly presents as appendiceal, cecal or ileac mass
- Can also involve liver, spleen and pancreas

Osmon et al. Mycoses.2015

Petrikkos et al. Clin Infect Dis.2012

What are the common clinical manifestations of GI mucormycosis?

- Abdominal pain 45% - 68%
- GI bleeding 48%
- Diarrhea 36%
- Fever 19%
- Change in bowel habits 10%

- Osmon et al. Mycoses.2015
- Quintero et al. Med Mycol.2022

Treatment and Outcomes of 31 pts with GI Mucor

- Of 28 cases, 16 (57%) died
- 9 (56%) had underlying hematologic malignancy/HSCT

Treatment	% Patients
Amphotericin +Surgery	74%
Amphotericin alone	16%
Surgery alone	3%
Surgery + alternative antifungal	7%

Osmon et al. Mycoses.2015

Systematic Review: 851 cases of Mucormycosis

Site of disease	Mortality n (%)
Rhino –cerebro-orbital	120 (42%)
Pulmonary	87 (51%)
Cutaneous	58 (31%)
Disseminated	75 (68%)
Gastrointestinal	39 (54%)
Species	**Mortality n (%)**
Rhizopus	101 (47%)
Mucor	26 (41%)
Cunninghamella	23 (77%)
Lichtheimia	21 (35%)
Apophysomyces	15 (44%)
Rhizomucor	11 (39%)
Saksenaea complex	6 (50%)

W. Jeong et al. Clinical Microbiology and Infection.2019

Multivariate model of risk factors for mortality among patients with zygomycosis.

Variable	OR (95% CI)	*P*
Extent of infection		
Localized	Reference	…
Disseminated	11.21 (5.79–21.73)	<.001
Infecting organism		
Rhizopus species	Reference	…
Cunninghamella species	2.78 (1.11–6.96)	.029
Diabetes		
None	Reference	…
Type I	0.31 (0.16–0.62)	.001
No underlying condition	0.38 (0.22–0.66)	.001
HIV infection	0.38 (0.15–0.94)	.037
Renal failure	7.16 (3.40–15.07)	<.001
Antifungal therapy		
None	Reference	…
Amphotericin B deoxycholate only	0.21 (0.13–0.35)	<.001
Lipid amphotericin only	0.10 (0.04–0.24)	<.001
Amphotericin formulation and azole	0.09 (0.03–0.29)	<.001
Other	0.14 (0.07–0.28)	<.001
Surgery as primary therapy	0.24 (0.15–0.37)	<.001

NOTE. Additional risk factors included within a similar model for analysis of site-specific infections are (with cutaneous infections as the reference): pulmonary infection (OR, 7.50; 95% CI, 2.84–19.80; *P* =< .001), rhinocerebral infection (OR, 6.39; 95% CI, 2.64–15.48; *P* =< .001), kidney infection (OR, 8.30; 95% CI, 2.54–27.16; *P* = .001), and gastrointestinal infection (OR, 22.51; 95% CI, 5.50–92.14; *P* =< .001).

Clin Infect Dis, Volume 41, Issue 5, 1 September 2005, Pages 634–653, https://doi.org/10.1086/432579

Subsequent course

- Patient was discharged home on posaconazole
- Family/patient changed GOC to restorative, had 5 hospitalizations, c/b CMV Viremia, recurrent C diff colitis, hypothyroidism, line related PsA bacteremia, pressure injury to the heels causing osteomyelitis
- Continued on posaconazole with good trough levels
- Doing well at recent clinic visit, diarrhea resolved, getting wound care for heel and abdomen

Summary

- GI Mucormycosis is not very common and often missed, can involve gastric and intestinal sites, has high mortality
- Commonly presents as abdominal pain, GI bleed, diarrhea, fever
- Surgical debridement + antifungal therapy may have better outcomes
- Can consider combination antifungal therapy (Ambisome + azole) (Evidence limited with only small and retrospective studies)
- In vitro studies of clinical isolates indicate that posaconazole may be the most active of the extended spectrum azoles, but activity varies based on *Mucorales* species type.