In-vitro Empfindlichkeitsprüfung: Ergebnisse haben klinische Relevanz

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... . Evaluation of antifungal activity **in vitro** and **in vivo**. - Polak - Zitiert von: 93

Antimycotic efficacy of bifonazole in vitro and in vivo. - NCBI

www.ncbi.nlm.nih.gov/pubmed/6683530 - Diese Seite übersetzen

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Arzneimittelforschung. 1983;33(4):517-24. **Antimycotic** efficacy of bifonazole **in vitro** and **in vivo**. Plempel M, Regel E, Büchel KH. The new imadozolyl derivative ...

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... in **vivo** Untersuchungen zwischen den **Antimykotika** ... - Hantschke - Zitiert von: 12

[PDF] Resistenz gegenüber Antimykotika
www.p-e-g.org/archiv_tmp/bad_honnef_symposium.../groll.pdf
Tentative Reihendilutionsmethode (NCCLS M38-P). Zahlreiche andere, z.T. standardisierte Methoden. » Keine eigenständige **in vitro** / **in vivo** Korrelation.

A. Groll, 2003

Tagung, gehalten in Köln vom 29.3. bis 2.4.1977

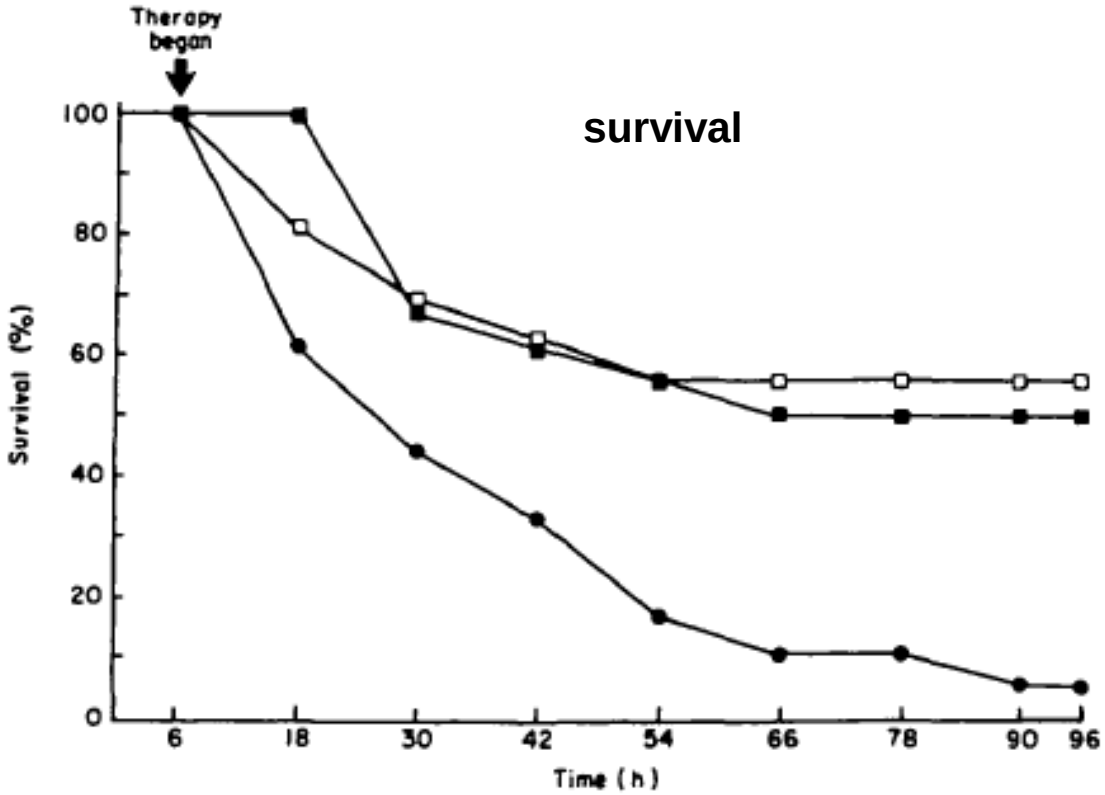
https://books.google.de/books?isbn=366221587X
G.K. Steigleder, H. Aulepp - 2013 - Medical
I. Haller, Wuppertal: Vergleichende experimentelle Prüfung moderner **Antimykotika in vitro** und **in vivo** . . . . . 187 M. Plempel, Wuppertal: Experimentelle ...

Comparison of the investigational drug, LY146032, with vancomycin in experimental pneumonia due to methicillin-resistant *Staphylococcus aureus*

Phyllis A. Kephart and Anthony L. Esposito

Hamster

survival



Vancomycin

Ly146032

Figure 1. Effect of antibiotic therapy on the survival of hamsters challenged intratracheally with 2×10^9 cfu MRSA. □, Vancomycin, $n = 16$; ■, LY146032, $n = 18$; ●, saline, $n = 18$.

In vitro Resistenztestung – Einfluss des Mediums

Influence of DMSO on antifungal activity during susceptibility testing in vitro

Kevin C. Hazen *

Table 2
Summary of the effect of DMSO on MIC-2 results and growth controls.

Effect on growth	Effect on MIC-2			Total
	None	Increase	Decrease	
None	22	5	3	30
Increase	24	1	3[a]	28
Decrease	6	3	0	9
Total	52	9	6	67

[a] Two with a MIC-2 change of 2 doubling dilutions. Both involved NKZ.

Diagnostic Microbiology and Infectious Disease 75 (2013) 60–63

Abhängigkeit von Testmethode

Comparison of Different In Vitro Tests to Detect *Cryptococcus neoformans* Not Susceptible to Amphotericin B

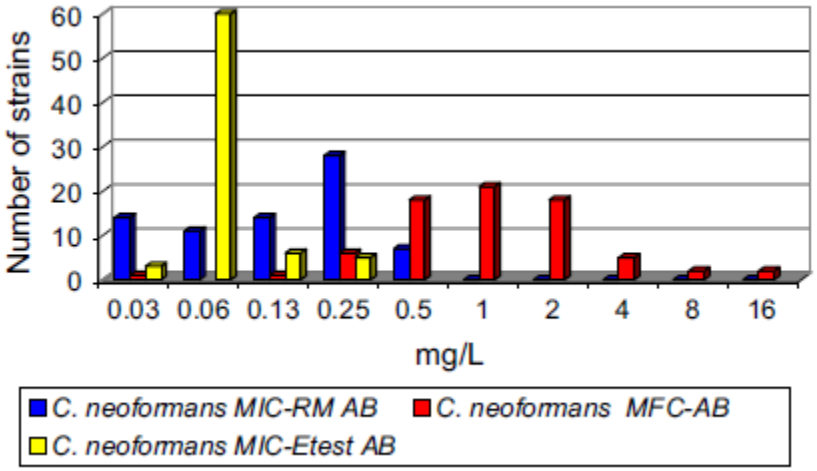


Fig. 2 Distribution of amphotericin B MIC-RM, MFC, and MIC-Etest values for 74 *C. neoformans* isolates. The MFC-AB *bars* disposed to right of the graphic indicate that some isolates were not susceptible to amphotericin B (≥2 mg/L). *MIC-RM AB* minimal inhibitory concentration-reference method, *MFC-AB* minimal fungicidal concentration, *MIC-Etest AB* minimal inhibitory concentration Etest, *AB* amphotericin B

Table 3 Values of amphotericin B by using different in vitro assays against 74 *C. neoformans* isolates

Susceptibility test	Amphotericin B values in mg/L			
	Range	Mode	GM	MIC-90
MIC-RM	0.03–0.5	0.25	0.13	0.25
MFC	0.06–16	1	1.83	16
MIC-Etest	0.002–0.25	0.064	0.03	0.125
Neo-Sensitabs™ tablet[a]	22–50[a]	35[a]	33.9[a]	NE

MIC-RM minimal inhibitory concentration-reference method, *MFC* minimal fungicidal concentration, *MIC-Etest* minimal inhibitory concentration Etest, *GM* geometric mean, *MIC-90* MIC at which 90 % of isolates tested are inhibited, and *NE* not evaluable

[a] Value expressed in mm

Abhängigkeit von Testmethode

Caspofungin MICs Correlate with Treatment Outcomes among Patients with *Candida glabrata* Invasive Candidiasis and Prior Echinocandin Exposure

Ryan K. Shields,[a] M. Hong Nguyen,[a] Ellen G. Press,[a] Cassaundra L. Updike,[a] Cornelius J. Clancy[a,b]

TABLE 1 Echinocandin MICs determined against 120 clinical strains of *Candida glabrata*

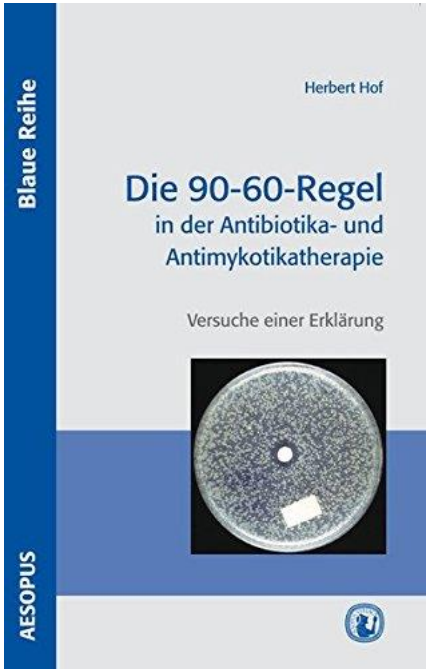
	No. of isolates at MIC (μg/ml) (no. of isolates showing mutation) of:										
Test	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	≥8	EA[a] (%)
BMD-RPMI (visual)				4 (1)	16 (1)	85 (1)	10 (2)	3 (3)		2 (2)	
BMD-RPMI (OD)				2	21 (2)	71 (2)	20 (1)	4 (3)	1 (1)	1 (1)	98
BMD-RPMI (DMSO)				1	30	78 (3)	5 (2)	4 (3)	1 (1)	1 (1)	93
BMD-AM3	5	78	24 (3)	6 (3)	2 (1)	3 (1)	1 (1)			1 (1)	14
YeastOne		1	14	48 (1)	37 (1)	11 (1)	6 (4)	1 (1)		2 (2)	90
Etest		4	3	39	57	11 (4)	2 (2)		2 (2)	2 (2)	96

[a] Essential agreement with BMD-RPMI results.

90-60-Regel in der Bakteriologie

Mit einen in-vitro wirksamen Medikament werden 90% der Patienten gesund.

Mit einem in-vitro unwirksamen Medikament werden 60% der Patienten gesund.



Bakteriologie

Table 1. The "90-60 rule": the range of correlations between susceptibility and outcome in studies of bacterial infections.

Reference	Type(s) of infection	Drug(s) administered	Outcome measurement	Measurement used to determine susceptibility	Cases with successful outcome, % (no. of cases/total no. of cases), by susceptibility class		*P*
					Susceptible[a]	Resistant	
[11]	Bacteremia and fungemia	Various	Mortality	MIC[b]	73 (224/309)	48 (10/21)	.02
[12]	Bacteremia and fungemia	Various	Mortality	MIC[b]	89 (594/665)	77 (97/126)	<.001
[10]	Serious bacterial infections	Various	Clinical response	MIC	81 (219/271)	4 (1/27)	<.001
[13]	Pneumococcal otitis media	Amoxicillin/clavulanic acid	Clinical response	MIC	80 (149/186)	68 (15/23)	.26
[14]	Pneumococcal otitis media	Cefuroxime	Clinical response	MIC	94 (44/47)	78 (29/37)	.05
[15]	Pneumococcal otitis media[c]	Cefaclor or cefuroxime	Bacteriologic response	MIC	95 (55/58)	45 (9/20)	<.001
[16]	Pneumococcal otitis media[c]	Cefaclor or azithromycin	Bacteriologic response	MIC	89 (23/26)	24 (6/25)	<.001
[17]	*Bacteroides* bacteremia	Various	Bacteriologic response	MIC	88 (60/68)	57 (4/7)	.06
[18]	Moderate-to-severe bacterial infections	Ciprofloxacin	Bacteriologic response	AUC/MIC ratio	82 (37/45)	26 (5/19)	<.001
[19]	Bacterial infections	Aminoglycosides	Clinical response	Peak/MIC ratio	~90[d]	~55[d]	
[3]	Bacterial infections[e]	Cefotaxime	Bacteriologic response	Zone diameter	92 (1464/1591)	63 (31/49)	<.001
[3]	Bacterial infections[e]	Ciprofloxacin	Bacteriologic response	Zone diameter	91 (1652/1815)	62 (8/13)	.004
Total	—	—	—	—	89 (4521/5081)	59 (215/366)	<.001

John H. Rex[1] and Michael A. Pfaller[2] las Antifungal Susceptibility Testing Come of Age? **Clinical Infectious Diseases** 2002; 35:982–9

Mykologie

Table 3. Range of correlations of susceptibility testing with outcome for fungal infections

Reference	Type(s) of infection	Drug administered, dosage in mg/day	Outcome measurement	MIC used to determine susceptibility, μg/mL	Cases with successful outcome, % (no. of cases/ total no. of cases), by susceptibility class		*P*
					Susceptible	Resistant	
[5]	Candidiasis, mostly mucosal	Fluconazole, 100	Clinical response	≤8	98 (248/253)	76 (37/49)	<.001
[31]	Mucosal candidiasis	Fluconazole, 100–200	Clinical response	MIC relative to dose	80 (28/35)	46 (6/13)	.034
[32]	Mucosal candidiasis	Fluconazole, 100	Clinical response	≤8	96 (49/51)	0 (0/15)	<.001
[33]	Mucosal candidiasis	Fluconazole, 100–400	Clinical response	≤32	88 (14/16)	0 (0/5)	.001
[5]	Mucosal candidiasis	Itraconazole, 200	Clinical response	≤0.125	88 (162/184)	59 (47/80)	<.001
[32]	Mucosal candidiasis	Itraconazole, 200	Clinical response	≤0.5	98 (48/49)	6 (1/17)	<.001
[32]	Mucosal candidiasis	Ketoconazole, 400	Clinical response	<0.125	94 (46/49)	11 (2/18)	<.001
[33]	Mucosal candidiasis	Ketoconazole, ~400	Clinical response	<0.06	94 (17/18)	0 (0/3)	.003
[5]	Candidiasis, mostly invasive	Fluconazole, >100; median, 400	Clinical response	≤32	82 (146/178)	46 (18/39)	<.001
[28]	Invasive candidal infections	Fluconazole, 400	Clinical response	≤32	77 (23/30)	0 (0/2)	.073
[29]	Candidemia	Fluconazole, mostly 100–200	Clinical response	<8	52[a]	<14[a]	.03
[46]	Cryptococcal meningitis	Fluconazole, ~400	Clinical response	<16	91 (21/23)	0 (0/5)	<.001
[52]	Disseminated histoplasmosis	Fluconazole, 600–800	Clinical response	<5	97 (36/37)	71 (20/28)	.004
Total	—	—	—	—	91 (838/923)	48 (131/274)	<.001

NOTE. All MICs were determined by NCCLS M27-A [8] or a closely related variant of that method. *P* values determined by Fisher's exact test.

[a] Published data do not provide additional detail.

Fluconazol: Dosis/MHK-Ratio

TABLE 6. Relationship between dose/MIC ratio and clinical response in fluconazole treatment of mucosal and invasive candidiasis

Dose/MIC	% Clinical success (n/N)[a]				
	Rex et al. (85)[b]	Clancy et al. (18)[c]	Lee et al. (38)[c]	Takakura et al. (100)[c]	Total
≥400	99 (115/116)	89 (8/9)			98 (23/125)
100–300	98 (129/132)	60 (6/10)			95 (35/142)
50–75	92 (34/37)	0 (0/1)	79 (19/24)		86 (3/62)
25–37.5	91 (30/33)	0 (0/1)	67 (4/6)	70 (144/206)	72 (78/246)
6.26–12.5	74 (35/47)	20 (1/5)		64 (16/25)	68 (2/77)
<6.25	65 (30/46)	0 (0/6)	0 (0/2)	55 (6/11)	55 (6/65)

[a] Abbreviations: n, number of successful treatment events; N, number of total patient-episode-isolate events.
[b] Mucosal infection study.
[c] Invasive candidiasis (candidemia) study.

CLINICAL MICROBIOLOGY REVIEWS, Apr. 2006, p. 435–447

Correlation of MIC with Outcome for *Candida* Species Tested against Voriconazole: Analysis and Proposal for Interpretive Breakpoints

M. A. Pfaller,[1]* D. J. Diekema,[1] J. H. Rex,[2] A. Espinel-Ingroff,[3] E. M. Johnson,[4] D. Andes,[5]

TABLE 4. Investigator assessment of efficacy versus baseline MIC for *Candida* species in primary and salvage therapy studies 603, 608, 309/604, and 301/606

MIC breakpoint (μg/ml)	Interpretive category	No. of isolates	% Success
≤0.25	S	189	77
0.5–2	SDD	39	54
≥4	R	21	62
≤0.5	S	211	73
1–2	SDD	17	65
≥4	R	21	62
≤1	S	221	74
2	SDD	7	43
≥4	R	21	62

JOURNAL OF CLINICAL MICROBIOLOGY, Mar. 2006, p. 819–826

Echinocandin Resistance, Susceptibility Testing and Prophylaxis: Implications for Patient Management

David S. Perlin,

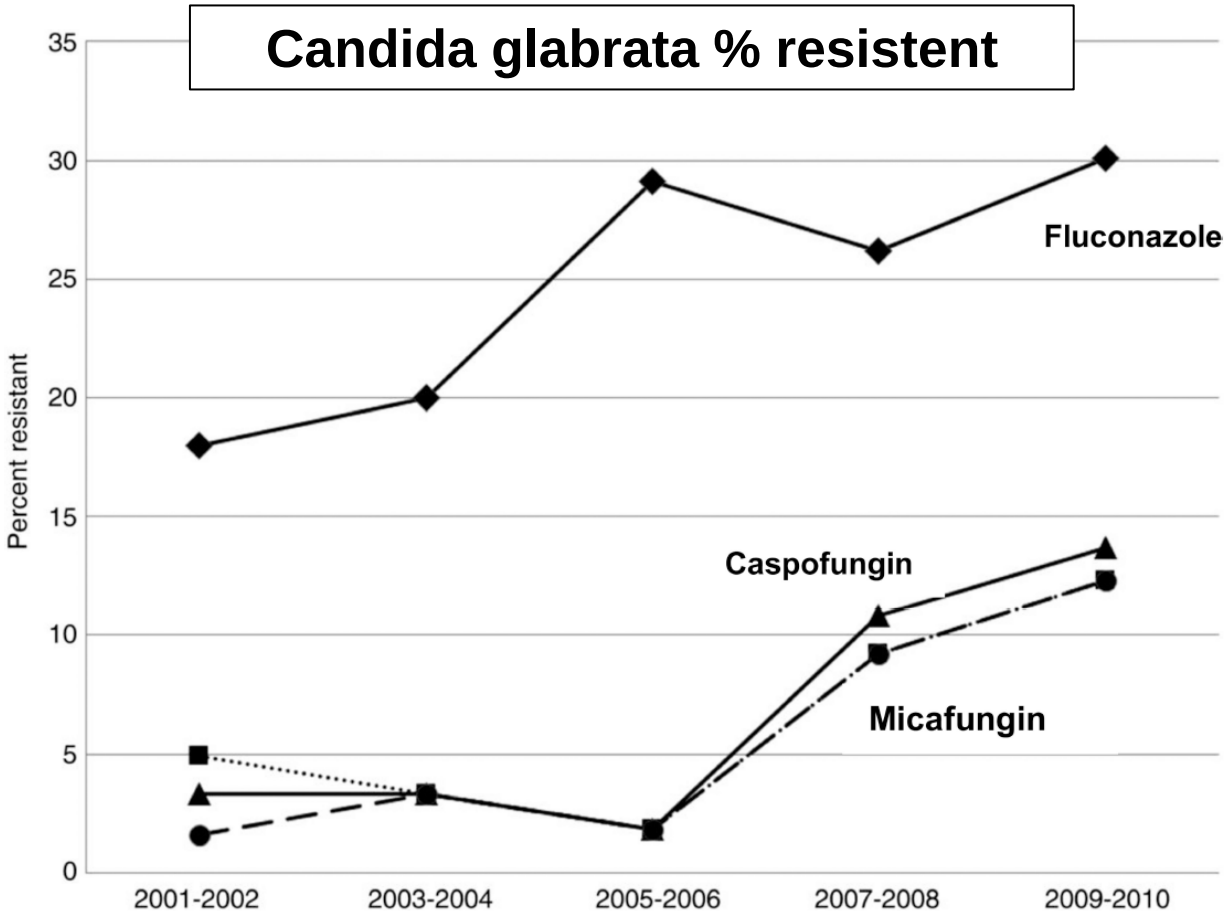


Fig 1.
Temporal trends in antifungal resistance of *Candida glabrata* isolates to fluconazole, anidulafungin, caspofungin, and micafungin. Adapted from Alexander et al. [59]

Drugs. 2014 September ; 74(14): 1573–1585.

Caspofungin MICs Correlate with Treatment Outcomes among Patients with *Candida glabrata* Invasive Candidiasis and Prior Echinocandin Exposure

Ryan K. Shields,[a] M. Hong Nguyen,[a] Ellen G. Press,[a] Cassaundra L. Updike,[a] Cornelius J. Clancy[a,b]

TABLE 5 Association of *FKS* mutations, prior echinocandin exposure, and echinocandin MICs with clinical failure

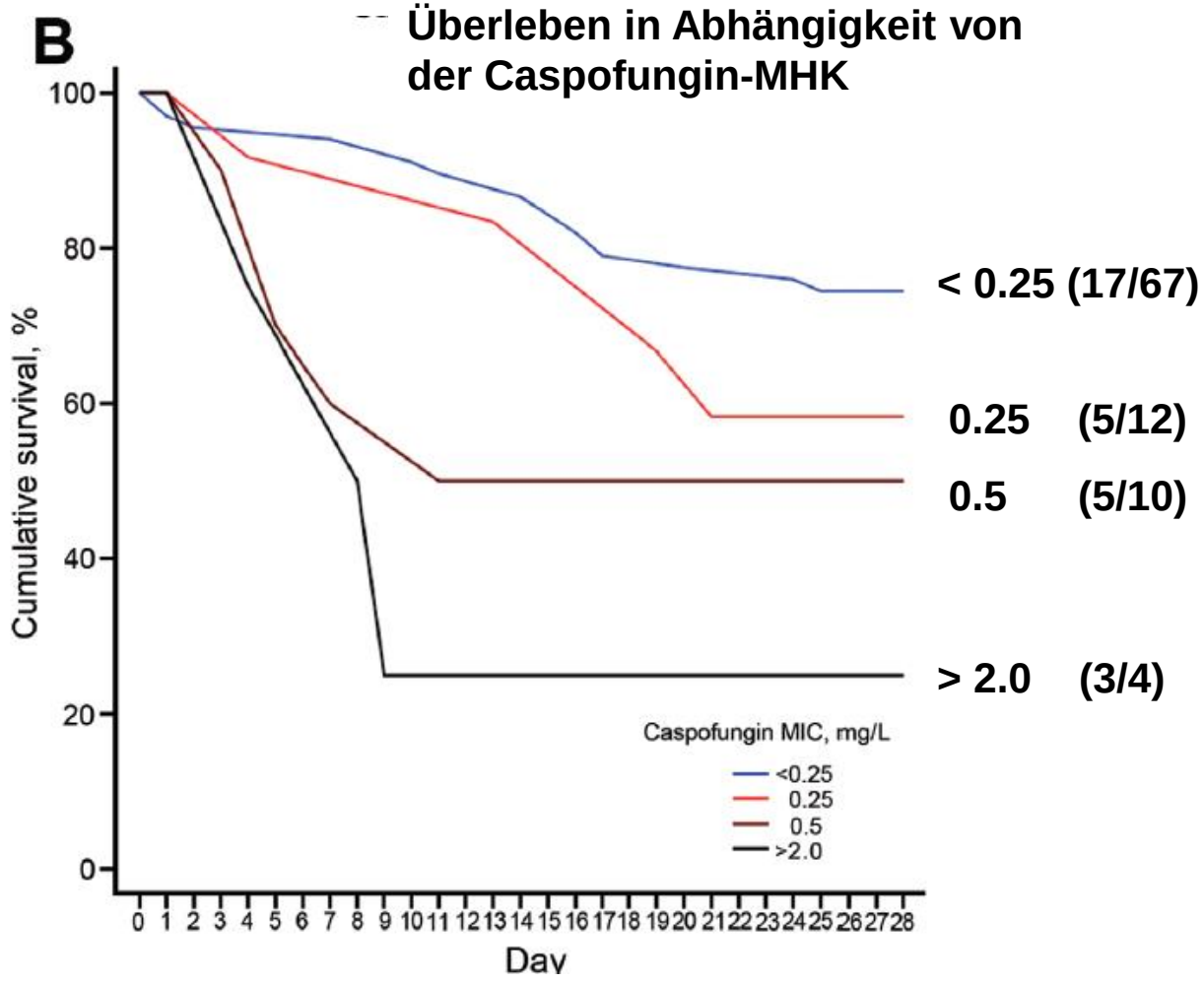
Predictor variable	No. of successes ($n = 44$)	No. of failures ($n = 22$)	*P* value	Odds ratio	95% CI	% PPV[a]	% NPV[b]
Presence of *FKS* mutation	1	9	0.0001	29.7	3.44–257.5	90 (9/10)	77 (43/56)
Prior echinocandin exposure	8	13	0.002	6.50	2.07–20.4	62 (13/21)	80 (36/45)
Caspofungin MIC of >0.5 μg/ml (BMD-RPMI)	6	7	0.10	2.96	0.85–10.3	54 (7/13)	72 (38/52)
Caspofungin MIC of >0.06 μg/ml (BMD-AM3)	2	8	0.002	12.0	2.27–63.4	80 (8/10)	75 (42/56)
Caspofungin MIC of >0.25 μg/ml (YeastOne)	6	9	0.03	4.39	1.31–14.7	60 (9/15)	75 (38/51)
Caspofungin MIC of >0.25 μg/ml (Etest)	3	11	0.0001	13.7	3.24–57.7	79 (11/14)	79 (41/52)

[a] Positive predictive value (PPV) is the percentage of positive tests associated with failure.
[b] Negative predictive value (NPV) is the percentage of negative tests associated with success.

Drug-Resistant *Candida glabrata* Infection in Cancer Patients

Dimitrios Farmakiotis,[1] Jeffrey J. Tarrand, and Dimitrios P. Kontoyiannis

Überleben in Abhängigkeit von der Caspofungin-MHK



< 0.25 (17/67)

0.25 (5/12)

0.5 (5/10)

> 2.0 (3/4)

Probleme bei systemischen Hyphomyzeten-Infektionen

Erreger	**Resistente Erreger waren bislang selten**
	Standardisierung der Resistenztestung erst kürzlich
	Resistenztestungen werden nicht überall durchgeführt
Medikamente	**Wirkungmechanismus zum Teil unklar (Amphotericin B)**
	Keine einfache Dosis-/Konzentrationsbeziehung
	Variable Pharmakokinetik und -dynamik
Patienten	**Relativ seltene Erkrankung**
	Relativ hohe Letalität durch Grunderkrankung
	Diagnosekriterien waren lange Zeit uneinheitlich
	Wenige gesicherte Infektionen
	Infektionsdiagnose spät

Therapeutic drug monitoring of voriconazole helps to decrease the percentage of patients with off-target trough serum levels

Jesús Guinea[1,2,3,4,*], Pilar Escribano[1,2,3],

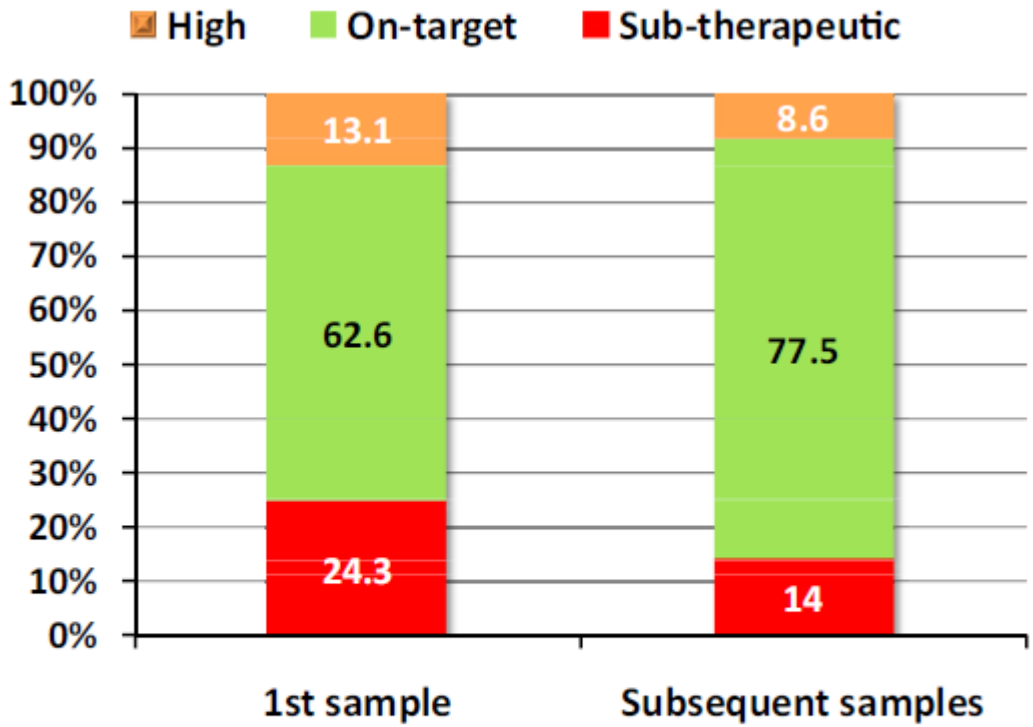


FIGURE 1. Proportion of first and subsequent samples with sub-therapeutic, on-target, and high voriconazole levels. This Figure is reproduced in color in the online version of *Medical Mycology*.

Medical Mycology, 2016, 0, 1–8
doi: 10.1093/mmy/myv099

Probleme bei systemischen Hyphomyzeten-Infektionen

Erreger	Resistente Erreger waren bislang selten
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Medikamente	Wirkungmechanismus zum Teil unklar (Amphotericin B)
	Keine klare Dosis-/Wirkungsbeziehung
	Variable Pharmakokinetik und -dynamik
Patienten	**Relativ seltene Erkrankung**
	Relativ hohe Letalität durch Grunderkrankung
	Diagnosekriterien waren lange Zeit uneinheitlich
	Wenige gesicherte Infektionen
	Infektionsdiagnose spät

Aspergillus to Zygomycetes: Causes, Risk Factors, Prevention, and Treatment of Invasive Fungal Infections

O. A. Cornely

Table 2
Mortality Rates for Specific Organism in IFIs.

Organism	Mortality (%)
Aspergillus species [43, 44]	
Overall case fatality rate	58
AIDS	86
HSCT	32–87
Leukemia/lymphoma	49
Blastomyces dermatitidis [3]	
Immunocompromised	30–49
Candida species [17, 45]	
Overall	10–49
Neutropenic	48

Infection 2008; 36: 296–313

Causes of Death in a Contemporary Cohort of Patients with Invasive Aspergillosis

Carolina Garcia-Vidal[1,2*], Maddalena Peghin[3],

152 Patienten mit Aspergillose:

Letalität 60 % (92/152)

***Aspergillus*-related N = 62**

***Aspergillus*-unrelated N = 36**

PLOS ONE | DOI:10.1371/journal.pone.0120370 March 24, 2015

In-vitro testing of susceptibility to amphotericin B is a reliable predictor of clinical outcome in invasive aspergillosis

C. Lass-Flörl[a*], G. Kofler[a], G. Kropshofer[c], J. Hermans[d], A. Kreczy[b], M. P. Dierich[a] and

Table II. MIC of amphotericin B against the isolated *Aspergillus* spp.

Species	*n*	MIC (mg/L)
A. terreus	9	⩾2
A. fumigatus	2	<2
	6	⩾2
A. flavus	4	<2
	8	⩾2

Table III. MIC of amphotericin B in relation to survival from disseminated fungal infections

	Outcome of disseminated infection		
MIC (mg/L)	dead	survivors	*P* value (Fisher's test)
<2	0	6	
⩾2	22	1	<0.001

Journal of Antimicrobial Chemotherapy (1998) **42**, 497–502

Azole Resistance in *Aspergillus fumigatus*: Can We Retain the Clinical Use of Mold-Active Antifungal Azoles?

Paul E. Verweij,[1] Anuradha Chowdhary,[2] Willem J. G. Melchers,[1] and Jacques F. Meis[1,3]

Table 3. Reported Mortality Rates in Patients With Invasive Aspergillosis in Different T

		Aspergillus Disease
Era	IA	Comment
c-AmB era	65% [2]	122 of 187 patients receiving c-AmB died.
	71.6% [55]	187 of 261 patients with IA died.
Azole era	27.5% [57]	9-wk mortality: 39 of 142 patients receiving voriconazole monotherapy.
	28.5% [58]	Population-based study analyzing 8563 aspergillosis cases in France.
Azole resistant	100% [44]	Culture-positive patients with proven and probable IPA treated with voriconazole (5/5)
	88% [45]	8 HSCT patients with culture-positive, azole-resistant IA, of whom 7 died.
	100% [54]	ICU patients with culture-positive azole-resistant IA died (10/10), compared with 21 of 28 (75%) with azole-susceptible IA.

Emergence of azole-resistant invasive aspergillosis in HSCT recipients in Germany

J. Steinmann[1]*†, A. Hamprecht[2]†, M. J. G. T. Vehreschild[3,4], O. A. Cornely[3–5], D. Buchheidt[6], B. Spiess[6], M. Koldehoff[7], J. Buer[1], J. F. Meis[8,9] and P.-M. Rath[1]

Patient no.	Sex, age (years)	Underlying disease	Type of mutation	MIC (mg/L) ITC	VRC	POS	Antifungal treatment	Discharge status (100 days after ARAF detection)	Cause of death
1	M, 46	AML	TR_{34}/L98H	>16	2	0.5	CAS	died	sepsis
2	M, 54	AML	WT	>16	4	0.5	VRC	died	relapse, MOV
3	F, 65	AML	TR_{34}/L98H	>16	4	0.5	POS	died	sepsis, MOV
4	M, 66	Acute biphenotype leukaemia	TR_{34}/L98H	>16	2	0.5	L-AMB, later VRC	died	sepsis, MOV
5	F, 58	MDS RAEB-II	TR_{34}/L98H	>16	2	0.5	VRC	died	sepsis, MOV
6	F, 38	Plasma cell leukaemia	TR_{34}/L98H	>16	2	0.5	VRC	alive	—
7	M, 43	CLL Binet C	TR_{46}/Y121F/ T289A	>16	16	0.5	L-AMB, later VRC	died	GvHD, MOV
8	F, 52	Follicular B-NHL grade IIIa	TR_{46}/Y121F/ T289A	1	>16	0.5	L-AMB, later CAS	died	sepsis

7/8 Patienten verstorben, aber nicht an der *Aspergillus*-Infektion (alleine).

J Antimicrob Chemother 2015; **70**: 1522–1526

Role of Antifungal Susceptibility Testing in Non-*Aspergillus* Invasive Mold Infections

Frederic Lamoth[1,2,3,4*], Lauro Damonti[3], Barbara D. Alexander[1,2]

226 **Table 3. Response to amphotericin B therapy at week 6 for various MIC cut-offs (N=10) [1]**

MIC cut-off [µg/ml]	Response rate		P value
	MIC ≤ cut-off	MIC > cut-off	
0.25	2/2 (100%)	3/8 (38%)	0.40
0.5	5/6 (83%)	0/4 (0%)	0.05
1	5/7 (71%)	0/3 (0%)	0.17
2	5/7 (71%)	0/3 (0%)	0.17
4	5/8 (63%)	0/2 (0%)	0.44

227

228 [1] *Rhizopus* spp. (6), *Mucor* spp. (1), *Cunninghamella* spp. (1), *Scedosporium apiospermum* (1),

229 *Purpureocillium lilacinum* (1).

For amphotericin B, an MIC≤0.5 µg/ml was significantly associated with better 6 week outcomes.

JCM Accepted Manuscript Posted Online 23 March 2016
J. Clin. Microbiol. doi:10.1128/JCM.00318-16

Zusammenfassung

Relevanz der Ergebnisse von Empfindlichkeitsbestimmungen

Candida	**Amphotericin B**	**?**
	Azole	**+++**
	Echinocandine	**++**
Aspergillus	**Amphotericin B**	**+**
	Azole	**++**
	Echinocandine	**?**
Non-*Aspergillus*-Spezies	**Amphotericin B**	**(+)**