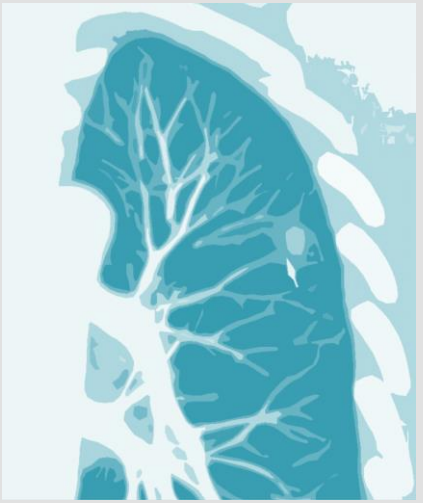
Tailored Antifungal Modification in Breakthrough Mold Infections



Russell E. Lewis

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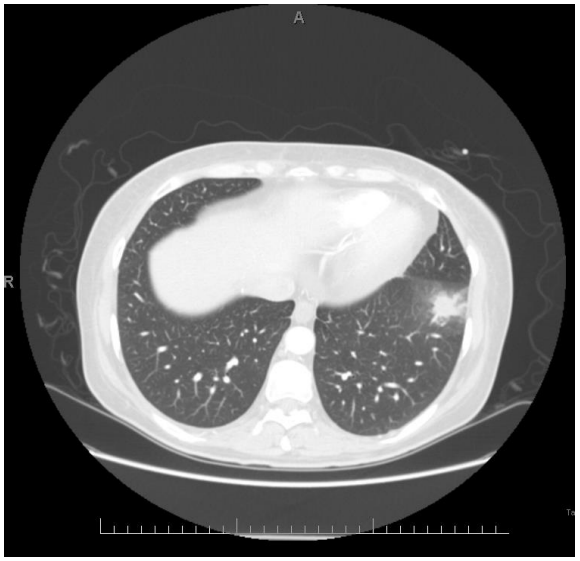
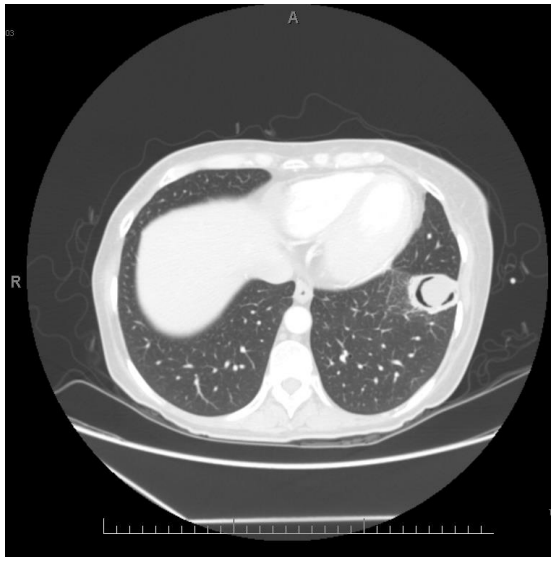
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Bologna

Clinical case

- 45 year-old patient with AML and documented pulmonary aspergillosis during remission-induction chemotherapy
  - *A. fumigatus* grown from BAL fluid
- Fungal pneumonia responded with:
  - voriconazole + caspofungin, → voriconazole
  - neutrophil recovery
  - complete hematological remission



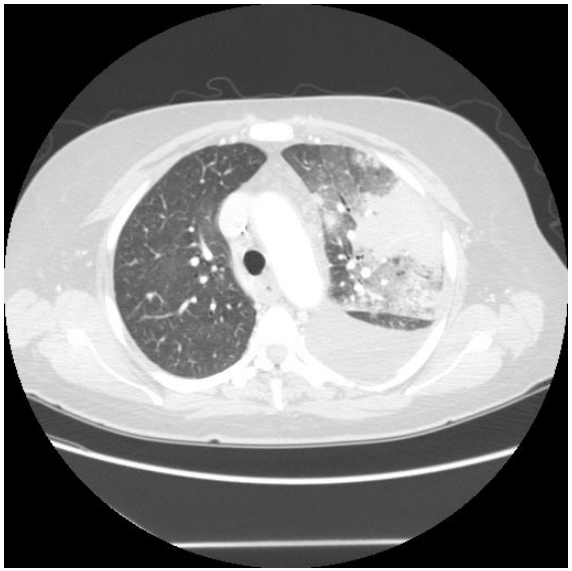
June 6th



July 17th

Clinical case cont.

- While in CR and non-neutropenic, she returns with symptoms of acute onset, community-acquired pneumonia
- Repeat CT: Rapidly worsening infiltrate in area of prior cavitation
- Galactomannan negative
- Voriconazole level 1.2 mcg/mL



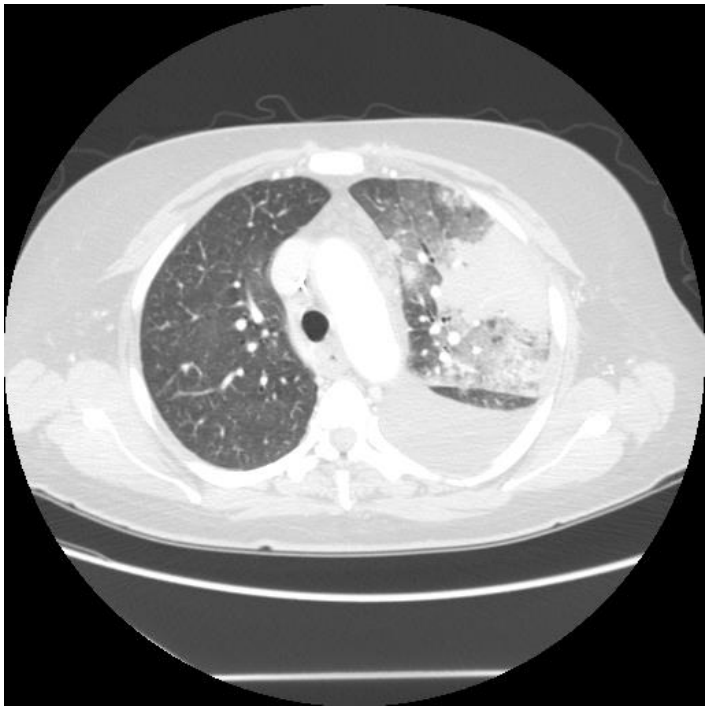
August 29th

"In view of the severity of this fungal infection relapse, the patient was started on **HEAT** therapy"

Breakthrough infections can elicit irrational antifungal regimens!

Highly **E**ffective **A**ntifungal **T**herapy=

caspofungin 100 mg/d +
liposomal amphotericin B 5mg/kg/d +
voriconazole 4 mg/kg q12h



Repeat BAL:
Legionella +
Aspergillus cx, GM -

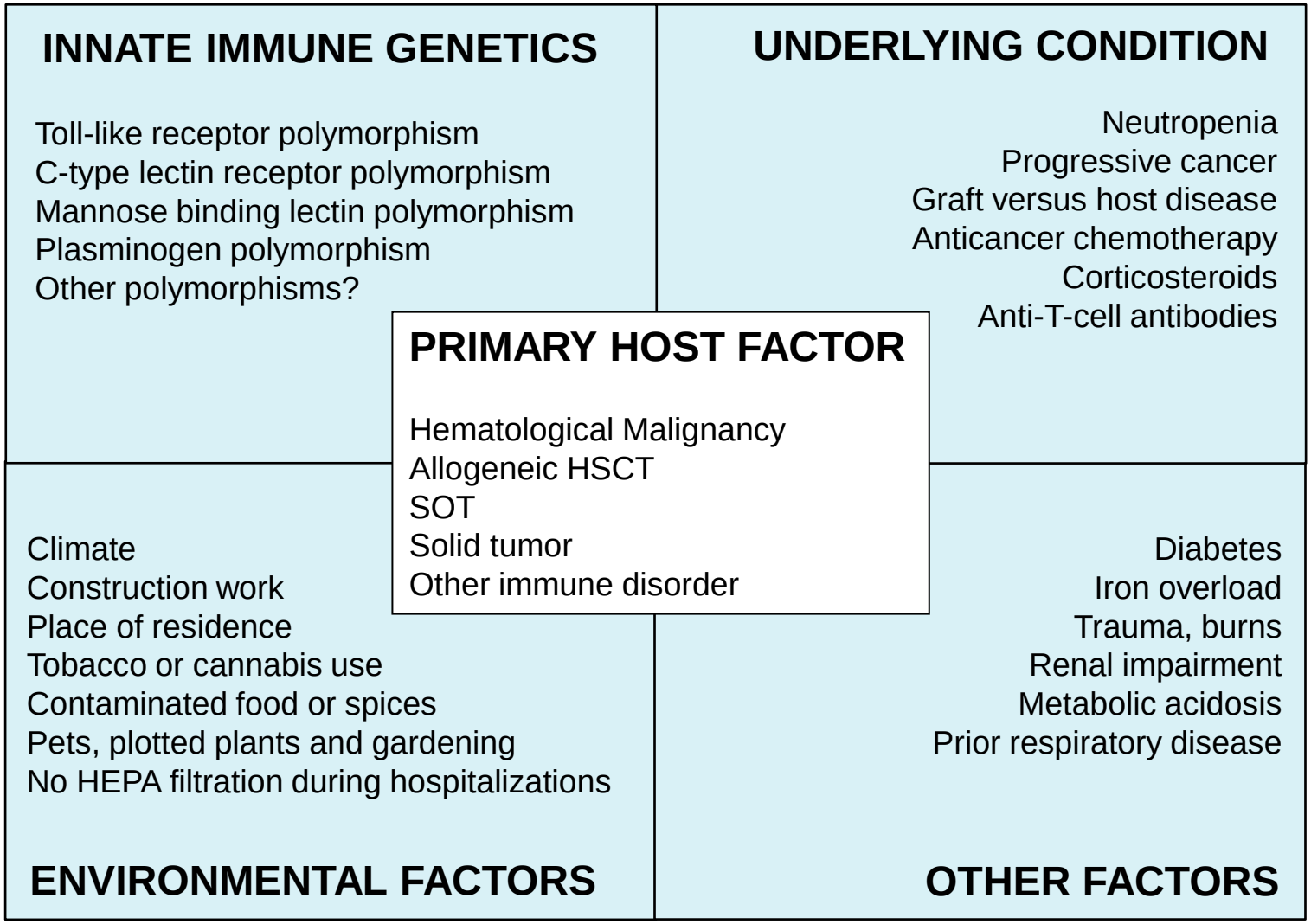
Consider that:

- Non-neutropenic, CR
- Adequate voricon. level (1.2 mcg/mL)
- Community-acquired pneumonia with rapid evolution

Principles for tailored antifungal therapy in suspected breakthrough infection

- Host risk (immunosuppression status)
- Diagnostic certainty
- Spectrum of pathogens
- Resistance
- Pharmacology

How to define patient risk for mold infection



Herbrecht et al. Ann NY Acad Sci 2012;1272:23-30.

17 candidate variables

Development (2005-2008)
840 patients,
1,709 admissions

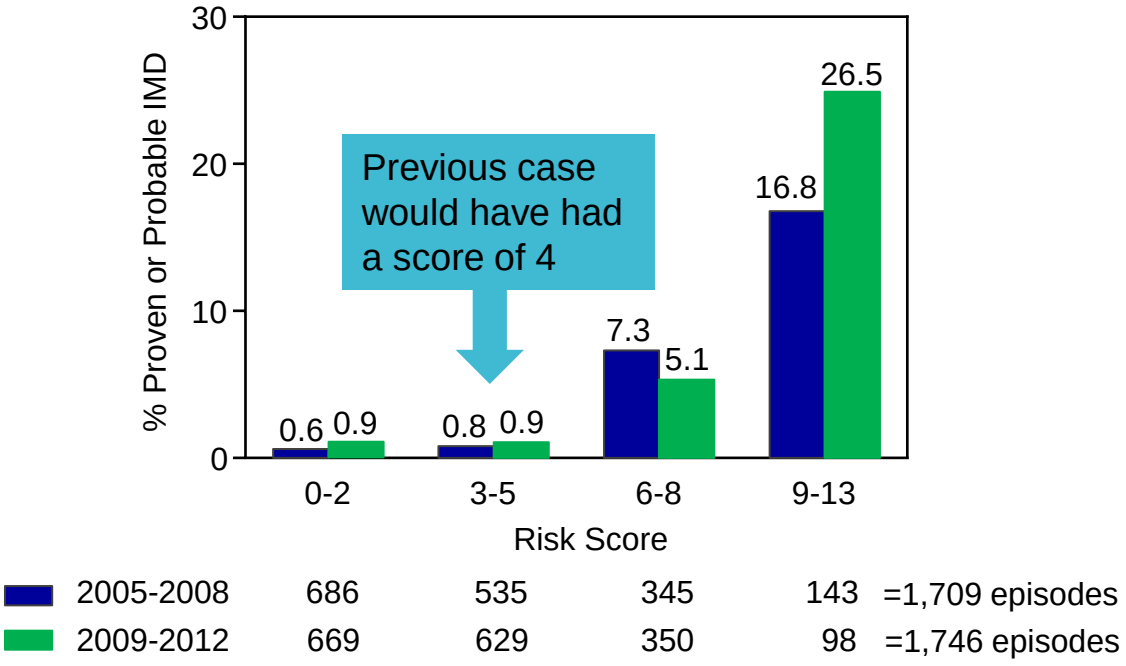
Validation (2009-2012)
855 patients,
1,746 admissions

OPEN ACCESS Freely available online PLOS ONE

A Risk Prediction Score for Invasive Mold Disease in Patients with Hematological Malignancies

Marta Stanzani[1*], Russell E. Lewis[2], Mauro Fiacchini[1], Paolo Ricci[1], Fabio Tumietto[2], Pierluigi Viale[2], Simone Ambretti[3], Michele Baccarani[1], Michele Cavo[1], Nicola Vianelli[1]

1 Institute of Hematology, Department of Hematology and Clinical Oncology, "Lorenzo e Ariosto Seràgnoli" S'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy, 2 Clinic of Infectious Diseases, Department of Internal Medicine, Geriatrics and Nephrologic Diseases, S'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy, 3 Operative Unit of Microbiology, Department of Hematology, Oncology and Laboratory Medicine, S'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy



Risk score < 6, antifungal therapy may not be necessary at this time

Stanzani et al. PloS one. 2013;8(9):e75531.

Other possible risk factors for breakthrough infection

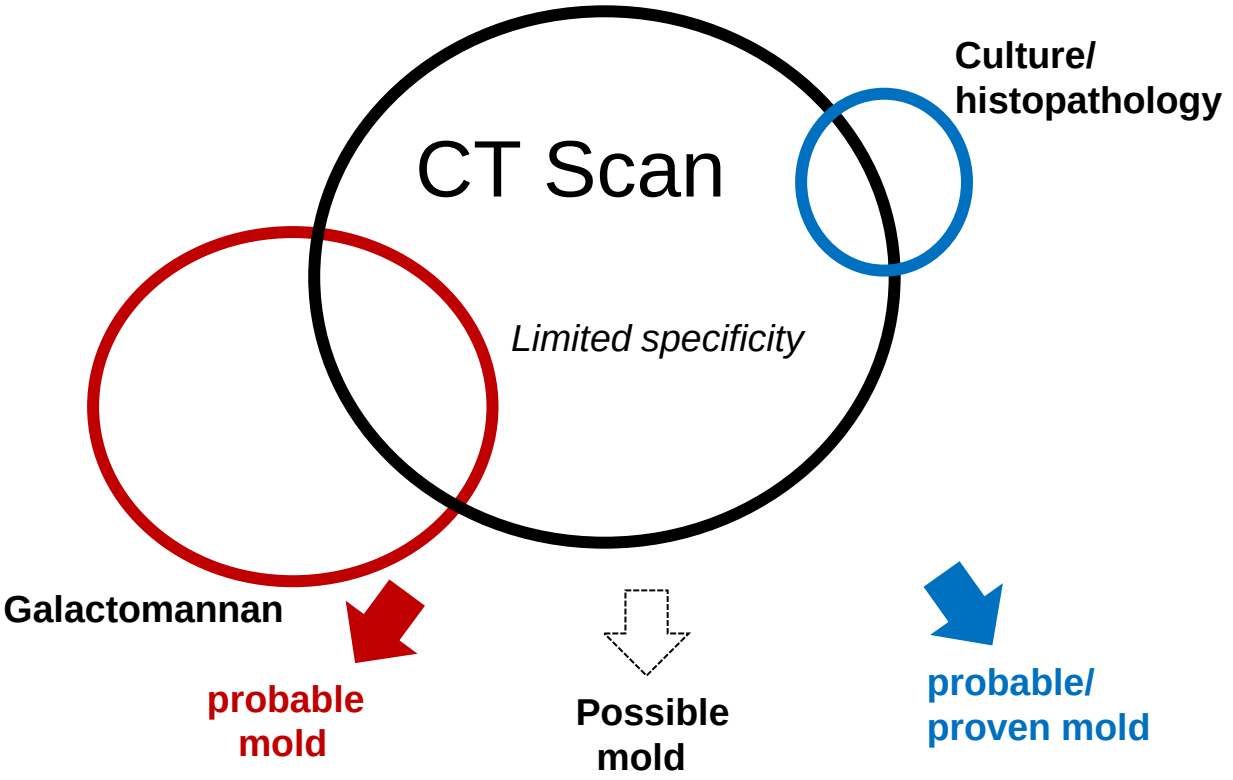
- Site of initial infection
  - For *Aspergillus* relapse, sinus > lung
- Incomplete resolution of imaging findings before subsequent chemotherapy
- Lack of 2° antifungal prophylaxis during subsequent allogeneic-HSCT
  - historical controls-29% to 33%
  - voriconazole 2° prophylaxis-6.7%*
- Administration of > 3 antibiotics
- Duration of antifungal therapy < 1 month

Sipsas & Kontoyiannis Clin Infect Dis 2006;42:1584-1591.
*Cordonnier et al. VOSIFI study. Haematologica 2011;95:1762-1768.

Framework for rational antifungal therapy in suspected breakthrough infection

- Host risk (immunosuppression status)
- Diagnostic certainty
- Spectrum of likely pathogens
- Resistance
- Pharmacology

Antifungal therapy typically triggered by symptoms or radiographic evidence of breakthrough infection



Nivoix et al. Clin Infect Dis 2008;47:1176.85
Kohno Clin Infect Dis 2008;47:1185-7

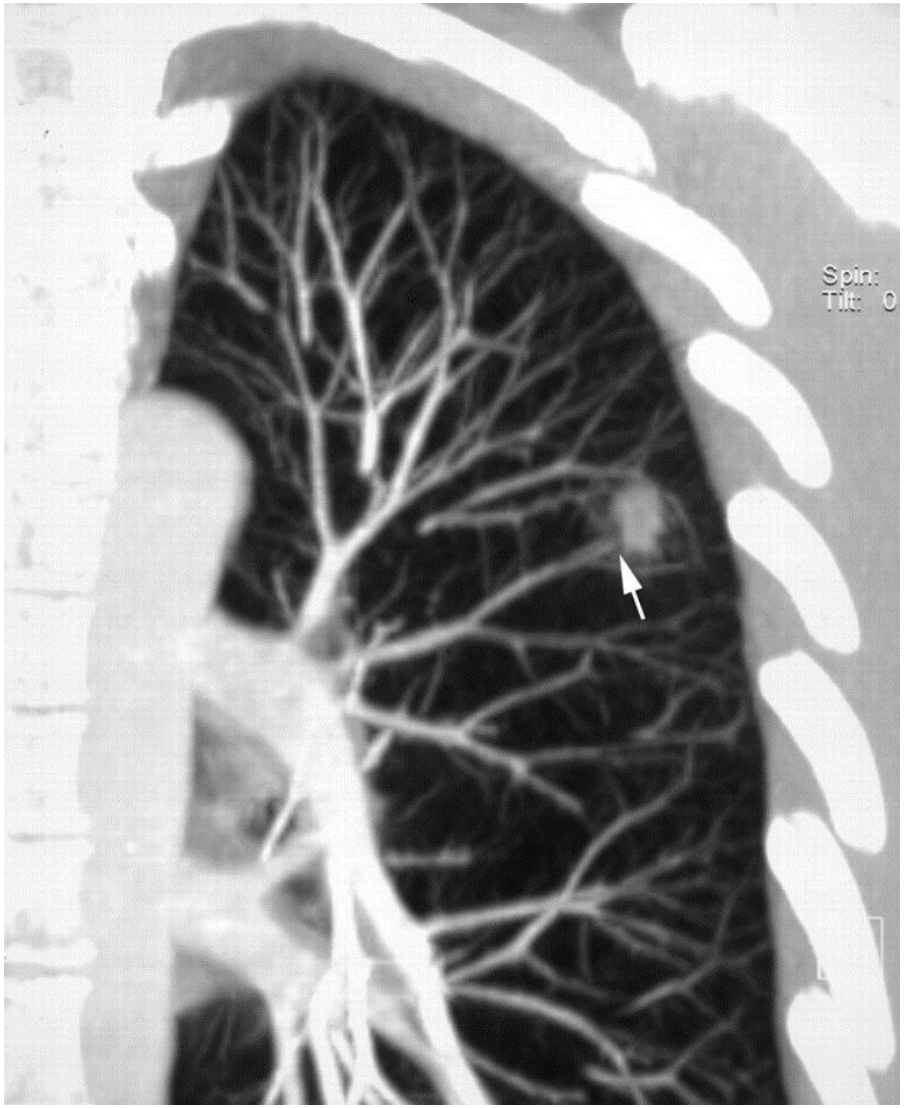
CT Pulmonary Angiography

Advantages

- Direct visualization of vessel occlusion associated with angioinvasion in nodular lesions
- Sensitivity not affected by antifungals
- Can be performed in any hospital rapidly with training and committed radiologists

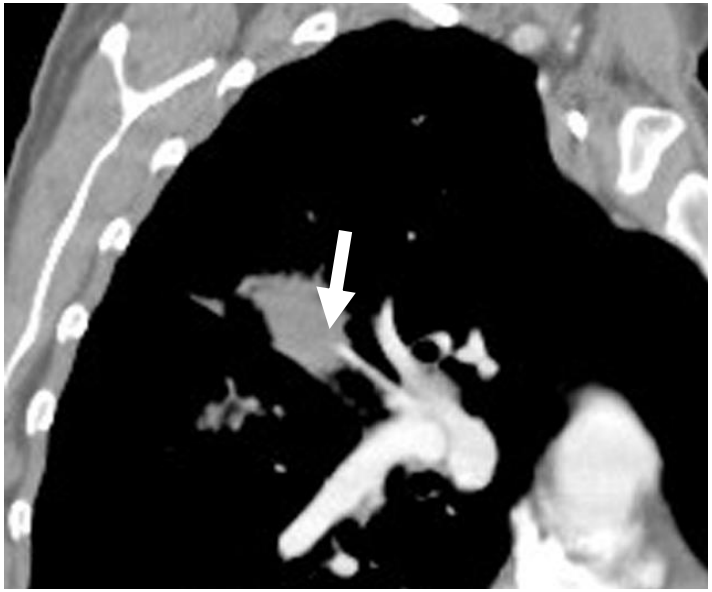
Disadvantages

- Need for contrast, additional radiation
- Lung apex/base, and nodules < 10 mm difficult to visualize
- Sensitivity may be diminished with old lesions (neovascularization)

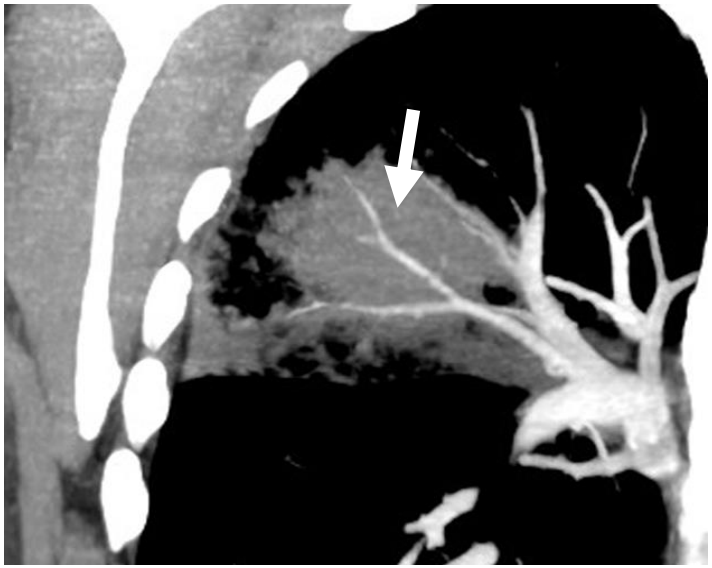


Sonnet S et al. AJR 2005;184:746-751

Pulmonary angiography differentiates mold vs. bacterial pneumonia



CTPA positive, proven mold disease



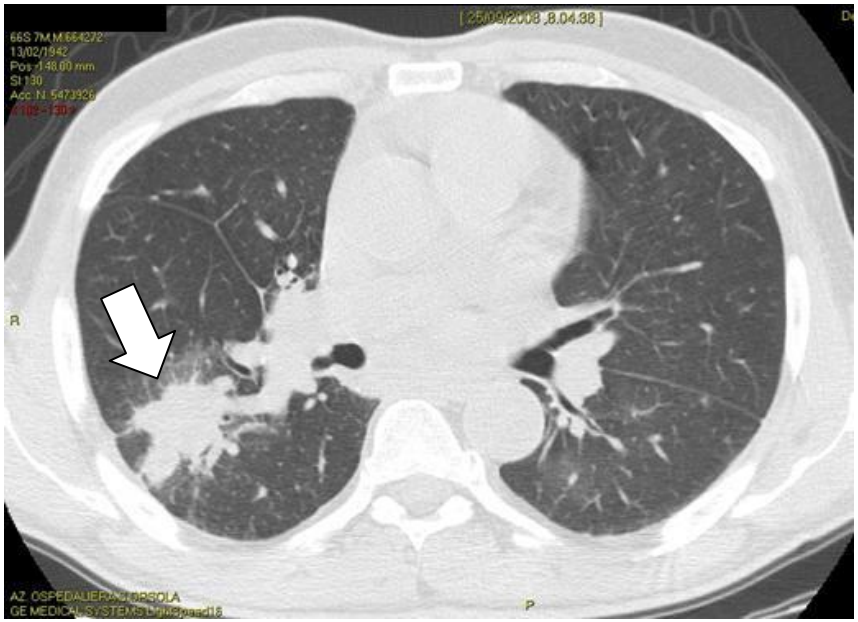
CTPA negative, bacterial PNA

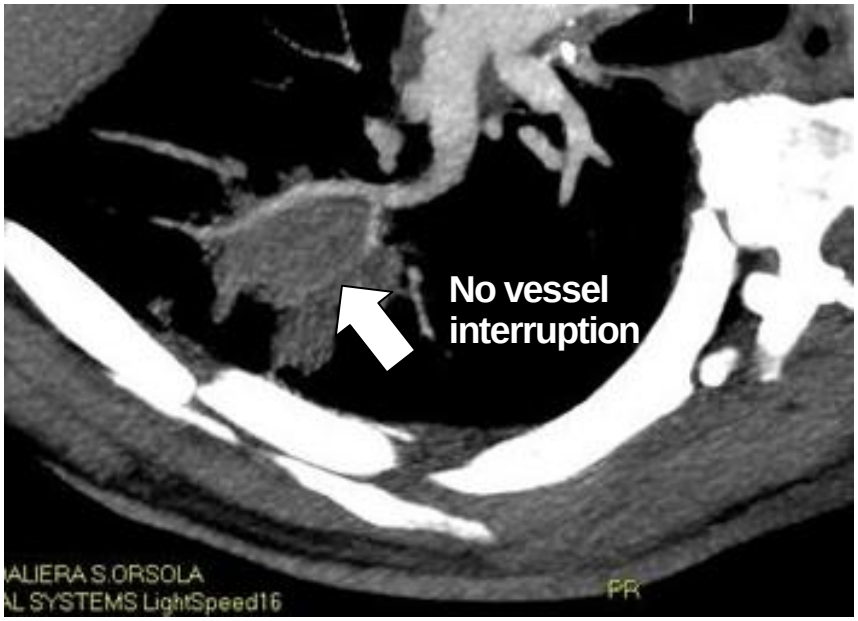
In Bologna, highly concordant with BAL galactomannan, more sensitive than serum galactomannan

Stanzani et al. Clin Infect Dis 2012;54(5):610-6.

Pulmonary angiography differentiates mold vs. malignancy breakthrough

Lymphoma relapse in lung of extensively-treated patient presenting with fever





Stanzani et al. Clin Infect Dis 2012;54(5):610-6.

Performance of CT angiography

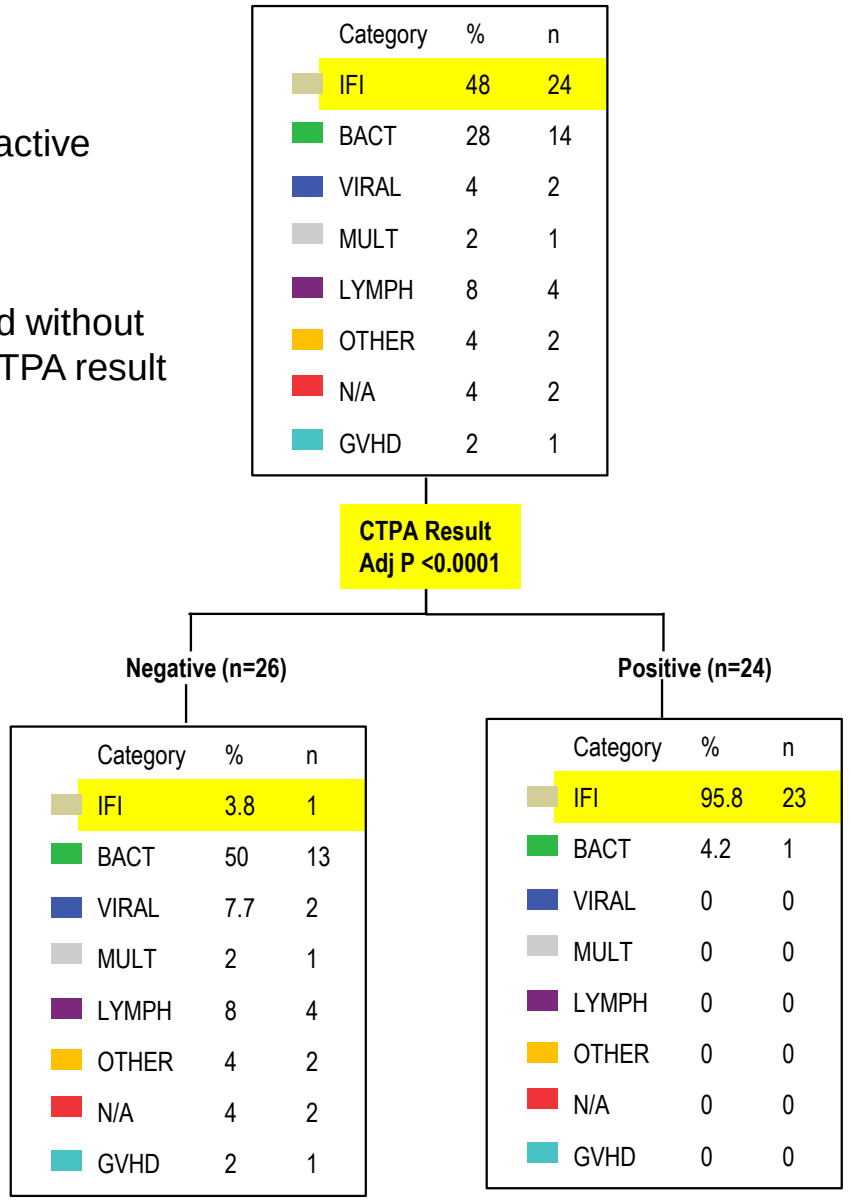
EORTC possible cases of invasive mold disease (n=50)

Unpublished Bologna data

Chi-Square Automatic Interaction Detection (CHAID)
Decision Tree Analysis (

21/50 (42%)
receiving mold-active prophylaxis

Diagnosis coded without knowledge of CTPA result



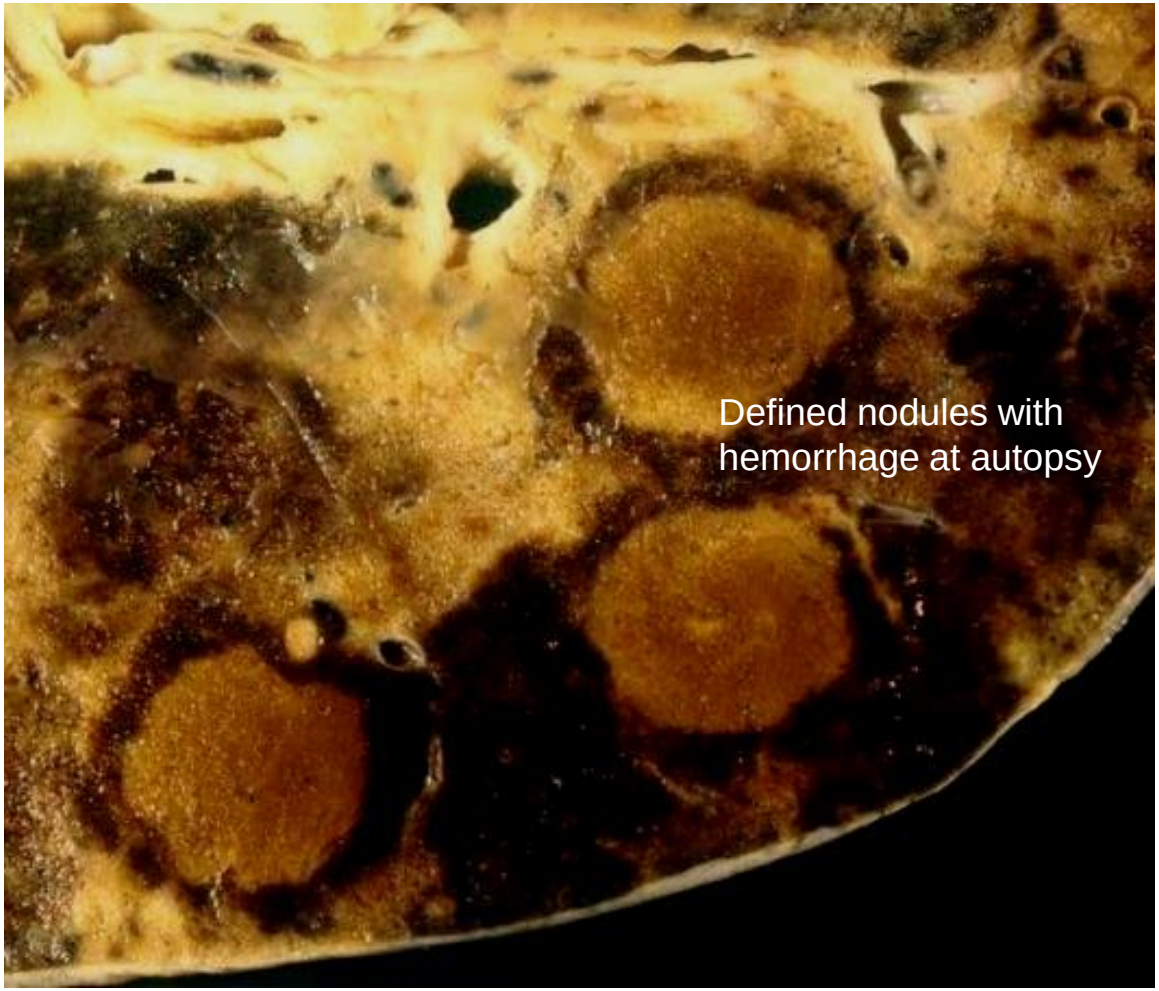
Limitation: Does not differentiate which mold (BAL or tissue diagnosis still needed); but reduces unnecessary antifungal therapy!

Principles for tailored antifungal therapy in suspected breakthrough infection

- Host risk (immunosuppression status)
- Diagnostic certainty
- Spectrum of likely pathogens
- Resistance
- Pharmacology

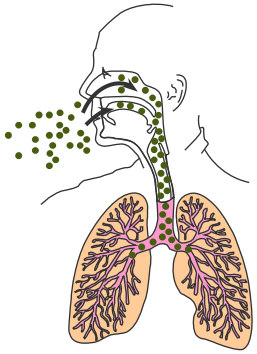
Majority of IA breakthrough cases relapse at previous site with same pathogen

Reactivation of latent, subclinical infection not previously eradicated by antifungal therapy

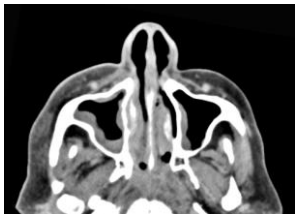


Sipsas & Kontoyiannis. Clin Infect Dis 2006;42:1584-1591.
Shibuya et al. J Infect Chemother 2004;10:138-45.

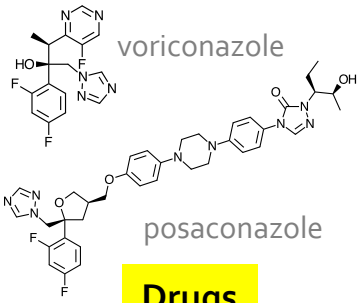
Breakthrough infections with other pathogens



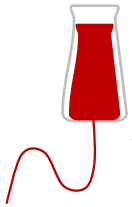
Exposures? Environment



Radiology

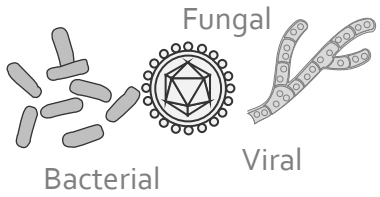


Drugs

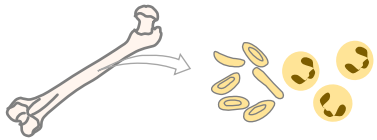


Iron overload?

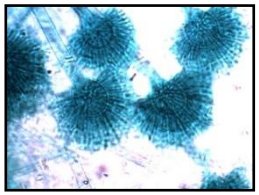
Hyperglycemia?



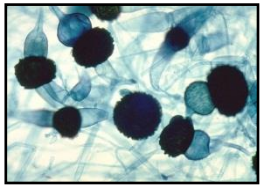
Concomitant infections



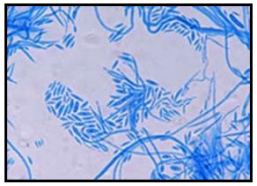
Underlying patient disease, immunosuppression



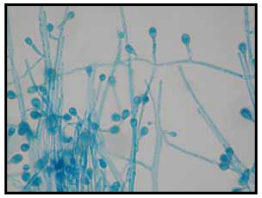
Resistant *Aspergillus?*



Mucorales



***Fusarium* spp.**



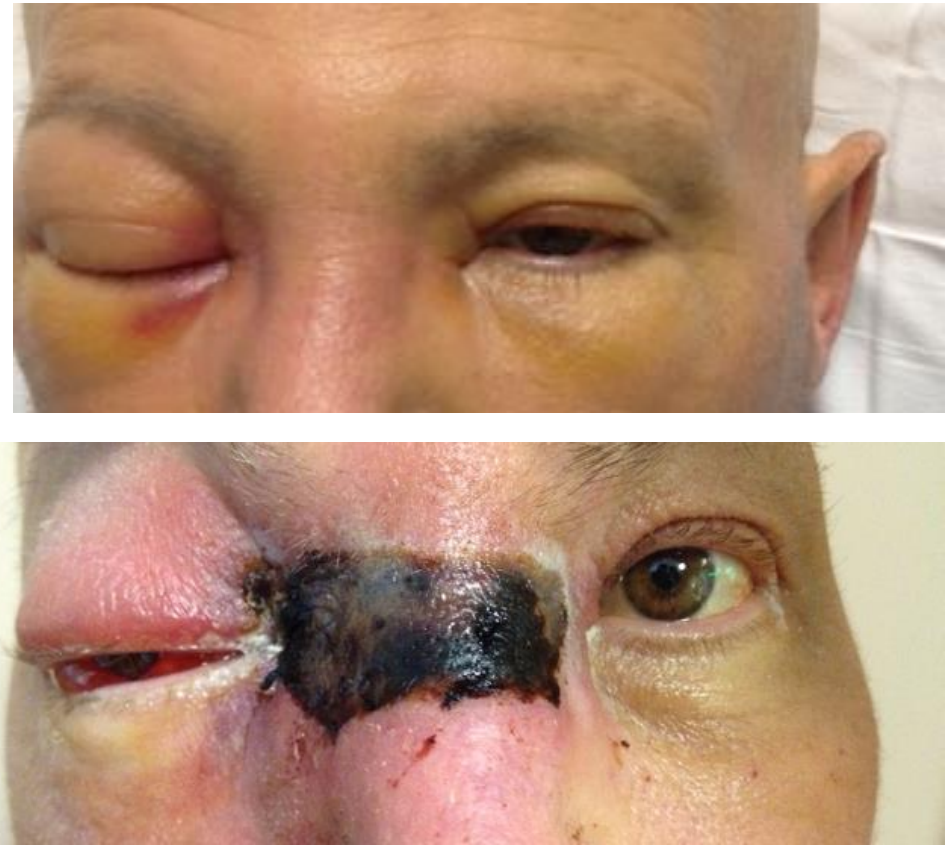
***Scedosporium* spp.**

Local epidemiology

Imperfect understanding of how these factors interaction to define patient risk

Problem with breakthrough mucormycosis

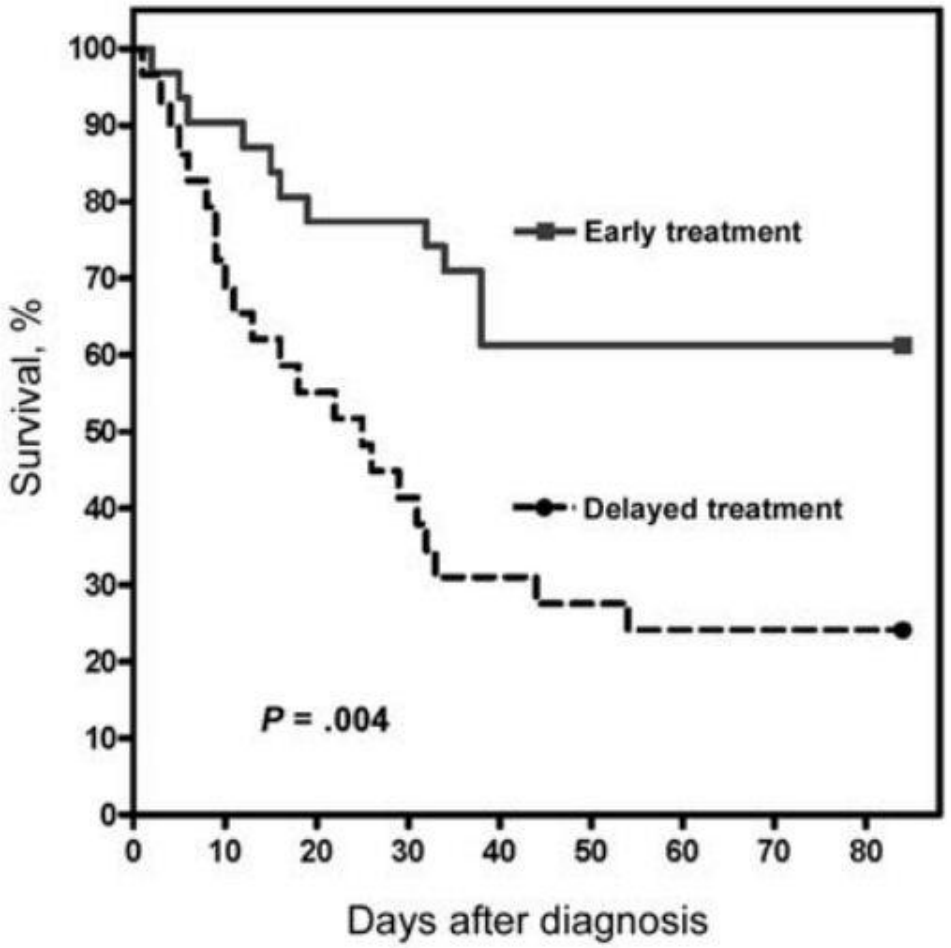
Rapid progression (< 24 hours) of rhinocerebral mucormycosis with necrosis over the nasal bridge in a leukemic patient



Images courtesy of Mona Shiekh Sroujieh, University of Texas M. D. Anderson Cancer Center, Houston

Delay in amphotericin B administration > 5 days is associated with increased mortality from pulmonary mucormycosis (n=70 patients)

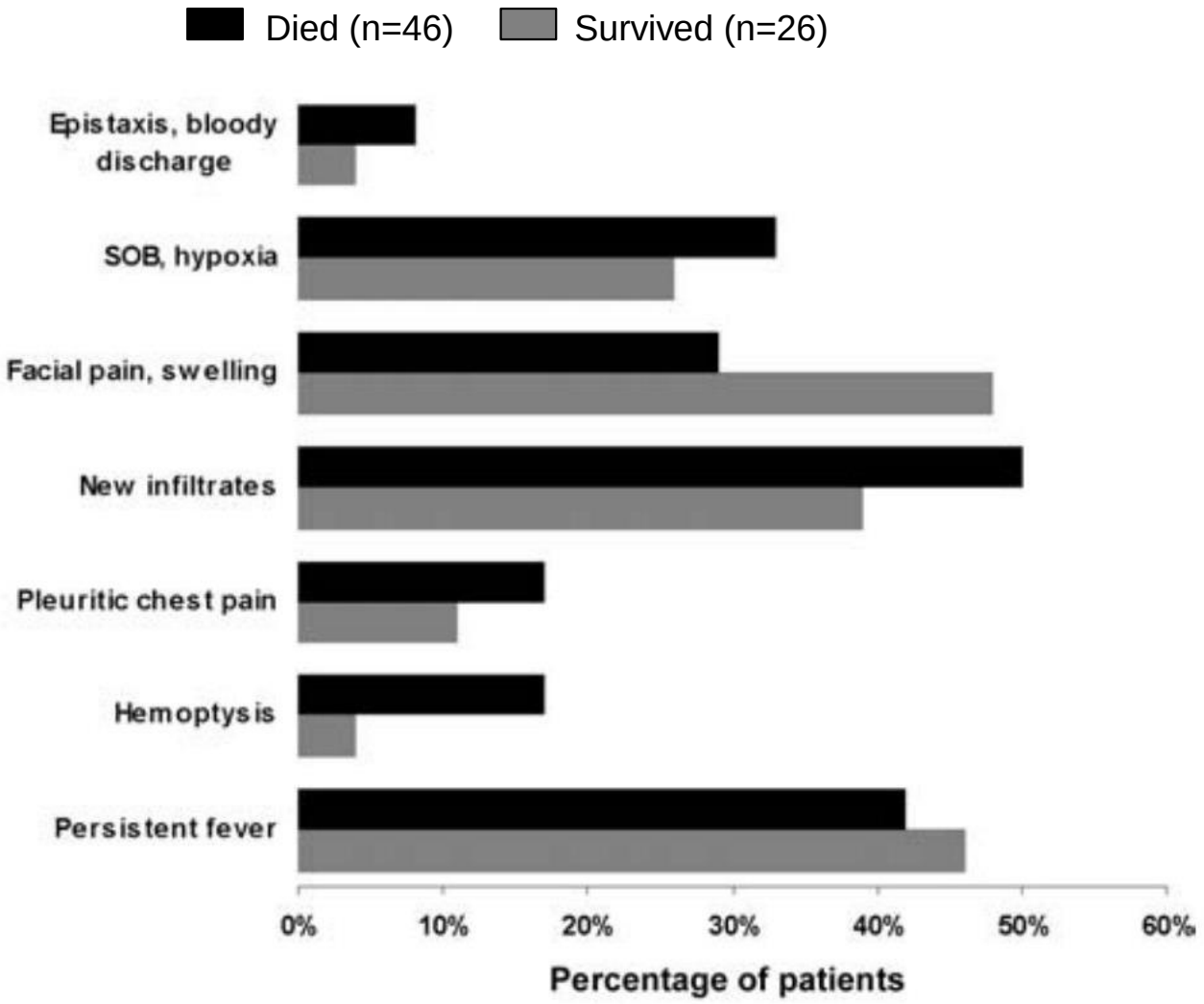
Delayed treatment (> 5 days) defined by CART analysis of mortality risk relative to treatment delay



Impact of earlier treatment evident across all periods of the study

Chamilos et al. Clin Infect Dis 2008;47:503-9.

Initial clinical presentation of non-surviving versus surviving patients with sinopulmonary mucormycosis (n=70)



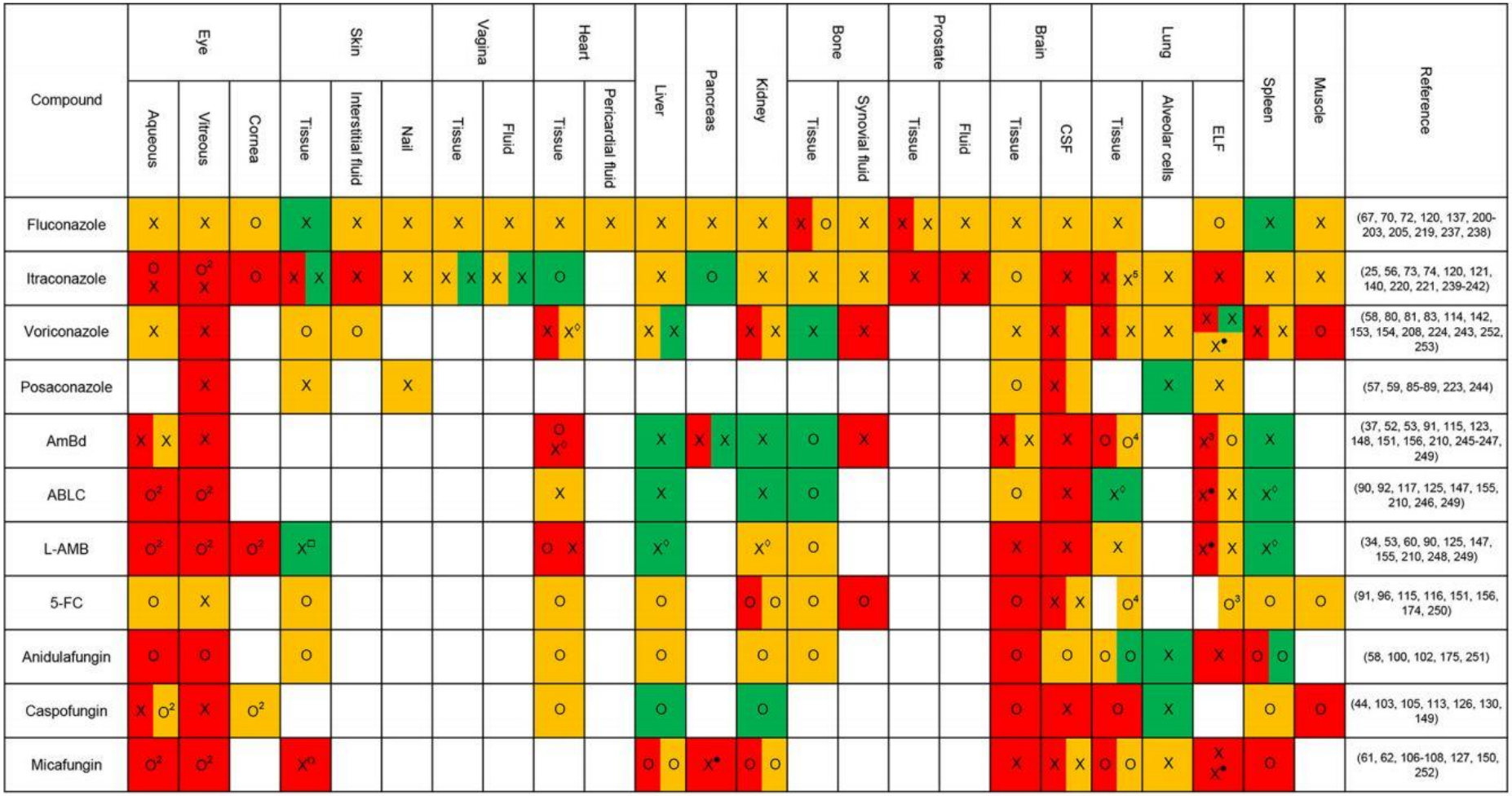
Chamilos et al. Clin Infect Dis 2008;47:503-9.

Therapeutic drug monitoring of triazoles

- Voriconazole/ posaconazole serum trough concentrations correlate with risk of breakthrough mold infection[1-4]
- TDM recommended in cases of suspected breakthrough infection[1,2]
  - True failure vs. inadequate (dose) exposure?
- Breakthrough mold infection in the setting of voriconazole levels > 1 mcg/mL → higher probability of mucormycosis[5]
- Need with new posaconazole formulations or isavuconazole?

1-Ashbee et al. J Antimicrob Chemother 2014;69:1162-76
2-Andes Pascual & Marchetti. Antimicrob Agent Chemother 2009;53:24-34
3-Park et al. Clin Infect Dis 2012;55:1080-87.
4-Pascual et al. Clin Infect Dis 2008,46:201-11.
5-Trifilio et al. Bone Marrow Transplant 2007;39:425-9.

Holes in the pharmacokinetic spectrum of antifungals?



Compound	Eye			Skin			Vagina		Heart		Liver	Pancreas	Kidney	Bone		Prostate		Brain		Lung			Spleen	Muscle	Reference
	Aqueous	Vitreous	Cornea	Tissue	Interstitial fluid	Nail	Tissue	Fluid	Tissue	Pericardial fluid				Tissue	Synovial fluid	Tissue	Fluid	Tissue	CSF	Tissue	Alveolar cells	ELF			
Fluconazole	X	X	O	X	X	X	X	X	X	X	X	X	X	X O	X	X X	X	X	X	X		O	X	X	(67, 70, 72, 120, 137, 200-203, 205, 219, 237, 238)
Itraconazole	O X	O^2 X	O	X X	X	X	X X	X X	O		X	O	X	X	X	X	X	O	X	X X^5	X	X	X	X	(25, 56, 73, 74, 120, 121, 140, 220, 221, 239-242)
Voriconazole	X	X		O	O				X $X^{\diamond}$		X X		X X	X	X			X	X	X X	X	X X $X^{\bullet}$	X X	O	(58, 80, 81, 83, 114, 142, 153, 154, 208, 224, 243, 252, 253)
Posaconazole		X		X		X												O	X		X	X			(57, 59, 85-89, 223, 244)
AmBd	X X	X							O $X^{\diamond}$		X	X X	X	O	X			X X	X	O O^4		X^3 O	X		(37, 52, 53, 91, 115, 123, 148, 151, 156, 210, 245-247, 249)
ABLC	O^2	O^2							X		X		X	O				O	X	$X^{\diamond}$		$X^{\bullet}$ X	$X^{\diamond}$		(90, 92, 117, 125, 147, 155, 210, 246, 249)
L-AMB	O^2	O^2	O^2	$X^{\square}$					O X		$X^{\diamond}$		$X^{\diamond}$	O				X	X	X		$X^{\bullet}$ X	$X^{\diamond}$		(34, 53, 60, 90, 125, 147, 155, 210, 248, 249)
5-FC	O	X		O					O		O		O O	O	O			O	X X	O^4		O^3	O	O	(91, 96, 115, 116, 151, 156, 174, 250)
Anidulafungin	O	O		O					O		O		O	O				O	O	O O	X	X	O O		(58, 100, 102, 175, 251)
Caspofungin	X	O^2	X	O^2					O		O		O					O	X	O	X		O	O	(44, 103, 105, 113, 126, 130, 149)
Micafungin	O^2	O^2		X^{Ω}							O O	$X^{\bullet}$	O O					X	X X	O O	X	X $X^{\bullet}$	O		(61, 62, 106-108, 127, 150, 252)

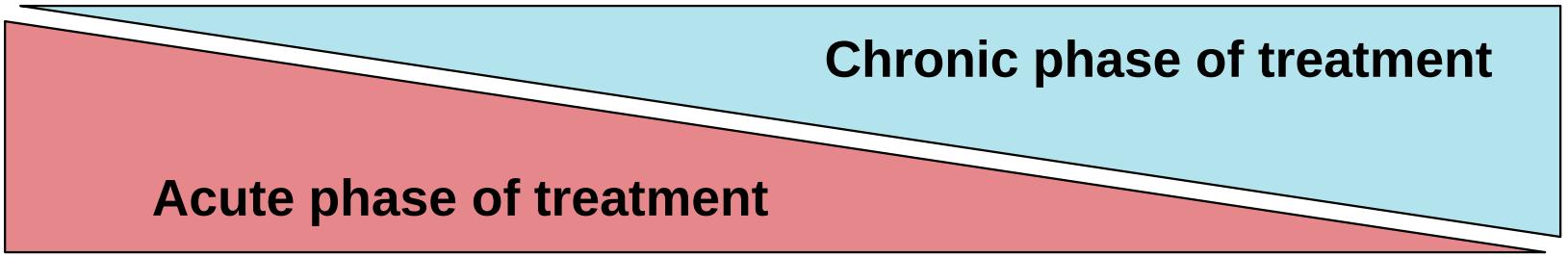
FIG 7 Concentrations in tissues and body fluids for each systemic antifungal agent relative to its concentration in plasma. X, human data; O, animal data. Colors illustrate differing ratios; multiple colors within a column give the range of published data. Red, from below level of detection to ≤0.5 times the plasma concentration; yellow, from >0.5 times to ≤5 times the plasma concentration; green, >5 times the plasma concentration; white, no data. ●, pleural fluid, buccal mucosa, or pancreatic pseudocyst; open diamond, based on autopsy data and human pharmacokinetics; Ω, wound fluid; o^2, only detected in inflamed eyes; o^3, bronchial secretions; x^3, below level of detection in bronchial secretions; o^4, pulmonary lymph; x^5, bronchial biopsy specimen.

0-0.5x >0.5-5x >5x No data X=human data, O= animal data

Felton, Troke & Hope, Clin Microbiol. Reviews 2014

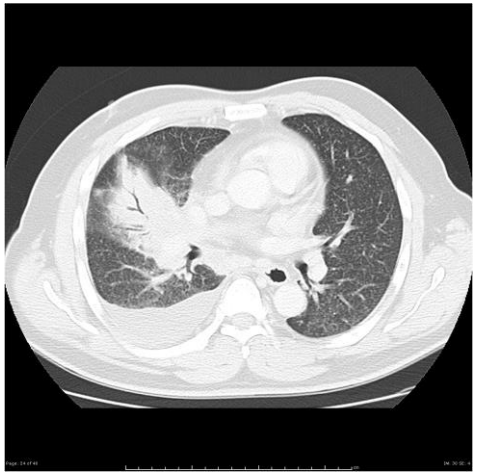
Different Factors to Consider When Empirically Selecting Antifungal Therapy

SPECTRUM / POTENCY	PK PREDICTABILITY	SAFETY	CONVIENENCE
Lipid AMB	Lipid AMB	Echinocandin	Voriconazole
Posaconazole	Echinocandin	Posaconazole	Posaconazole
Voriconazole	Posaconazole	Voriconazole Lipid AMB	Echinocandin Lipid AMB
Echinocandin	Voriconazole		
Pathogen ID MIC testing	TDM, Site of infection, Formulation	Toxicity risks, Drug Interactions	Oral therapy, Compliance



Immune-reconstitution syndrome (IRS) with mold infections

Proposed Model for IRS



Microbial antigen (fungi, HIV)

Iatrogenic immunosuppression

Immunological milieu that is anti-inflammatory and immunosuppressive

Appropriate antimicrobial therapy

Potent antiretroviral therapy

Withdrawal of immunosuppression

Administration of immunostimulatory molecules or cells

Proinflammatory responses

Immune reconstitution syndrome

Singh and Perfect. Lancet Infect Dis 2007

Tailored antifungal therapy for breakthrough mold infection?

Absolutely!

- Host risk (immunosuppression status)
- Diagnostic certainty
- Spectrum of pathogens
- Resistance
- Pharmacology

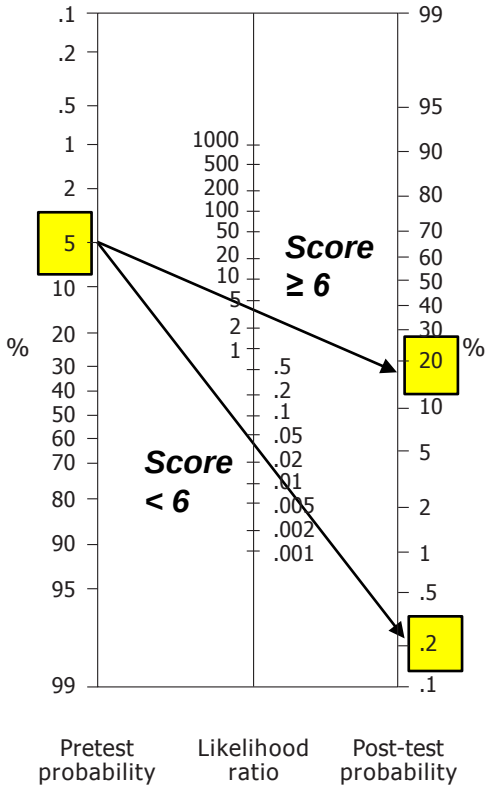
*Save **HEAT** therapy for your back!*

Backup slides

Can the risk score aid clinical decisions?

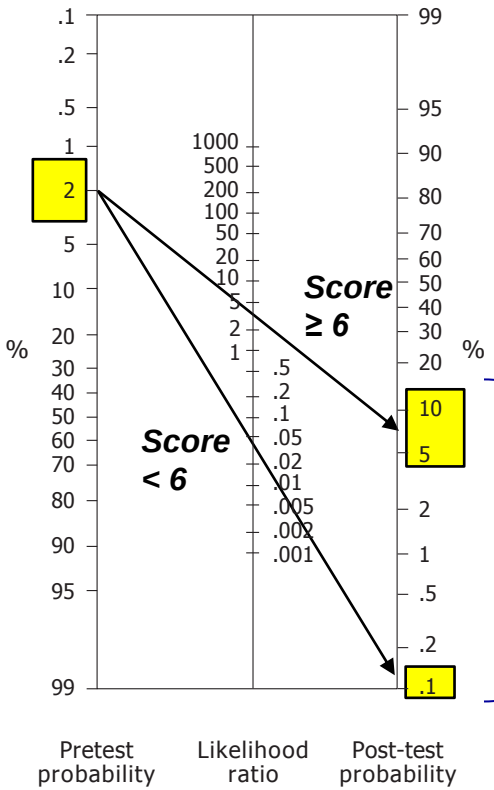
High-primary risk group
(>5% risk of IMD)

+LR 3.3; - LR -0.26



Lower- primary risk group
(2% risk of IMD)

+LR 3.3; - LR -0.26



Nearly 1/3 of proven or probable mold infections were documented in non-transplanted, *lower primary risk* groups with scores equivalent to patients undergoing AML/induction chemotherapy

- More intensive monitoring?
- Score targeted prophylaxis?

Stanzani et al. *Plos One* 2013

Toxicity concerns with CTPA

Contrast:

- ***Abdominal CT*** → 90 – 120 mL
- ***CTPA*** → 50 mL

No patient in our experience has developed nephrotoxicity

Radiation:

- ***Pulmonary HRCT*** → total body dose

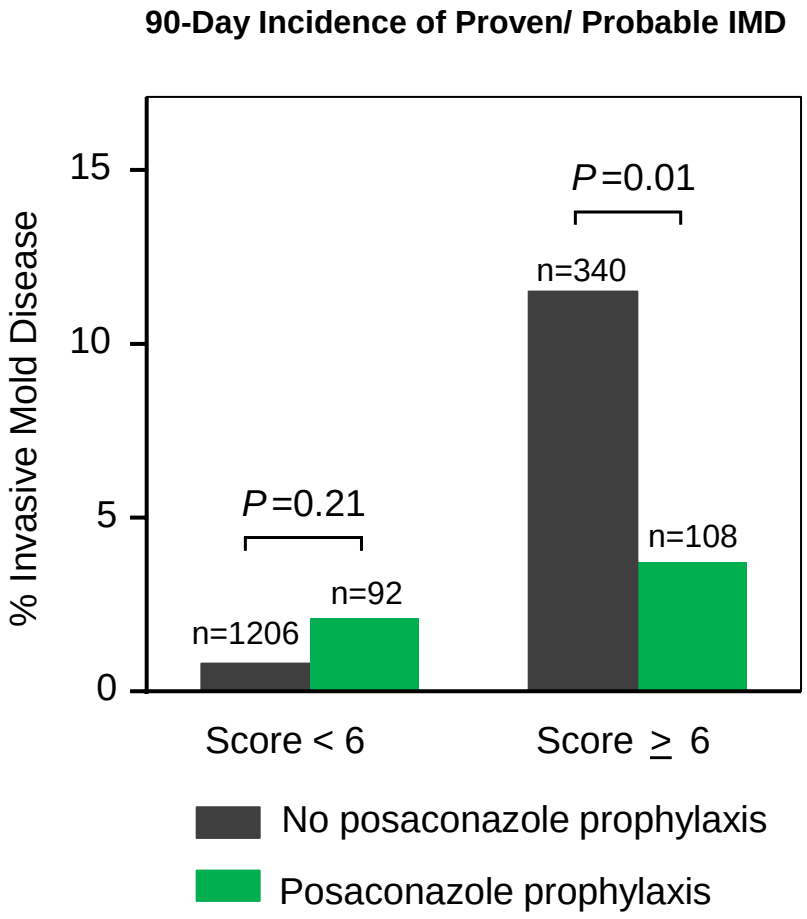
  DLP **400 mGy** (CTDI 10.3 mGy)

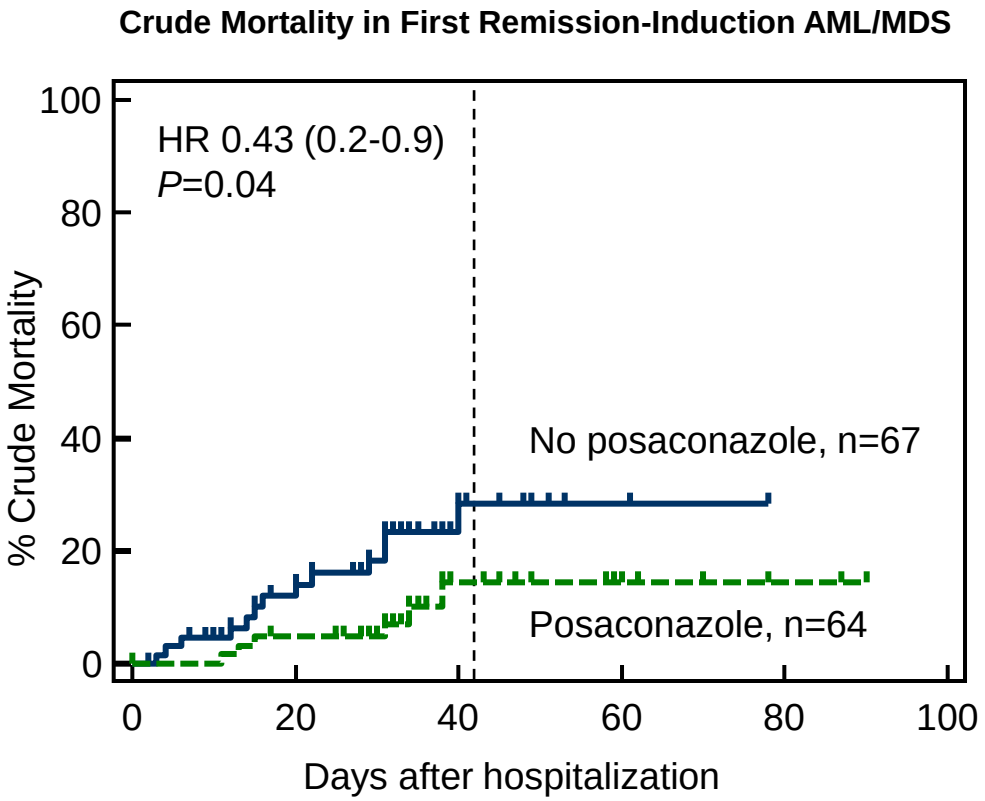
- ***CTPA*** → total body dose

  DLP **800 mGy** (CTDI 18 mGy)

Typical background radiation exposure per year: 2.4 mGy

Impact of Posaconazole Prophylaxis
Prospective Validation Cohort (2009-2012)





Stanzani et al. *Plos One* 2013