Salvage Therapy of Invasive Aspergillosis Refractory to Primary Treatment with Voriconazole

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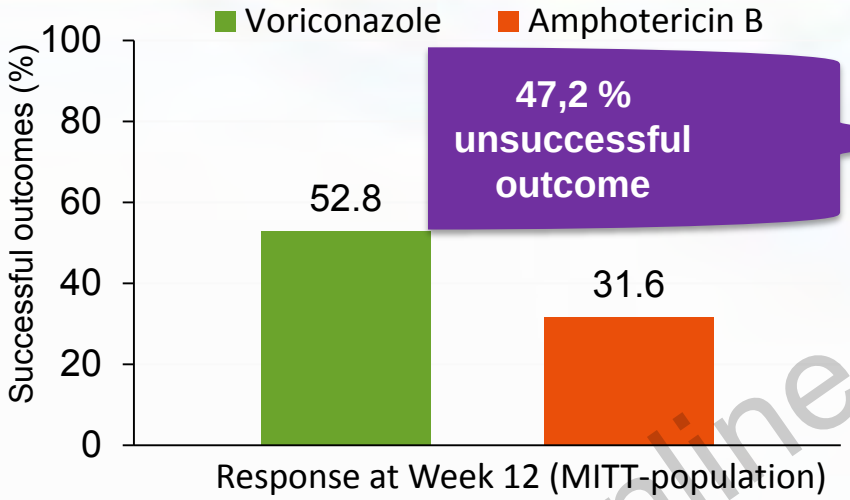
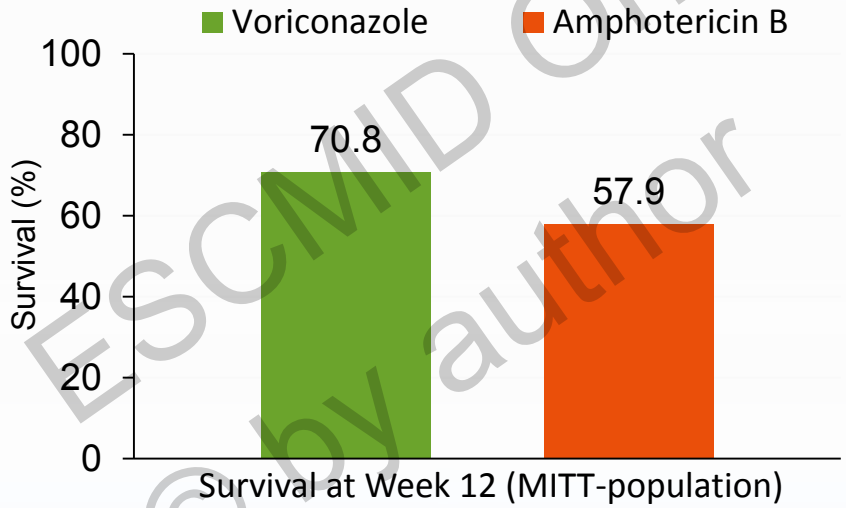
Current guidelines: first-line treatment of invasive aspergillosis

Drugs	IDSA[1]	UK[2]	ECIL[3]	DGHO[4]	Australia[5]
AmB DC	D	D	D	EII	Alternative
AmB-LS	AI	AI	BI	AII	Alternative
ABLC			BII		
ABCD			D		
Itraconazole			CIII		
Posaconazole					
Voriconazole	**AI**	**AI**	**AI**	**AI**	**Recommended**
Caspofungin		AI	CII		
Micafungin					
Combination	Not recommended	Discou-raged	Discou-raged	CIII	No supportive evidence

1. Walsh TJ et al. Clin Infect Dis 2008;46:327–60.
2. Prentice AG, et al. http://www.bcshguidelines.com/documents/fungal_infection_bcsh_2008.pdf
3. Maertens J et al. Bone Marrow Transplantation 2011; 46:709–18
4. Bohme A et al. Ann Hematol 2009;88:97–110
5. Thursky KA et al. Intern Med J 2008;38:496–520.

Primary treatment of invasive aspergillosis response rate and survival





Stable disease	5,6%
Failure of therapy*	38,2%
Indeterminate	3,5%

* Was defined by worsening disease

Herbrecht R et al. N Engl J Med 2002;347:408–15

Salvage treatment of invasive aspergillosis antifungal treatment options

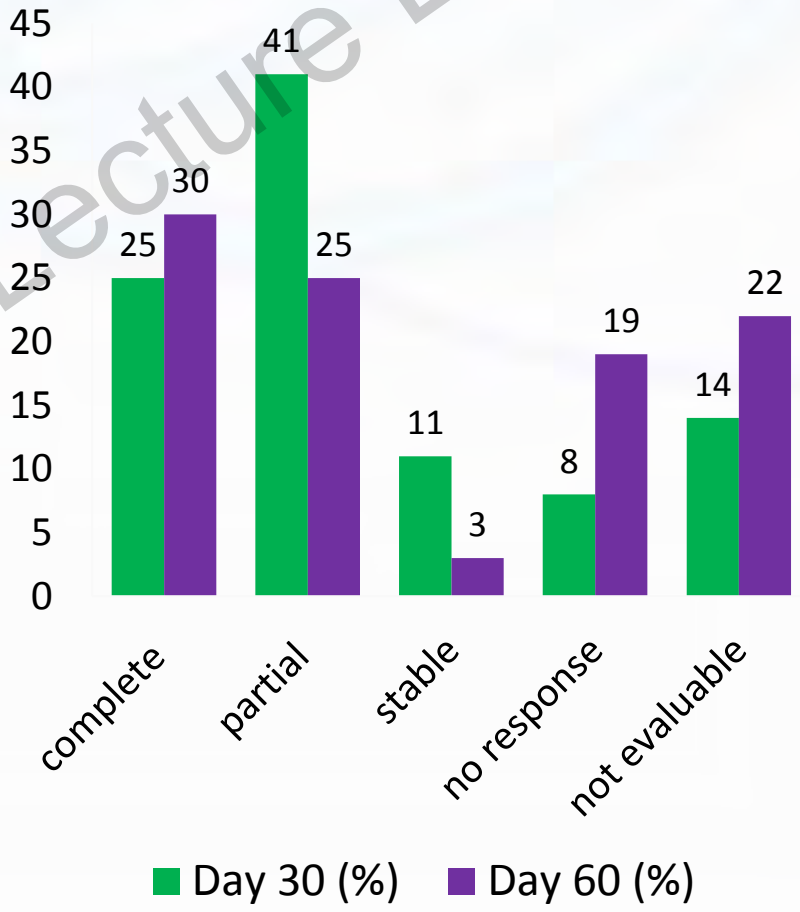
- **Same class of antifungal drug**
  - Usually with a broader spectrum
- **Change to another antifungal drug class**
  - Polyene
  - Echinocandin
- **Combine antifungal drugs**
  - Add on: voriconazole + polyene
  - Add on: voriconazole + echinocandin
  - Switch: polyene + echinocandin or other azole + echinocandin or other azole + polyene
  - Triple therapy

Salvage treatment of invasive aspergillosis refractory to voriconazole therapy

Antifungal agent		Reference
Liposomal AmB 3-5 mg/kg		Ringden JAC 1991; Ng AIM 1995; Hachem Cancer 2008
ABLC 5 mg/kg		Ito BMT 2005; Chandrasekar CID 2005; Walsh CID 2008; Hachem Cancer 2008
ABCD		Oppenheim CID 1995; Herbrecht Chem 1999
Itraconazole		
Posaconazole 400 mg bid		Walsh CID 2007; Hachem JAC 2008; Heinz Mycoses 2013
Caspofungin 70/50 mg		Maertens CID 2004; Kartsonis J Infect 2005; Betts Cancer 2006; Morrissey Mycoses 2007; Hiemenz EJCMID 2010; Maertens BMCID 2010; Egerer EJMR 2012; Leon-Gil REQ 2012
Micafungin 75-200 mg (?)		Denning J Infect 2006; Enoch J Infect 2014
Anidulafungin		
Combination		Maertens Cancer 2006; Raad Leukemia 2008

Posaconazole after previous therapy with voriconazole in invasive aspergillosis

- Retrospective, multi-center study
- 36 patients
  - Refractory: 23
  - Intolerant: 10
  - Both: 3
- Invasive aspergillosis
  - Proven: 1
  - Probable: 7
  - Possible: 28
- Evaluation @ day 30 and day 60
- No data review committee
- Definition of refractory not reported



Heinz WJ et al. Mycoses 2013; 56: 304-310

Definition of refractory invasive aspergillosis

General criteria for global responses to antifungal therapy

Outcome, response	Criteria
Success	
Complete response	Survival within the prespecified period of observation, resolution of all attributable symptoms and signs of disease and radiological abnormalities, and mycological evidence of eradication of disease
Death	Death during the prespecified period of evaluation, regardless of attribution

[a] In certain invasive fungal diseases (e.g., invasive mold diseases), stabilization of fungal disease during periods of severe immunocompromise provides evidence of efficacy of treatment and may be a reasonable short-term therapeutic goal until immune recovery occurs.

Progression of fungal disease:

Evidence of progressive fungal disease based on a composite of clinical, radiological, and mycological criteria

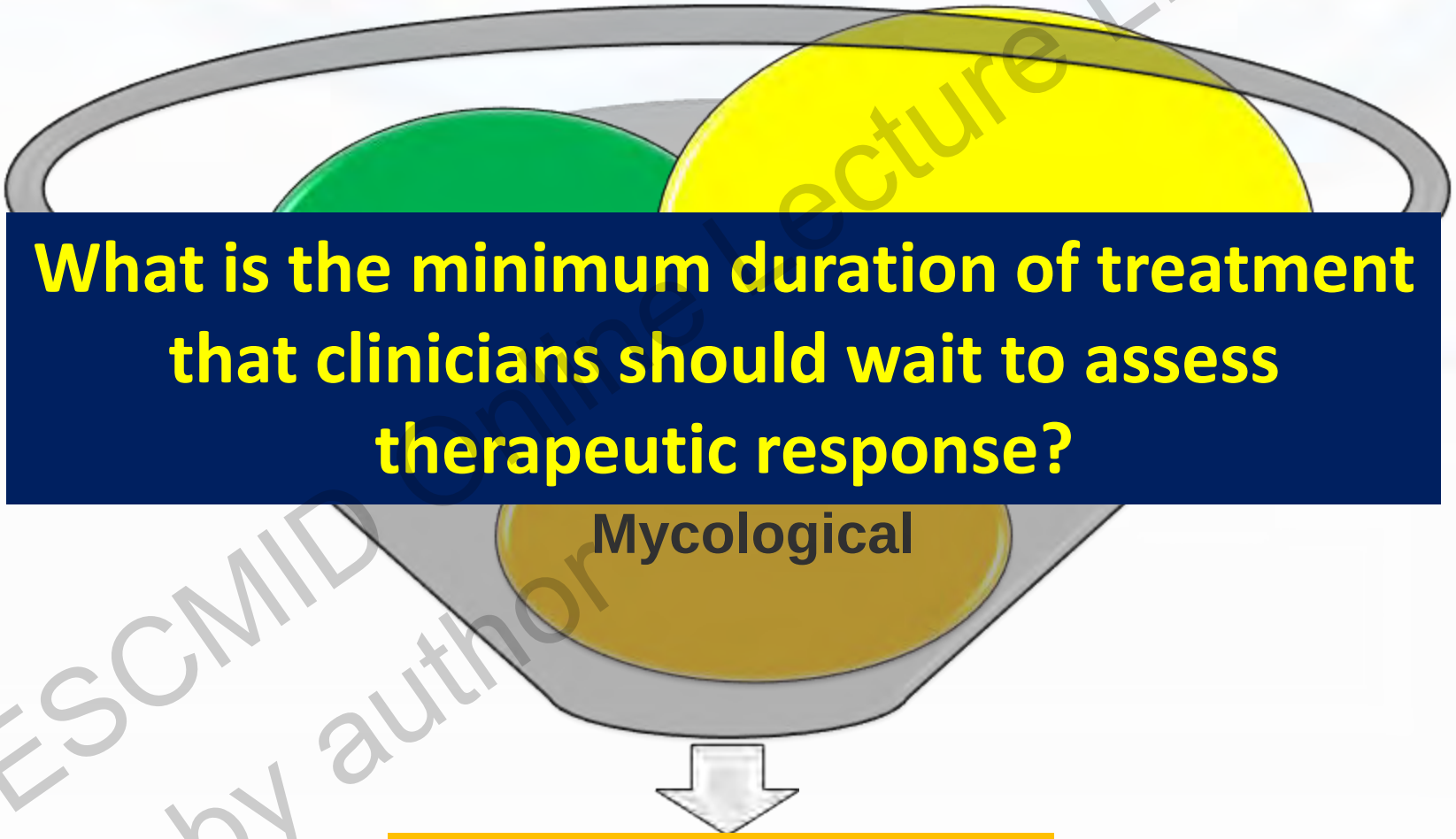
Segal B H et al. Clin Infect Dis 2008;47:674-683

Response to antifungal therapy in patients with invasive aspergillosis: Failure

- Stable response
- **Progression of disease**
  - *Worsening clinical signs or symptoms of disease AND*
  - *New sites of disease or radiological worsening of preexisting lesions; OR*
  - *Persistent isolation of Aspergillus species from infected sites*
- Death
  - *Of note: definitions do not mention serological markers*

Segal B H et al. Clin Infect Dis 2008;47:674-683

Response assessment of disease based on a composite outcome



The antifungal treatment conundrum

Clinical

- S&S are non-specific
- Absence of fever
- Dyspnea multifactorial
- Hemoptysis after neutrophil recovery

Radiological

- Early (up to 4-fold) increase of volume of lesions on CT
- IRIS
- Cavitation with neutrophil recovery
- Effects of surgery
- Inadequate knowledge about radiological evolution in non-neutropenics

Mycological

- Cultures often negative
- Repeated sampling not feasible
- Coexistent bacterial, viral, or fungal diseases
- Use of surrogate markers (galactomannan)?

Causes of antifungal therapy failure

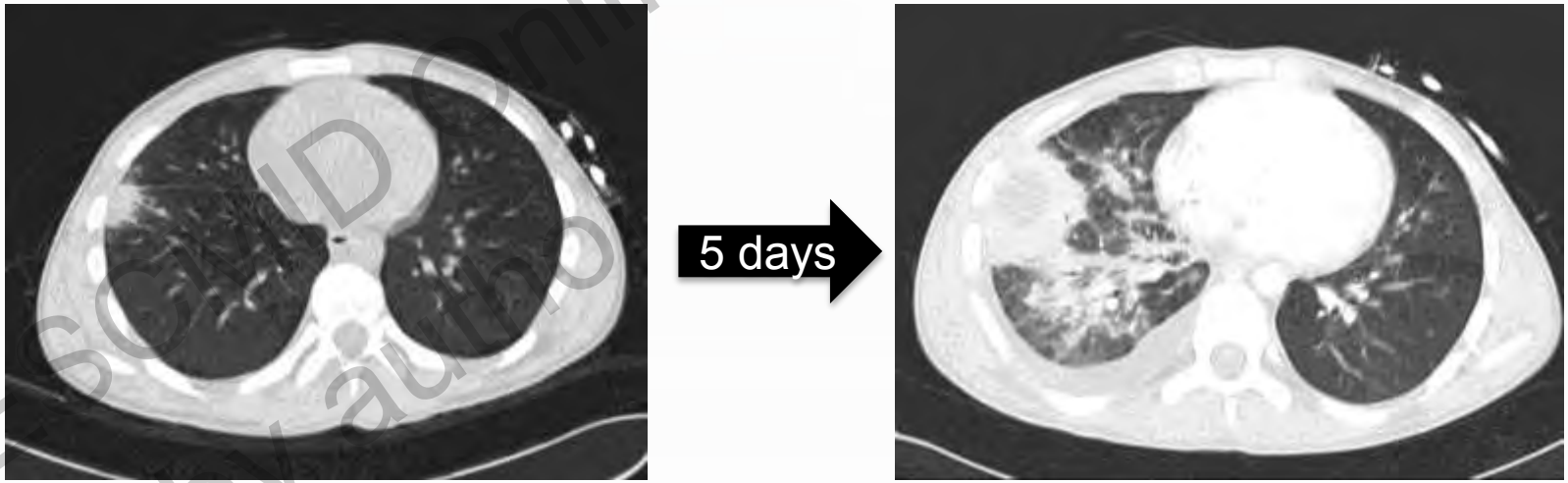
- **Host factors**
  - Severity of illness
  - Persistence of immunodeficiency (e.g., neutropenia or use of steroids)
- **Primary (intrinsic) drug resistance**
- **Wrong diagnosis**
- **Mixed infection**
- **Low concentration of the drug at the site of infection**
  - Pharmacokinetic and pharmacodynamic
  - Drug interactions
  - Biofilms
  - Poor vascular supply (e.g., abscess and necrotic tissue)
- **Drug toxicities and drug interactions**
- **Development of resistance (secondary)**
- **Misdiagnosis of failure – immune reconstitution inflammatory syndrome**

Nucci M and Perfect JR. Clin Infect Dis. 2008; 1426-1433

Approaching 'refractory' cases: a multi-step process

1. Diagnose 'antifungal therapy failure' appropriately

- Signs of persistent fungal infection may be related to other factors.
- Don't judge 'failure' too early.
- Review the diagnosis of aspergillosis. Are genus and species known?
- Exclude superinfections and/or mixed infections. Check cultures and/or histopathology
- Is the drug correct? Is the pathogen intrinsically resistant to the drug?



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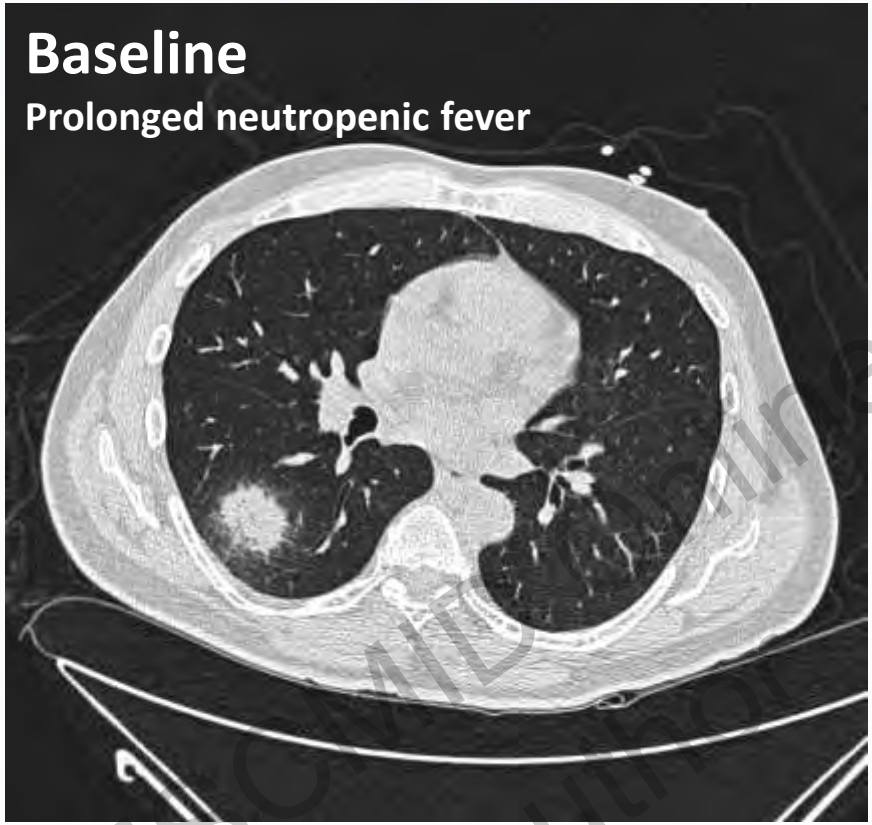
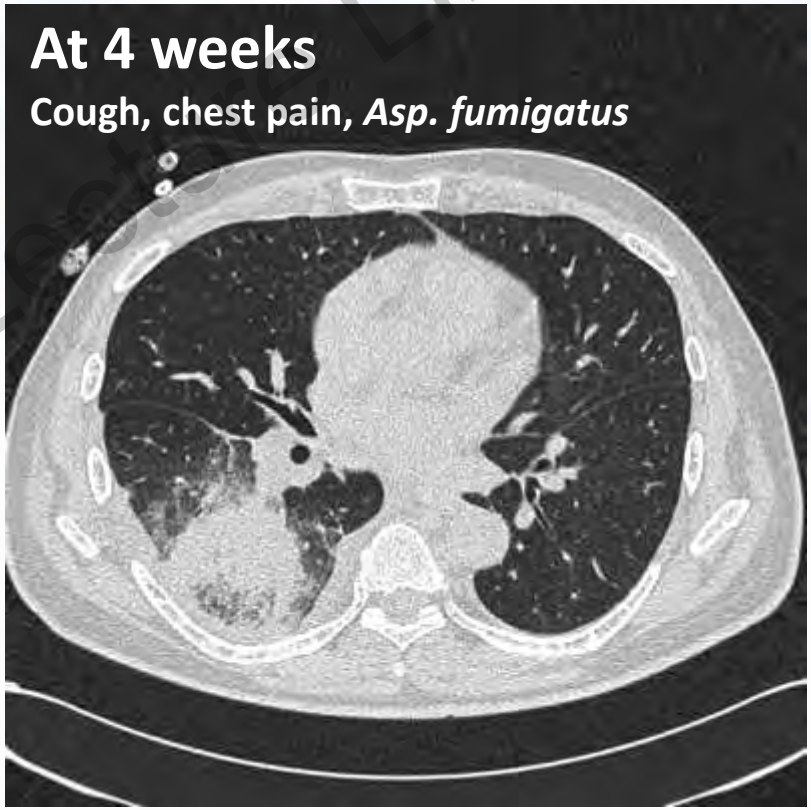
Approaching 'refractory' cases: a multi-step process

2. Is immune reconstitution syndrome a possibility?





Neutrophils: 0/µL **GM serum: 3.2** **GM BAL: 8.6**

Neutrophils: 12.360 /µL **GM serum: 0.8** **GM BAL: 1.2**

Immune Reconstitution Inflammatory Syndrome (IRIS)

- **Setting**: recovery from neutropenia or tapering of immunosuppression or HAART in AIDS patients
  - → check for other evidence of response!
- **IRIS working definition**
- New onset of or worsening clinical and radiological pulmonary findings consistent with an infectious/inflammatory pulmonary condition
- Temporal relationship with neutrophil recovery (or *tapering of immunosuppression*)
- Absence of new extra-pulmonary lesions
- ≥ 50% decrease in serum GMI titers without treatment modifications
- Subsequent resolution without treatment modification

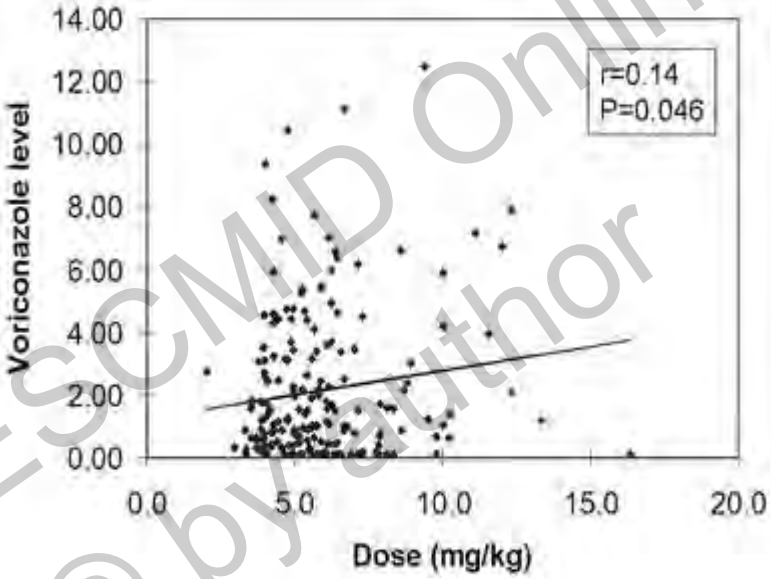
These patients may benefit from steroid treatment!

Miceli MH et al. Cancer 2007; 110: 112-120

Approaching 'refractory' cases: a multi-step process

3. Is the dose of the drug adequate?

- Voriconazole: non-linear pharmacokinetic profile in adults
  - Up to 100-fold inter-patient and intra-patient variation
- Levels <2 mg/L have been associated with a high failure rate in patients with confirmed IFI (Smith et al. AAC 2006;50:1570)
- Steady-state through levels (HPLC) measured in 87 patients
- Daily voriconazole dose: median 5.4 mg/kg



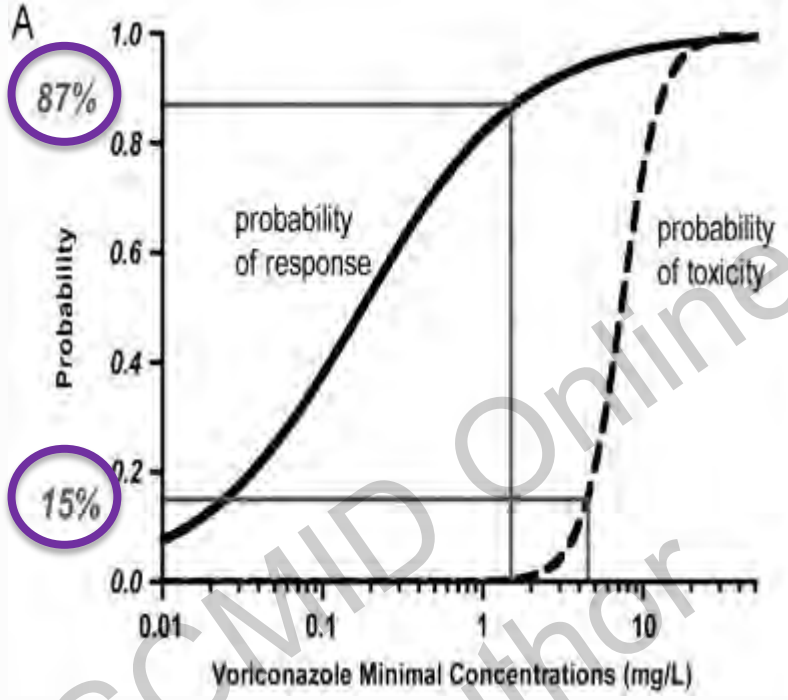
Vorico level	N	Dose (mg/kg)
< 0.2 (und.)	15 %	5.6
0.2 to 0.5	12 %	6.2
> 0.5 to 2.0	35 %	5.2
> 2.0 to 5.0	26 %	4.9
> 5.0	11 %	6.9

Trifilio et al. Cancer 2007

Trifilio S et al. Cancer 2007; 109: 1532-1535.

Population pharmacokinetics-based analysis (adults)

A



B

VRC trough plasma concentration (mg/L)	Probability of response of IFI to VRC therapy	Probability of grade 3 neurotoxicity associated with VRC
0.5	72%	0%
1.0	82%	0%
1.5	**87%**	0.3%
2.0	89%	1%
4.0	93%	11%
4.5	94%	**15%**
5.0	95%	21%
5.5	95%	27%

Pascual A et al. Clin Infect Dis 2012;55:381-390

Inadequate drug levels: interactions with metabolic enzymes and transporters

2C9

Substrate	Inhibitor
Voriconazole	Fluconazole
	Itraconazole
	Voriconazole

2C19

Substrate	Inhibitor
Voriconazole	Fluconazole
	Voriconazole

ENZYME SYSTEM

3A4

Substrate	Inhibitor
Itraconazole	Fluconazole
Voriconazole	Itraconazole
	Voriconazole
	Posaconazole

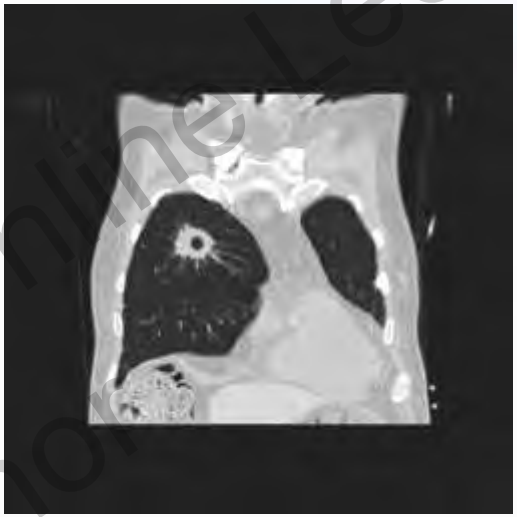
P-GP transporter

Substrate	Inhibitor
Posaconazole	Itraconazole
	Posaconazole

Brüggemann R et al. Clin Infect Dis 2009:48:1441-58 (adapted from Dr. Peter Donnelly)

Inadequate drug levels at site of infection

- Poor drug penetration in tissue
- Poor vascular supply (abscess; necrotic tissue)

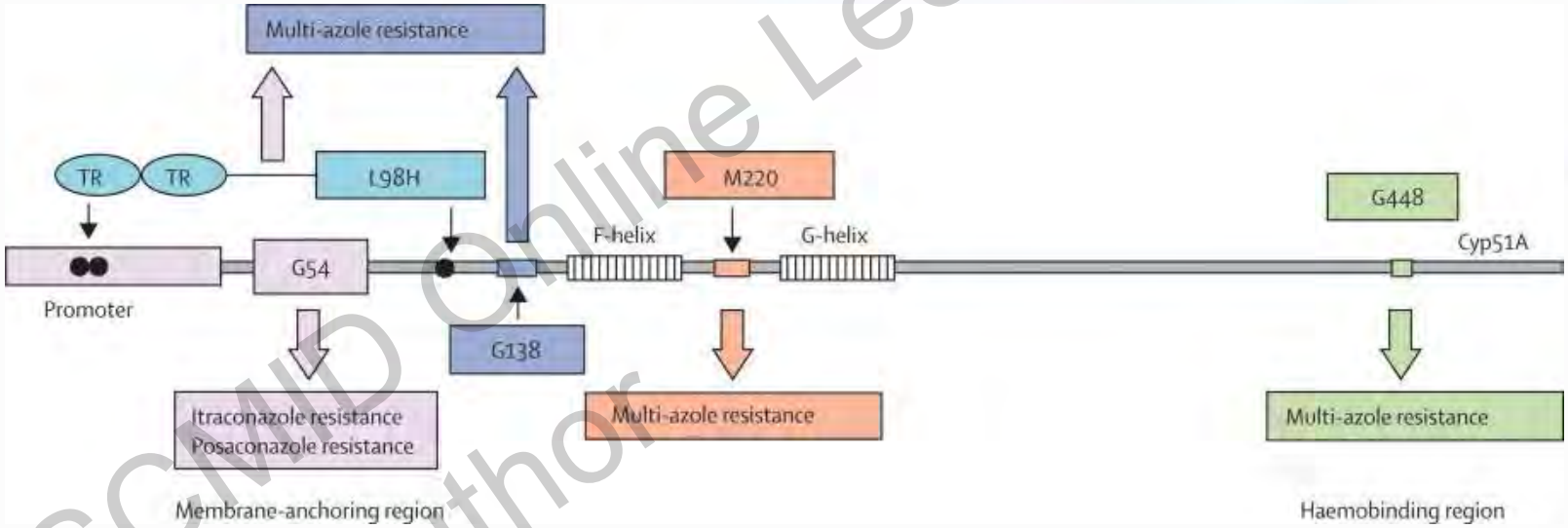


- Biofilm formation (prosthetic material)

Approaching 'refractory' cases: a multi-step process

4. Did the fungus develop resistance?

- Two routes: 'in-patient' and 'environmental'
- TR_{34}/L98H→ Pan-azole resistance

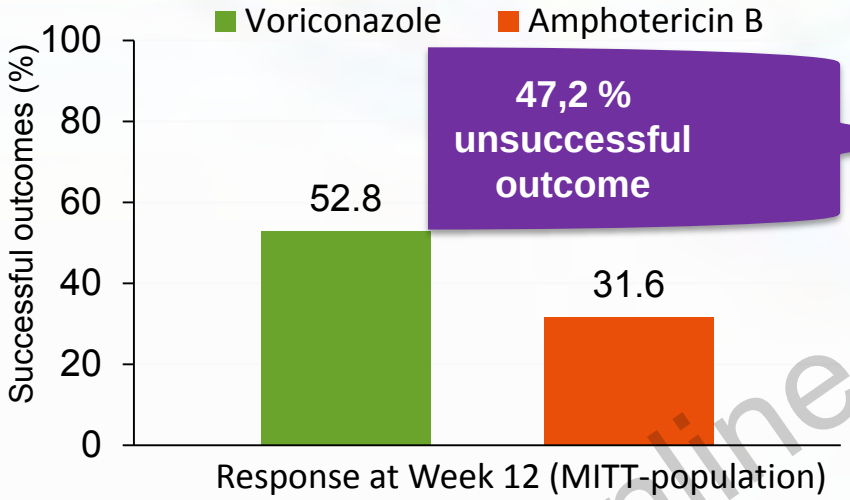


- TR_{46}/Y121F/T289A→ high-grade voriconazole resistance

Vermeulen E et al. Curr Opin Infect Dis 2013; 26: 493-500

Approaching 'refractory' cases: a multi-step process

5. Host factors are the most frequent cause of failure!



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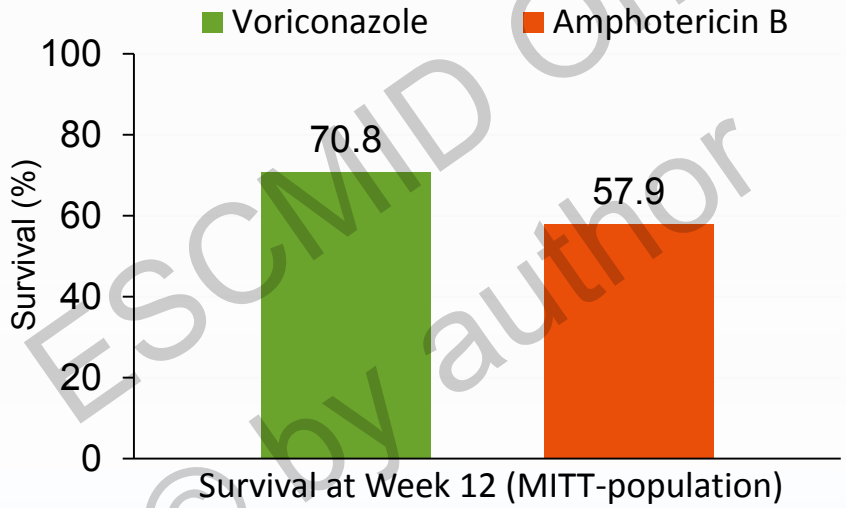

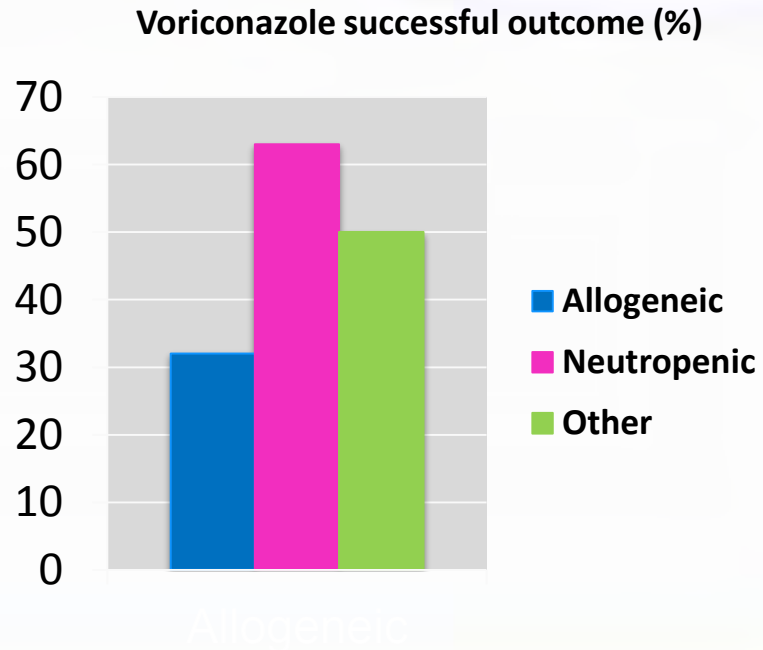

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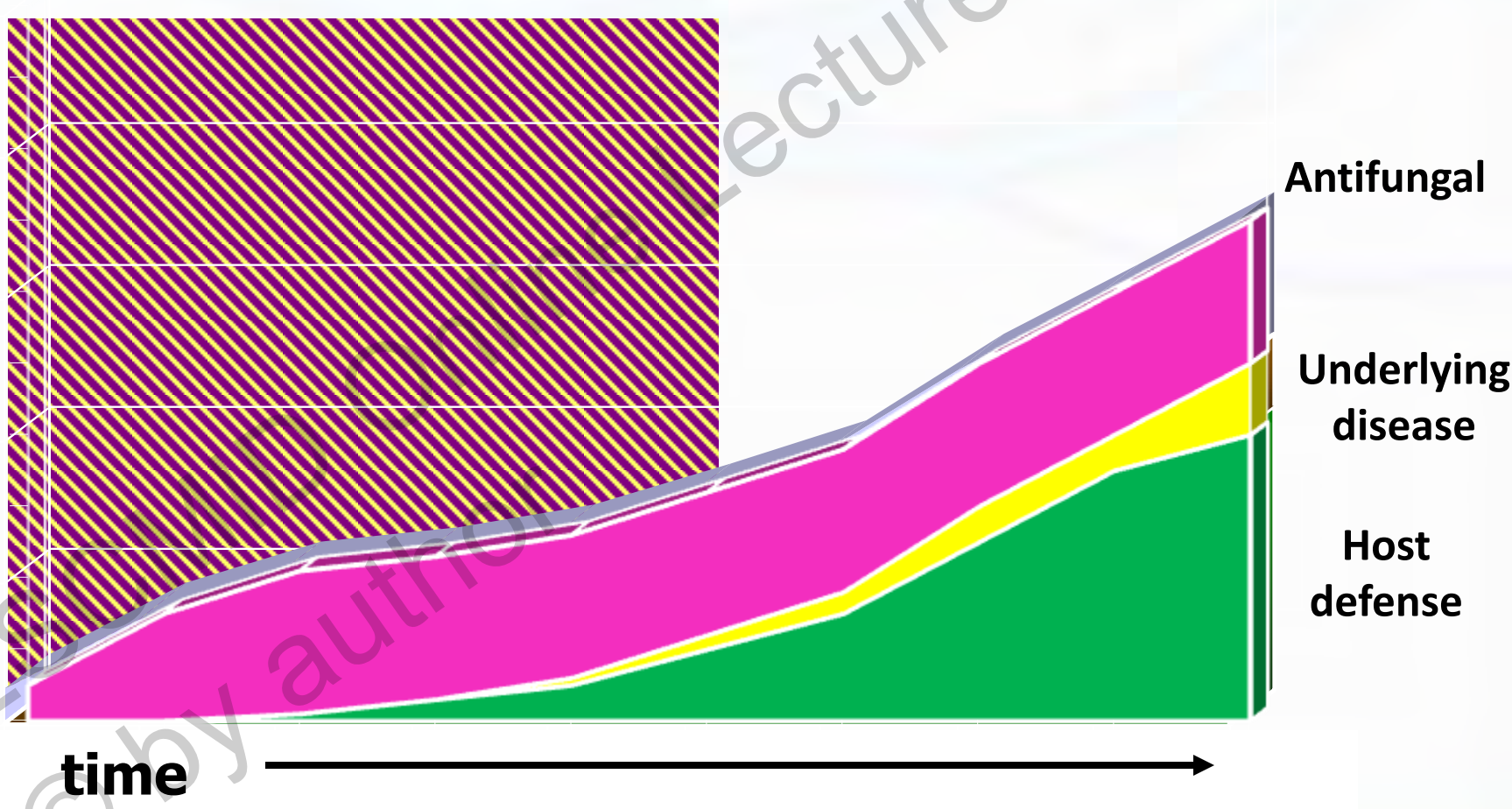

Courtesy Prof. Dr. Ben de Pauw

Conclusion(s)

- Antifungal treatment failure is a **diagnosis of exclusion**:
  - Persistence of clinical manifestations of infection at an appropriate time
  - Primary diagnosis confirmed
  - Superinfection and/or mixed infection ruled out
  - Choice of drug and dosage correct
  - Poor vascular supply ruled out
  - IRIS ruled out
- Management issues:
  - Identification to species level and (azole) susceptibility testing
  - Therapeutic drug monitoring (esp. azoles) and dose adaptation
  - Surgical intervention/removal foreign bodies may be needed
  - Adequate management of underlying disease
  - … **and : consider change in individual class of antifungal or combination therapy**
- Current tools to assess treatment response have enormous shortcomings