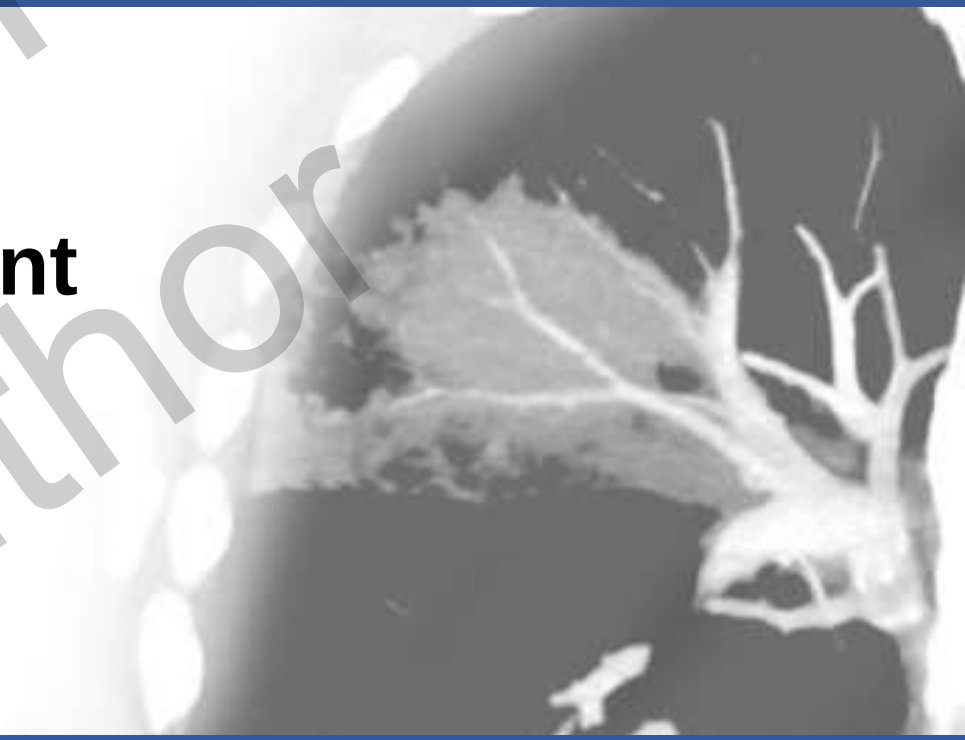
Session SY217: Controversies in fungal infection management
24 April 2018, 28° ECCMID, Madrid

Less useful than you think

In vitro susceptibility testing is ~~NOT useful~~ in the management of aspergillosis in patients with haematological malignancies



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Problems of using mould MICs to make clinical decisions

1. **Culture-based management of invasive mould disease is becoming less common**
2. **The MIC test has many methodological limitations**
3. **We really don't know the clinical predictive value of an MIC in the management of aspergillosis**
4. **MIC-based dosing adjustments can be a bad idea**

Problems of using mould MICs to make clinical decisions

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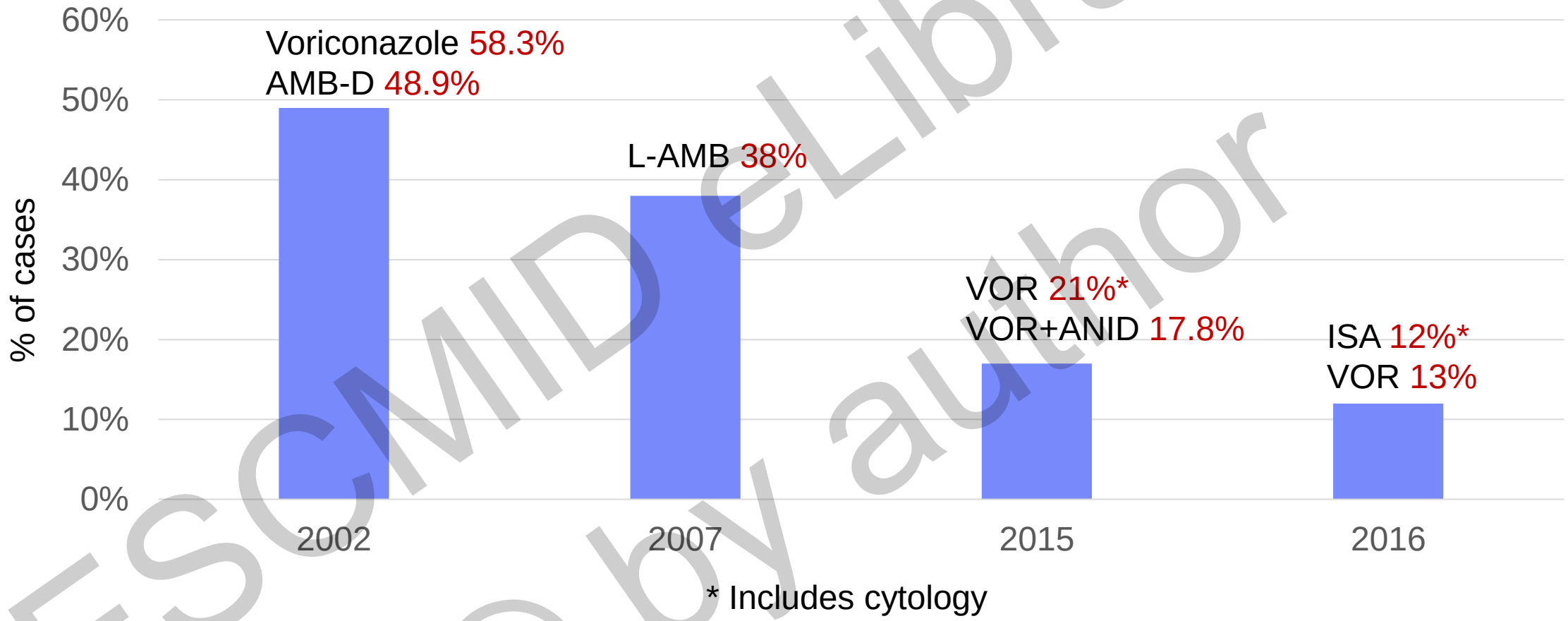
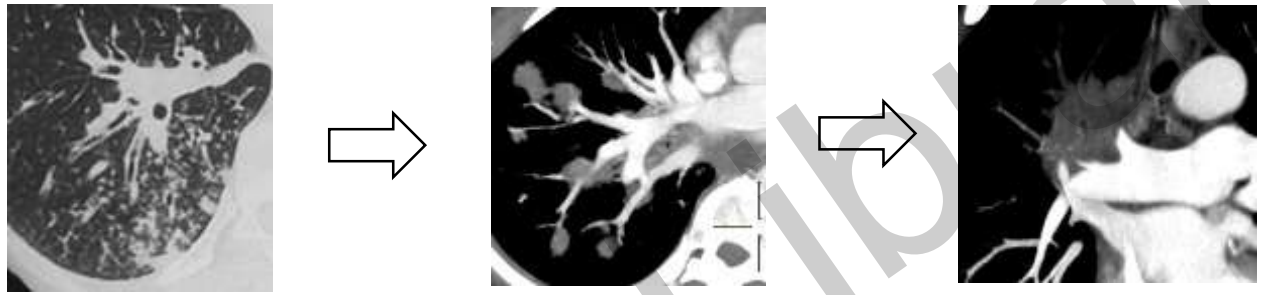
Culture-based diagnostics in randomized clinical trials of aspergillosis

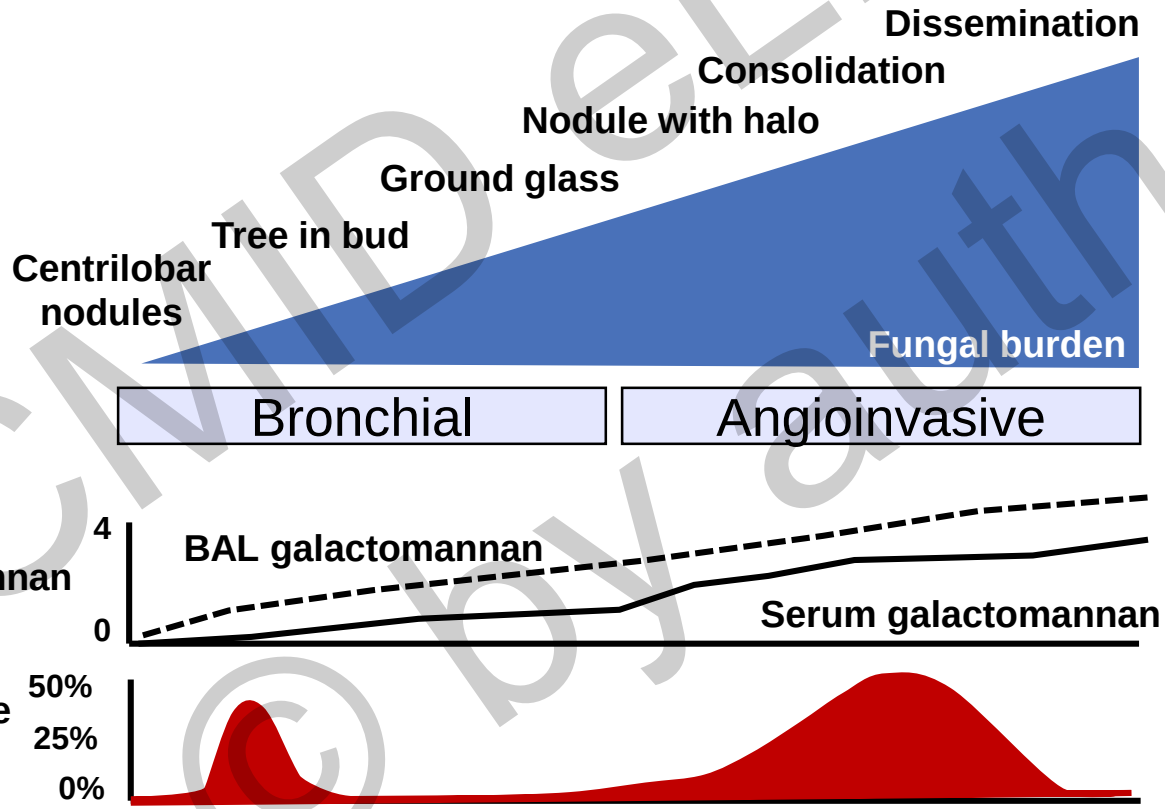


Seràgnoli Hematology Institute (2010-2016): varies between 18-36% percent

Maertens JA, et al. Lancet 2016; 387:760–769; Marr KA, et al. Ann Intern Med 2015;162:81–89.;
Cornely OA, et al. Clin Infect Dis 2007;44:1289–1297.; Herbrecht R, et al. N Engl J Med 2002;347:408–415

Culture diagnosis of aspergillosis by bronchoscopy is often biomodal

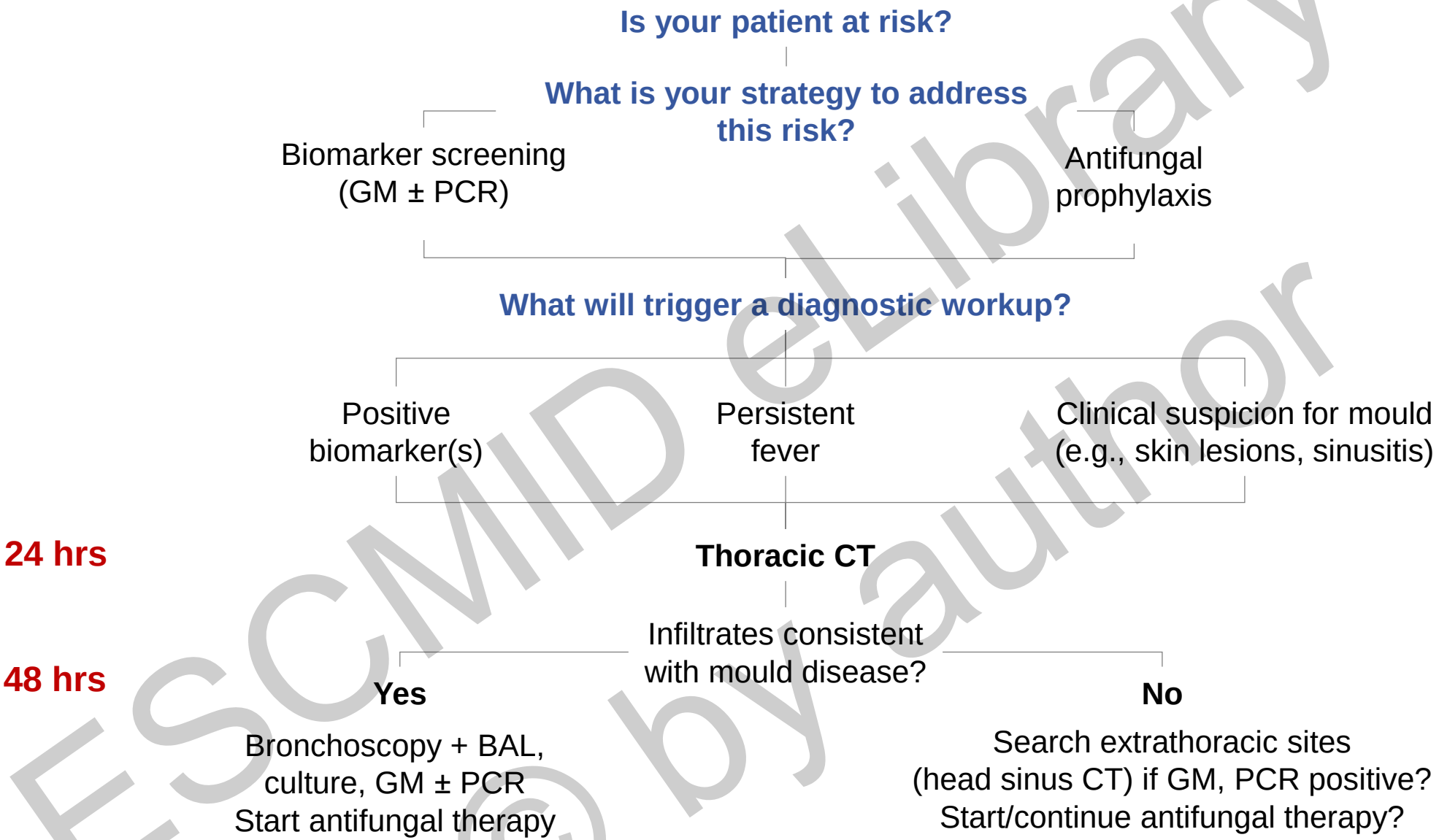




Affected by host immune status; pathogen virulence; antifungal therapy; and diagnostic techniques

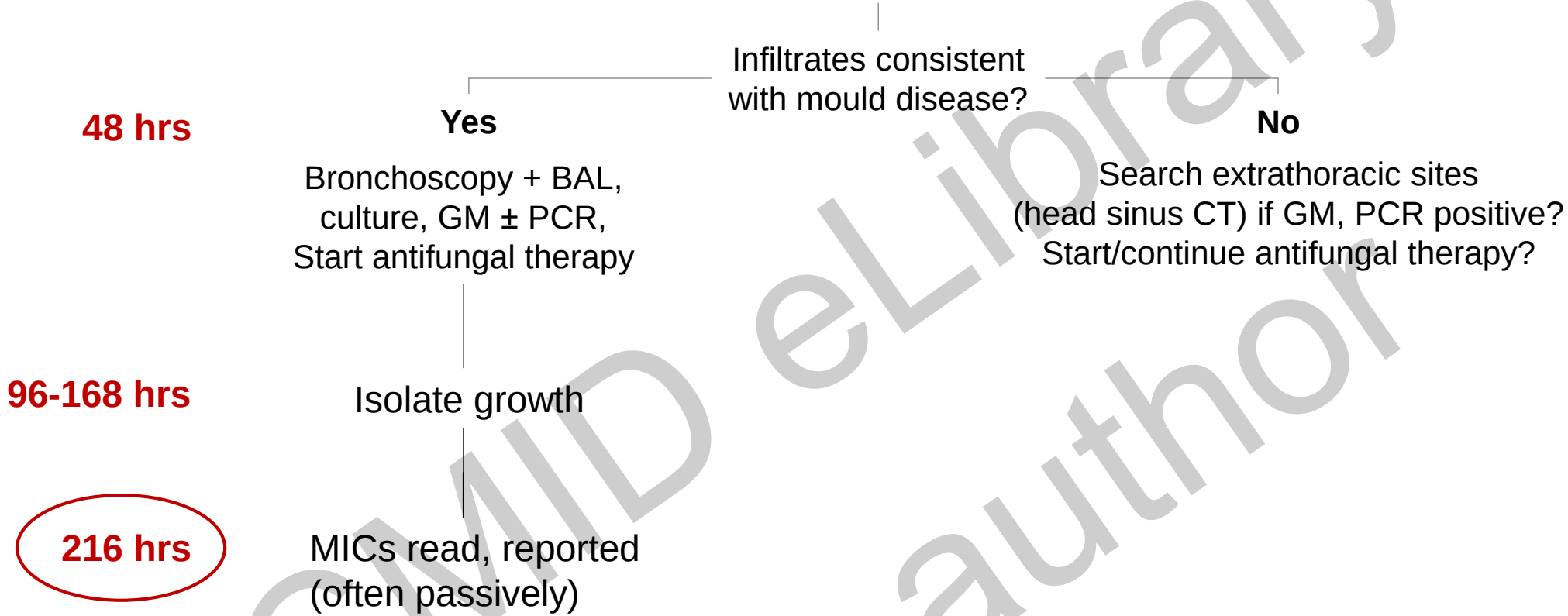
Nucci et al.Haematologica 2013;98:1657-1660. Shannon VR, et al. Bone Marrow Transplant 2010; 45: 647–655; Bergeron A, et al. Blood 2012; 119: 1831–7

Most therapeutic decisions are made before culture



Adapted from: Lamoth F, Calandra T. *J Antimicrob Chemother*. 2017;72:i19-i28.

Most therapeutic decisions are made before culture

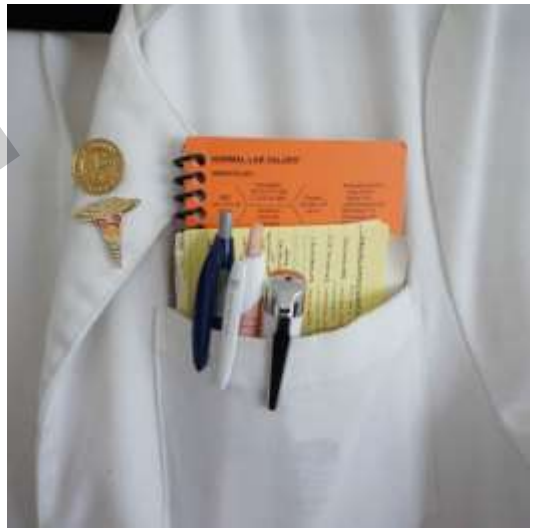


MIC testing useful only for treatment failure?

Adapted from: Lamoth F, Calandra T. *J Antimicrob Chemother*. 2017;72:i19-i28.

Aspergillus isolate surveillance/ Cumulative antibiograms?

- **2017 ESCMID-ECMM-ERS *Aspergillus* Guidelines**
  - Antifungal susceptibility testing should be performed regularly for epidemiological purposes including ≥ 100 isolates (**AIII**)
  - In settings with environmental azole resistance, no change to the primary regimen for IA is recommended when resistance rates are <10% (**AIII**).
  - If azole resistance rates are >10%,first-line therapy with voriconazole plus echinocandin (**BIII**) or liposomal amphotericin B (**BIII**) is recommended.



Isolates from probable/proven disease, colonizing isolates, environmental isolates? Stratify by patient prophylaxis status?

Multiple issues in construction and reporting in antimicrobial cumulative antibiograms (CLSI M39-A4)…what are the standards for moulds?

Ullmann AJ, et la.. Clin Microbiol Infect 2018 In press;

Problems of using mould MICs to make clinical decisions

1. Culture-based management of invasive mould disease is becoming less common

2. **Many methodological concerns with the MIC test and interpretation**

3. We don't know the clinical predictive value of an MIC

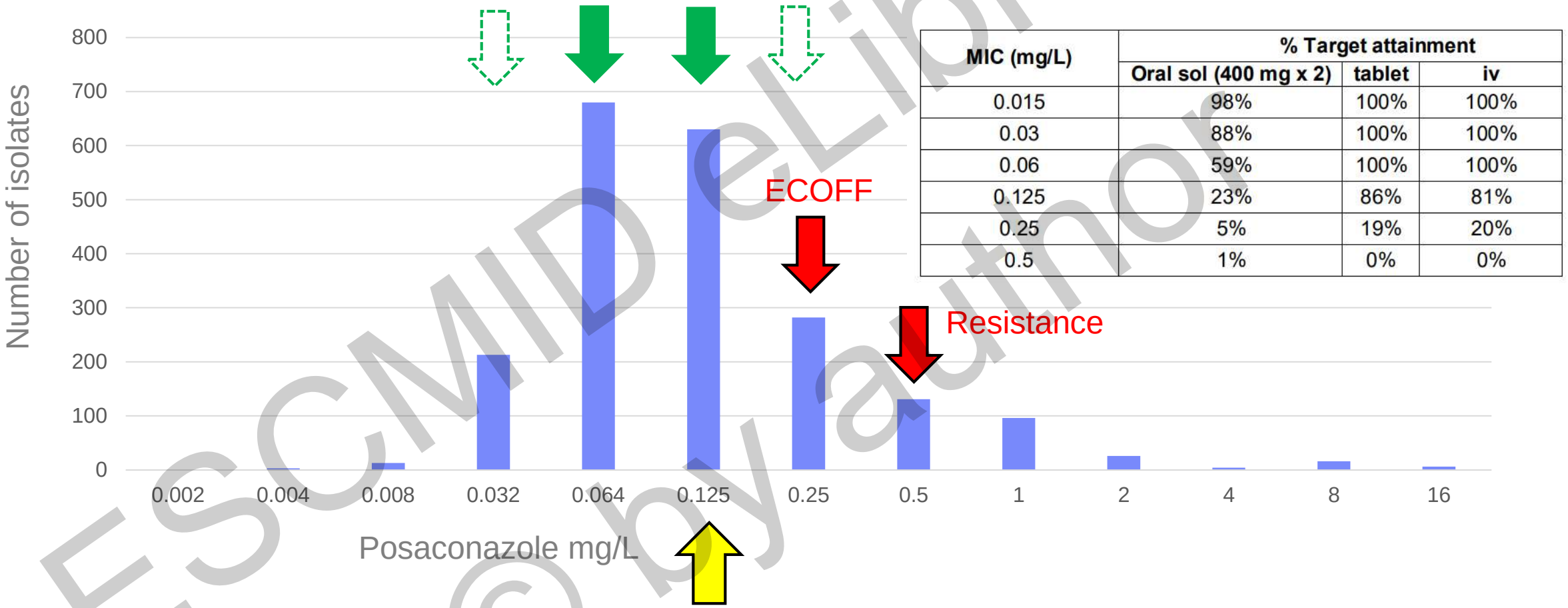
4. MIC-based dosing adjustments can be a bad idea

Mould susceptibility testing conditions

- Aerobic, high-glucose liquid medium
- Shape of microdilution well
- Defined high inoculum
- No immune cells
- No fluctuation in drug exposure
- No biofilms
- Drug stability?

Do current MIC methods have sufficient accuracy to detect resistance?

QC strain: A. fumigatus ATCC 204305



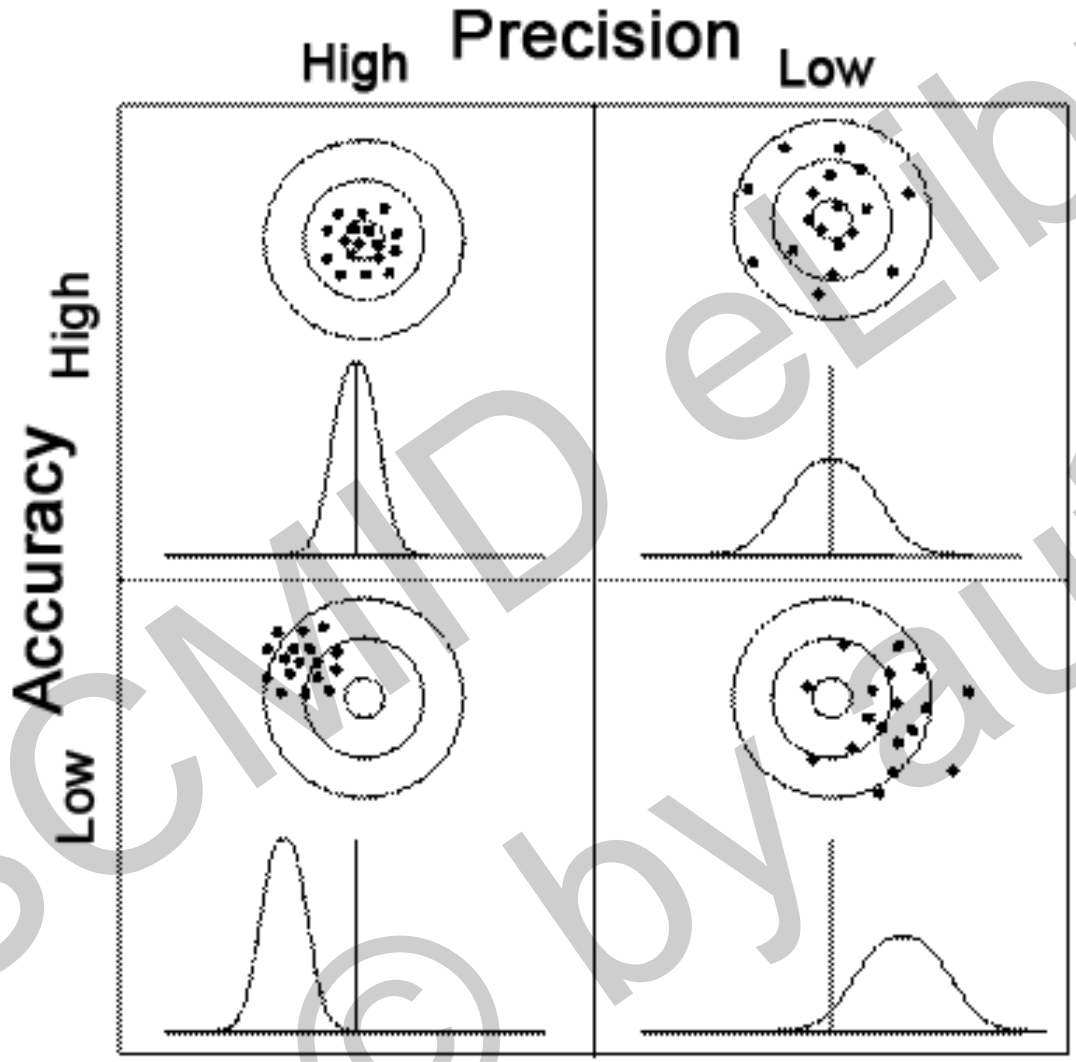
MIC (mg/L)	% Target attainment		
	Oral sol (400 mg x 2)	tablet	iv
0.015	98%	100%	100%
0.03	88%	100%	100%
0.06	59%	100%	100%
0.125	23%	86%	81%
0.25	5%	19%	20%
0.5	1%	0%	0%

Routine and extended internal quality control for antifungal susceptibility testing as recommended by EUCAST. Version 1.0, 2015. http://www.eucast.org

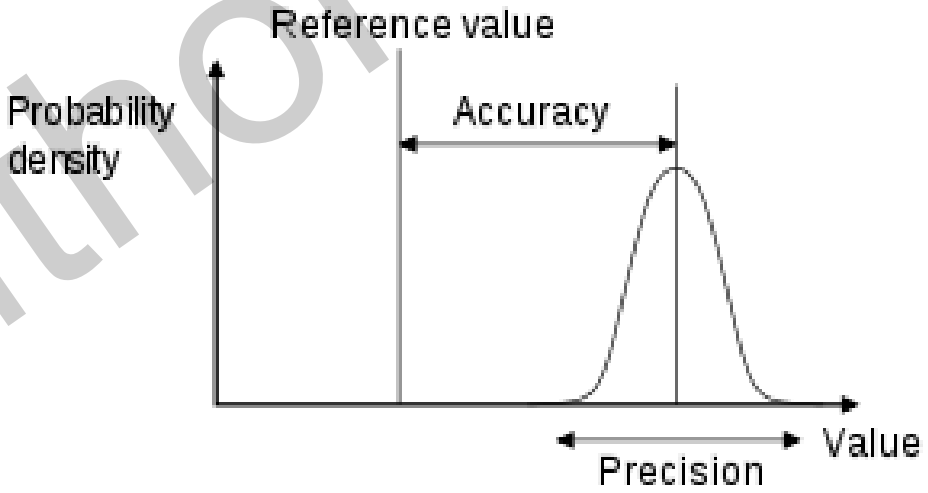
Should we believe a single MIC measurement generated with imprecise methods?

ECOFF Standpoint

Pharmacologist standpoint



Problem could be even worse if the laboratory is using a non-validated testing method



In vitro veritas?

"The problem of extrapolating laboratory results to the clinical situation presents such a minefield of difficulties that microbiologists usually prefer to concentrate on obtaining reproducible estimates of antimicrobial susceptibility in the laboratory, using standardized methods, **and leave the problem of clinical relevance to the physician.**"

Greenwood. *J Infect Dis* 1981;144:380-5.

Problems of applying mould MICs in the clinical setting

1. Microbiological culture-based management of invasive mould disease is becoming less common

2. Methodological concerns with the MIC test

3. **We really don't know the clinical predictive value of an MIC**

4. MIC-based dosing adjustments may be a bad idea

Has Antifungal Susceptibility Testing Come of Age?

John H. Rex[1] and Michael A. Pfaller[2]

[1]Division of Infectious Diseases, Department of Internal Medicine, Center for the Study of Emerging and Reemerging Pathogens, University of Texas–Houston Medical School; and [2]Molecular Epidemiology and Fungus Testing Laboratory, Departments of Pathology and Epidemiology, University of Iowa College of Medicine and College of Public Health, Iowa City

The in vitro susceptibility of an infecting organism to the antimicrobial agent selected for therapy is one of several factors that influence the likelihood that therapy for an infection will be successful. To appreciate the value of antifungal susceptibility testing, it is helpful to review the overall predictive utility of antibacterial susceptibility testing. After >30 years of study, in vitro susceptibility can be said to predict the response of bacterial infections with an accuracy that is well summarized as the "90-60 rule": infections due to susceptible isolates respond to therapy ~90% of the time, whereas infections due to resistant isolates respond ~60% of the time. On the basis of a growing body of knowledge, standardized susceptibility testing for selected organism-drug combinations (most notably, *Candida* species and the azole antifungal agents) has been shown to have similar predictive utility. Antifungal susceptibility testing is now increasingly and appropriately used as a routine adjunct to the treatment of fungal infections.

Susceptible:90% response
Resistance:60% response

Δ 30

***Extrapolated from immunocompetent patients with mono-microbial bacterial infections treated with single agent with predictable pharmacokinetics**

Rex JH, Pfaller MA. Clin Infect Dis 2002; 35: 982–989.

Does the 90/60 rule really fit for fluconazole in candidemia?

Susceptibility classification	No. of nonsurvivors/total no. in group (%) for indicated breakpoint criteria, incubation period, and growth inhibition end point							
	Alternative[a]				CLSI[b]			
	24 h		48 h		24 h		48 h	
	50%	80%	50%	80%	50%	80%	50%	80%
Susceptible	17/65 (26.1)	16/58 (27.6)	12/55 (21.8)	12/52 (23)	20/74 (27)	20/74 (27)	18/71 (25)	17/67 (25.4)
Intermediate/SDD	3/8 (37.5)	1/12 (8.3)	3/11 (27.3)	1/9 (11.1)	0/3 (0)	0/2 (0)	0/3 (0)	1/5 (20)
Resistant	4/10 (40)	7/14 (50)	9/18 (50)	11/21 (52.3)	4/7 (57.1)	4/8 (50)	6/10 (60)	6/10 (60)

[a] Susceptibility, MIC of <2 mg/liter; resistance, MIC of >4 mg/liter.
[b] Susceptibility, MIC of ≤8 mg/liter; resistance, MIC of ≥64 mg/liter.

Host factors, such as severity of illness and age, were more predictive of mortality than fluconazole MICs.

TABLE 1. CART analysis of the relationship of MIC versus mortality in patients with candidemia (data taken from reference 2)[a]

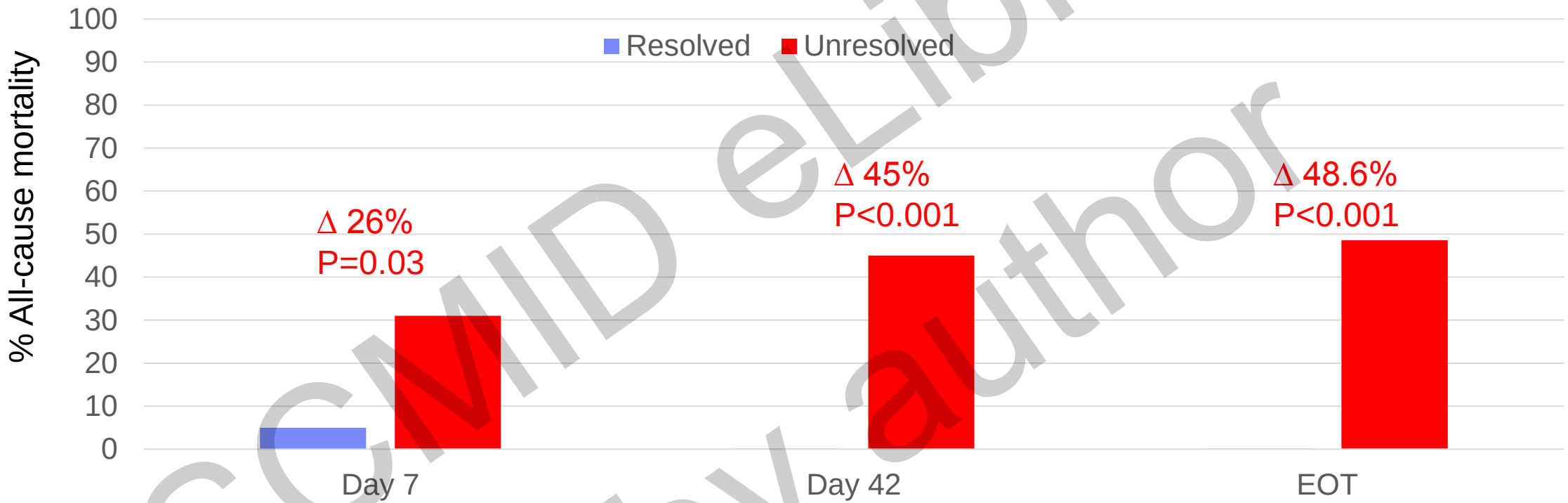
Incubation period and growth inhibition end point	MIC split (mg/liter)	Relative error[b]	ROC curve area[c]
24 h			
50%	≤32/>32	1.033	0.468
80%	≤4/>4	0.942	0.524
48 h			
50%	≤4/>4	0.883	0.560
80%	≤4/>4	0.714	0.646

[a] CART analysis (CART 6.0; Salford Systems, CA) was performed with the following methodological conditions: Gini method, minimum cost tree regardless of the size for selecting the best tree, 10 v-fold-cross-validation, equal priors, no costs, and no penalties.
[b] A relative error of 0 means no error, or a perfect fit, and 1 represents the performance of random guessing.
[c] A ROC curve area of 1 means a perfect prediction (100% sensitivity and 0% false positives), and 0.5 represents a random guess.

Random guessing?

Baddley JW, et al.Antimicrob Agents Chemother 2008; 52: 3022–3028.
Arendrup MC. Antimicrob Agents Chemother 2009; 53: 2704–5; author reply 2705–6.

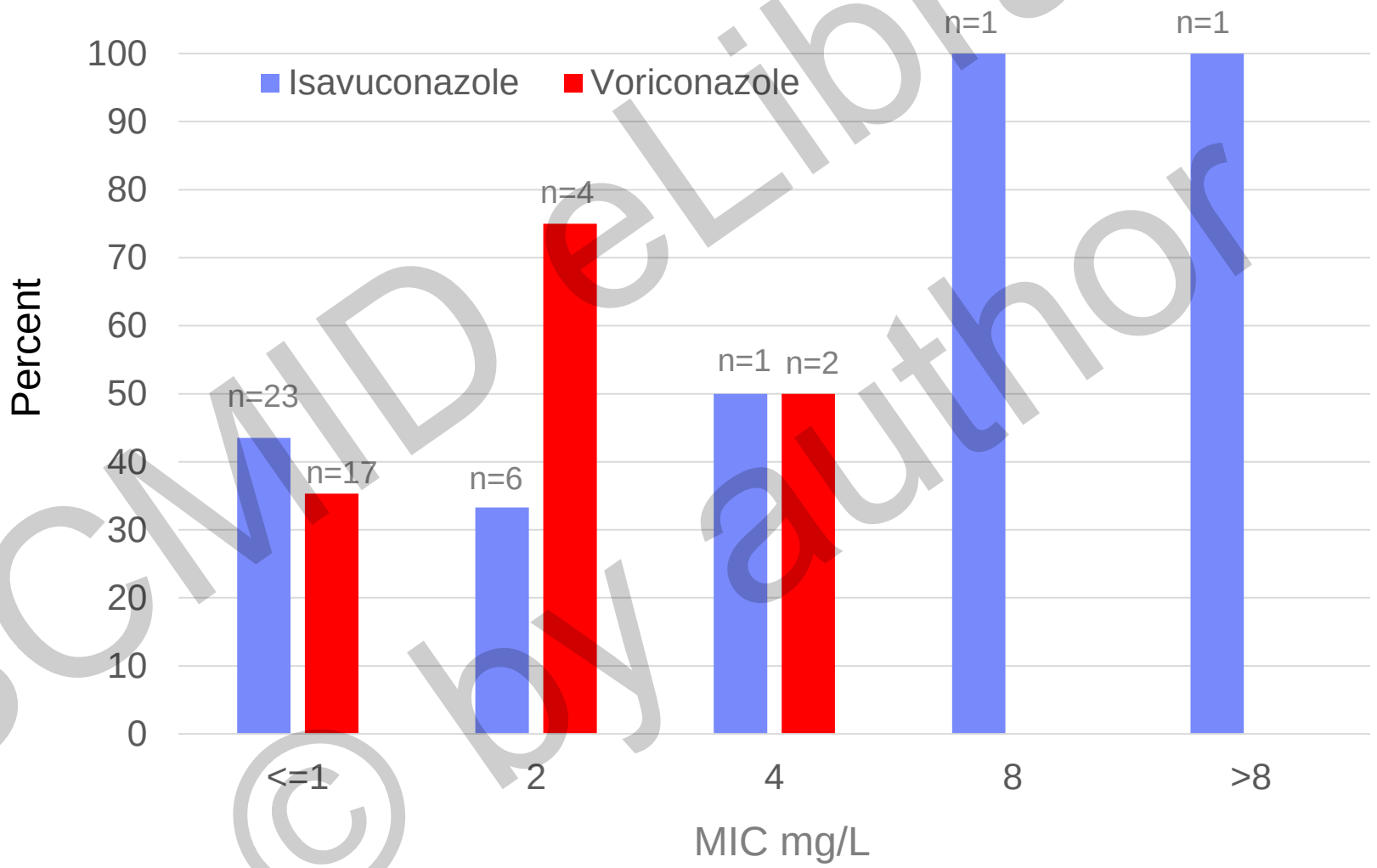
All-cause mortality in isavuconazole-treated patients with aspergillosis stratified by neutrophil recovery (Culture positive + GM positive)



What does the MIC beyond neutrophil recovery for aspergillosis?

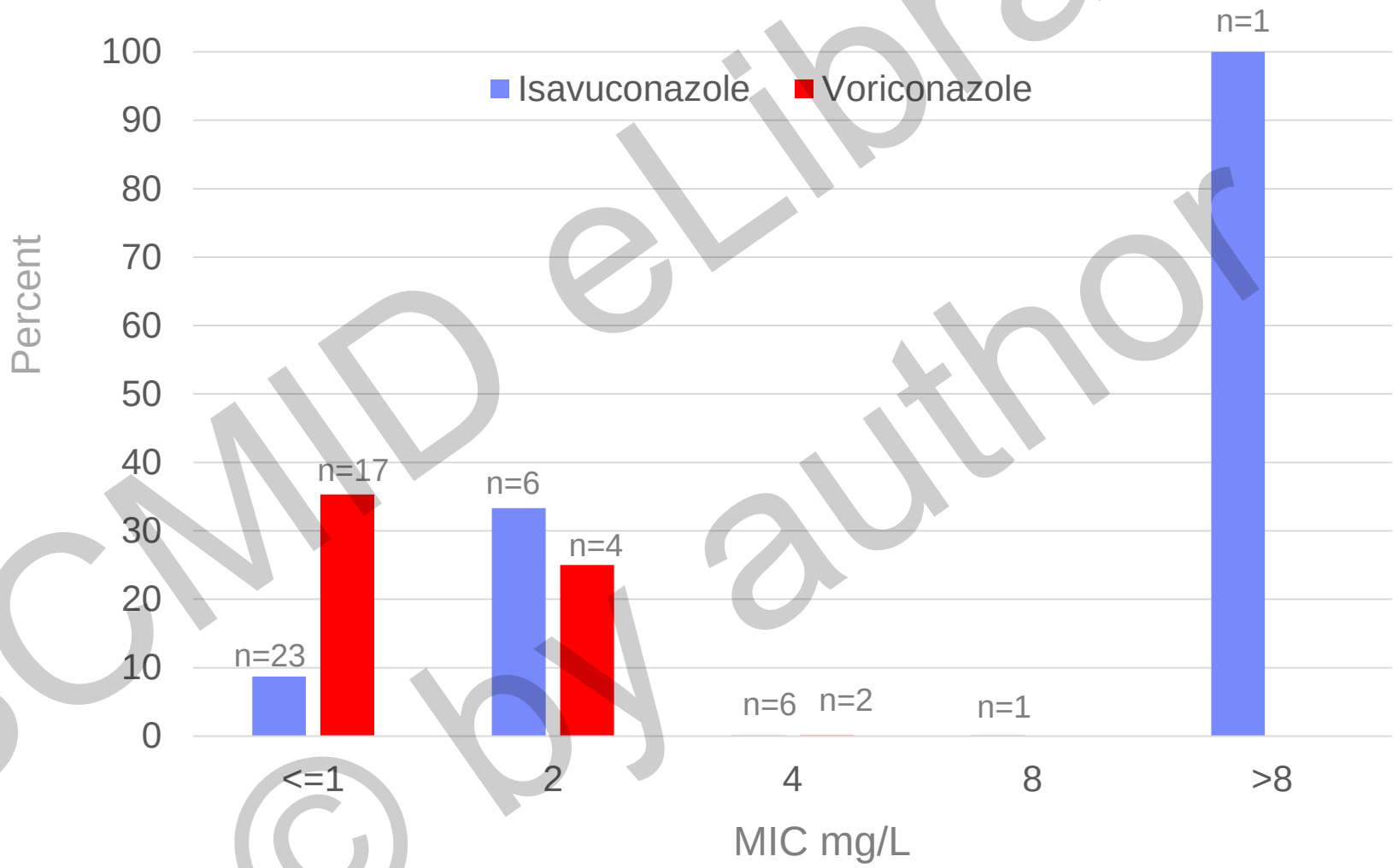
Kontoyiannis DP, et al. J Antimicrob Chemother 2017; 73: 757–763

Overall response at end of therapy in patients with positive baseline cultures (SECURE Trial)



Maertens JA,et al. Lancet 2016; 387: 760–769.

Day 42 all-cause mortality (SECURE Trial)



Maertens JA,et al. Lancet 2016; 387: 760–769.

Correlation of triazole MICs with outcome in aspergillosis?

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No significant relationship (P>0.05) was identified between the AUC/MIC ratio and mortality at day 42, the overall response at EOT, or the clinical response at EOT.

No relationship was observed between MIC values and outcome parameters.

Exposure-Response Relationships for Aspergillosis and Other Filamentous Fungi

Amit V. Desai,[a] Laura L. Kovanda,[a,b] William W. Hope,[b] David Andes,[c] Johan W. Mouton,[d] Donna L. Kowalski,[a] Robert W. Townsend,[a] Salim Mujais,[a] Peter L. Bonate[a]

Astellas Pharma Global Development, Inc., Northbrook, Illinois, USA[a]; University of Liverpool, Liverpool, United Kingdom[b]; University of Wisconsin, Madison, Wisconsin, USA[c]; Erasmus MC, Rotterdam, The Netherlands[d]

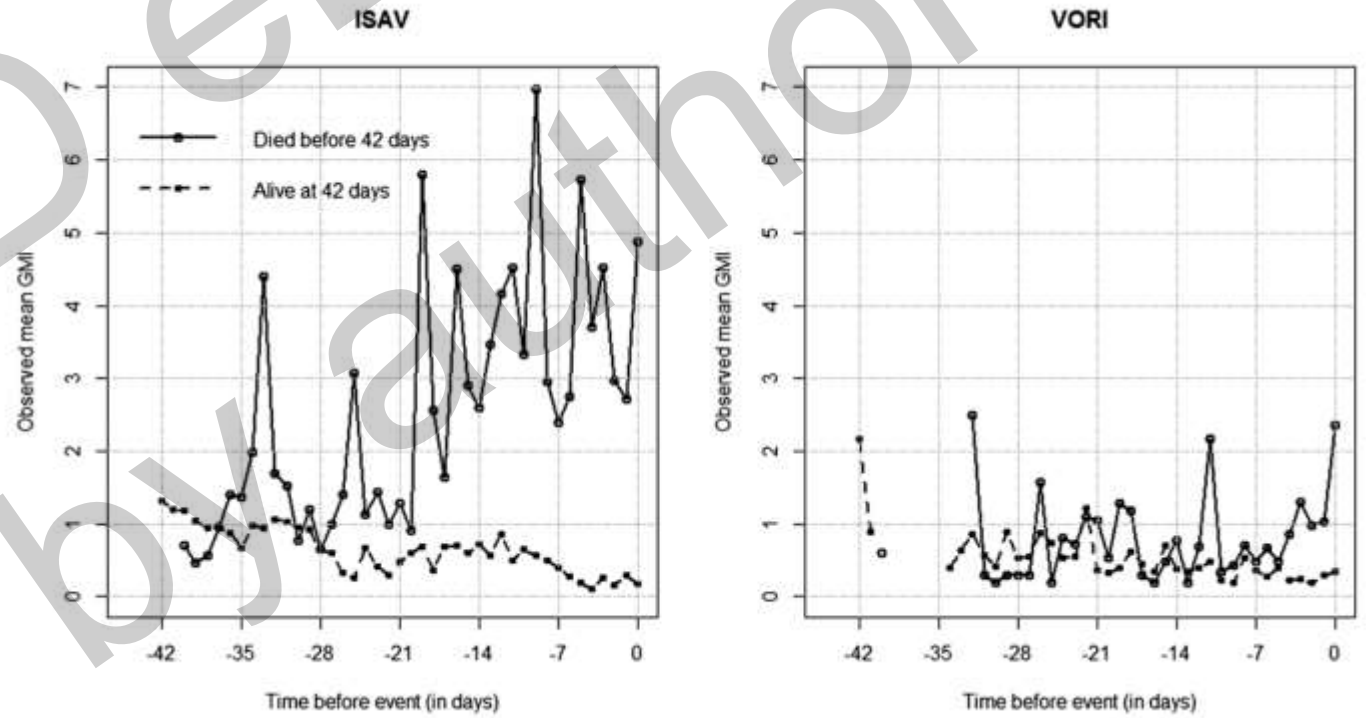
Desai AV, Kovanda LL, Hope WW *et al.* Antimicrob Agents Chemother 2017; 61.

Galactomannan trends are associated with outcome of aspergillosis

- By day 7, GMI increases of >0.25 units from baseline significantly increased the risk of death compared to those with no increase or increases <0.25 (hazard ratio, 9.766; 95% confidence interval [CI], 4.356–21.9; P< .0001).

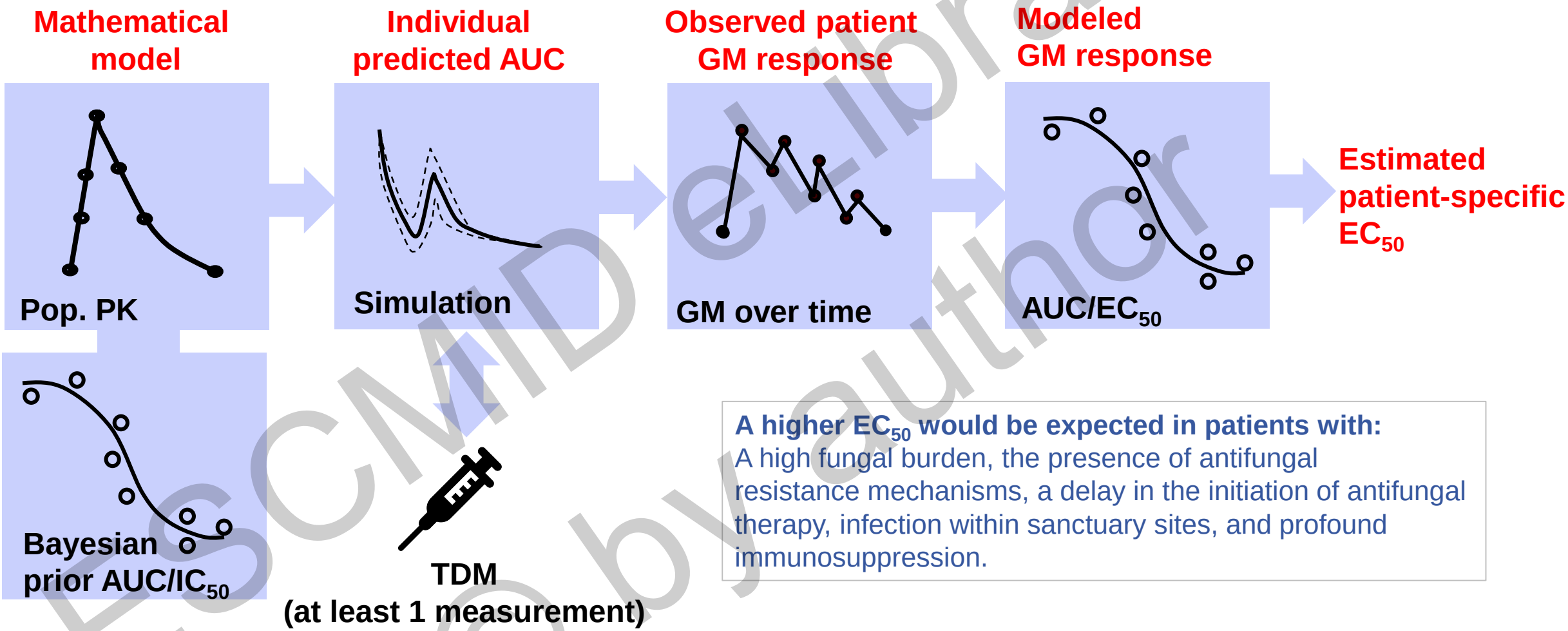
- For each unit decrease by day 7 from baseline, the odds of successful therapy doubled (odds ratio, 2.154; 95% CI, 1.173–3.955)

No prominent differences were found between drugs, neutropenic status, and GMI over time (P= .1127).



Kovanda et al. Clin Infect Dis 2017; 64: 1557–1563.

AUC/EC_{50} : An *in vivo* MIC for aspergillosis?



A higher EC_{50} would be expected in patients with:
A high fungal burden, the presence of antifungal resistance mechanisms, a delay in the initiation of antifungal therapy, infection within sanctuary sites, and profound immunosuppression.

Kovanda LL, et al. J Pharmacokinet Pharmacodyn 2017; 44: 143–151.

Problems of applying mould MICs in the clinical setting

1. Microbiological culture-based management of invasive mould disease is becomming uncommon
2. Methodological concerns with the MIC test
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J Antimicrob Chemother 2018; **73**: 564–568
doi:10.1093/jac/dkx427 Advance Access publication 5 December 2017

Journal of Antimicrobial Chemotherapy

MIC-based dose adjustment: facts and fables

Johan W. Mouton[1]*, Anouk E. Muller[1,2], Rafael Canton[3], Christian G. Giske[4], Gunnar Kahlmeter[5] and John Turnidge[6]

[1]Department of Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, The Netherlands; [2]Department of Medical Microbiology, Haaglanden Medical Centre, The Hague, The Netherlands; [3]Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYIS), Madrid, Spain; [4]Department of Laboratory Medicine, Division of Clinical Microbiology, Karolinska Institute and Karolinska University Hospital, Stockholm, Sweden; [5]Department of Clinical Microbiology, Central Hospital, 351 85, Växjö, Sweden; [6]Adelaide Medical School, University of Adelaide, Adelaide, Australia

MICs are not strict minimum but rather *observable* minimum subject to change. Therefore, the MIC does not represent a concentration that can be compared to any *in vivo* concentration found during treatment.

MICs are inaccurate unless performed in multiple replicates. Results are subject to biological and assay-related variation.

Therefore…MICs from an infecting strain are not sufficiently accurate for calculation of individual PK:PD targets and could result in underdosing if by chance the reported MIC is on the low end of values observed if MIC test was performed multiple times.

A 4-fold variation in the MIC could result in a 8-fold difference in antifungal dosing

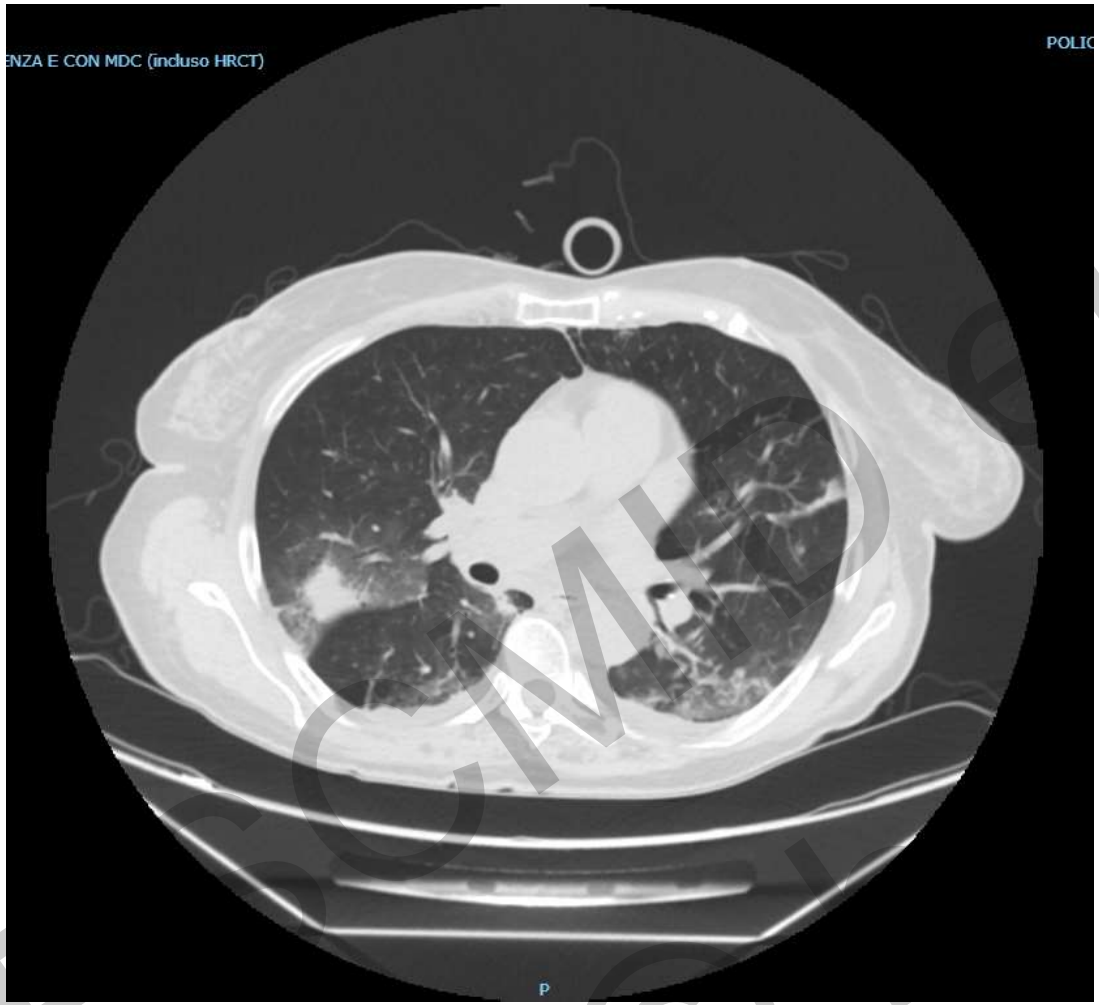
What should be the dosing target for PK/PD calculations?

Table 1. Suggested interpretation of the MIC for target attainment under various conditions

MIC found	Interpretation for target attainment
Within WT, ≤ECOFF	ECOFF
>ECOFF	MIC + two 2-fold dilutions[a]

[a]Number of dilutions could be higher or lower than two depending on the proficiency of the lab and the drug–species distribution.

and yet, MICs sometimes are useful…



65 y/o female with AML, fever, severe respiratory difficulty, H1N1 influenzae, ANC 250

BAL grew *A. terrreus,* GM 3.1

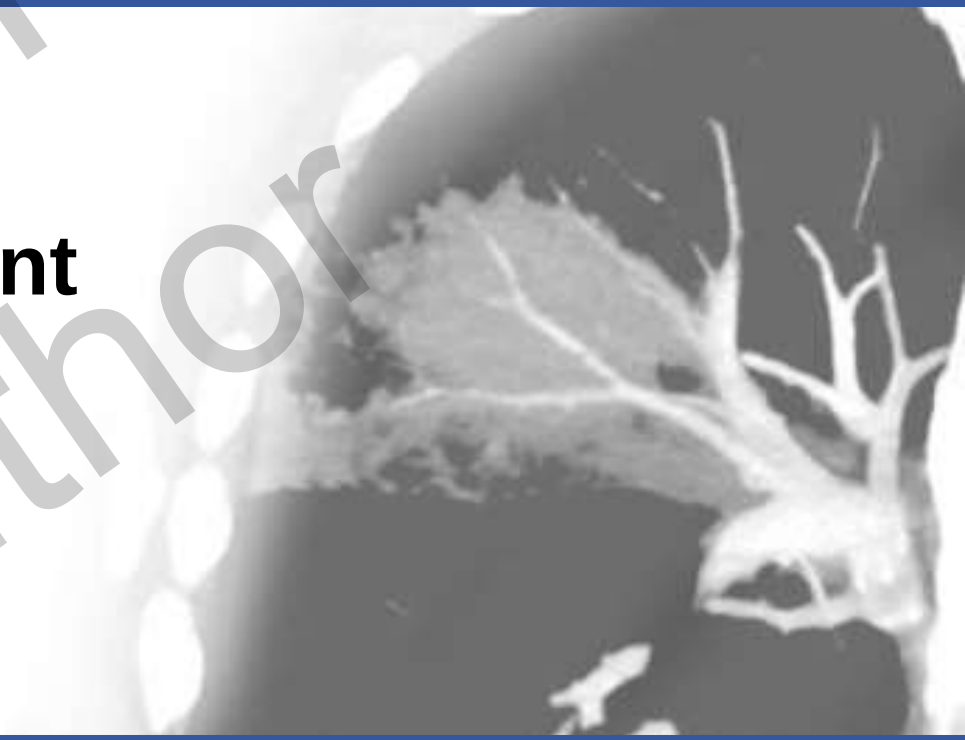
Antifungal	**MIC**	**EUCAST Interp.**
Amphotericin B	4 mg/L	R
Anidulafungin	>4 mg/L	R
Caspofungin	>4 mg/L	R
Micafungin	>4 mg/L	R
Isavuconazole	2 mg/L	R
Voriconazole	1 mg/L	S
Posaconazole	0.06	S

“Medicine is a science of uncertainty, and an art of probability”

Sir William Osler, M.D.
(1849-1919)

Less useful than you think

In vitro susceptibility testing is ~~NOT useful~~ in the management of aspergillosis in patients with haematological malignancies



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