Echinocandine und Surfactant Faktor

Markus Zeitlinger

Übersicht

MEDICAL UNIVERSITY OF VIENNA

- Wieso kommen wir auf die Idee?
- Die eingesetzten Methoden und Resultate
- Ausblick auf andere Kompartimente

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Wann ist eine Therapie adequat?

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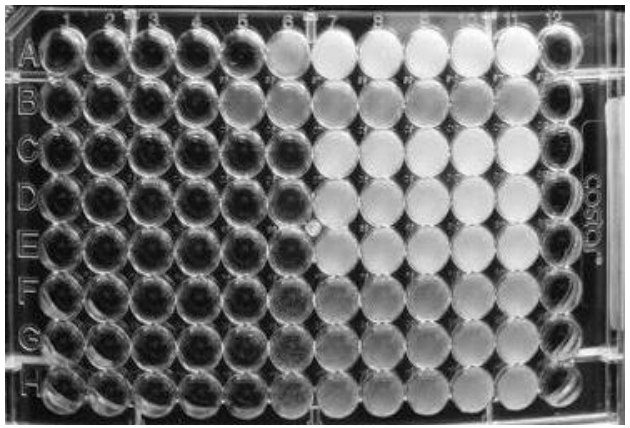
CLINICAL AND LABORATORY STANDARDS INSTITUTE



PK/PD

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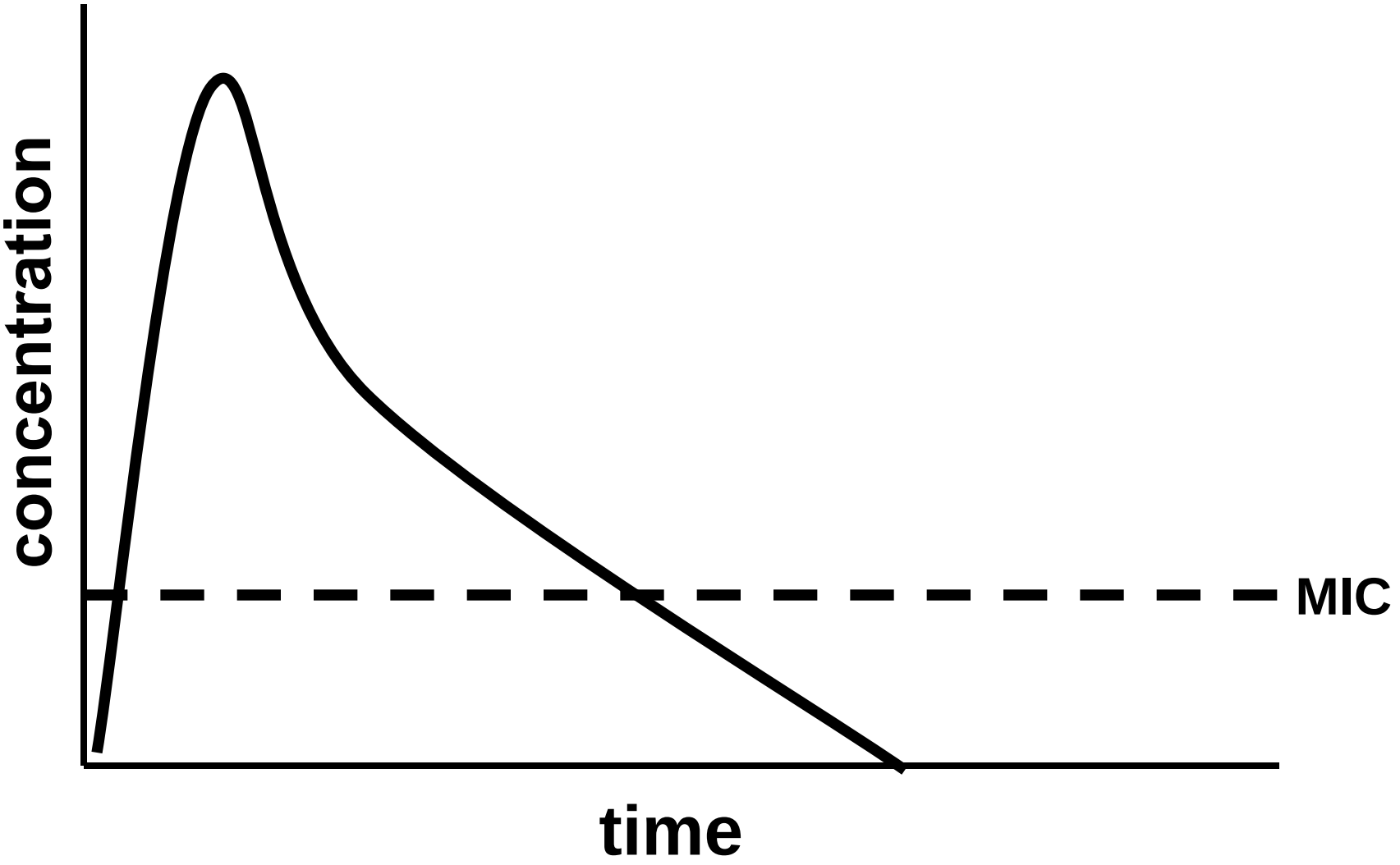

PK/PD Schussfolgerungen

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Antimicrob Agents Chemother. 2010 Aug;54(8):3451-9. doi: 10.1128/AAC.01647-09. Epub 2010 May 3.

Intrapulmonary pharmacokinetics and pharmacodynamics of micafungin in adult lung transplant patients.

Walsh TJ[1], Goutelle S, Jelliffe RW, Golden JA, Little EA, DeVoe C, Mickiene D, Hayes M, Conte JE Jr.

We conclude that a single 150-mg intravenous dose of micafungin resulted in plasma, ELF, and AC concentrations that exceeded the MIC90 of A. fumigatus for 24 h…supporting its potential activity for prevention and early treatment of pulmonary aspergillosis.

Antimicrob Agents Chemother. 2009 Dec;53(12):5102-7. doi: 10.1128/AAC.01042-09. Epub 2009 Sep 21.

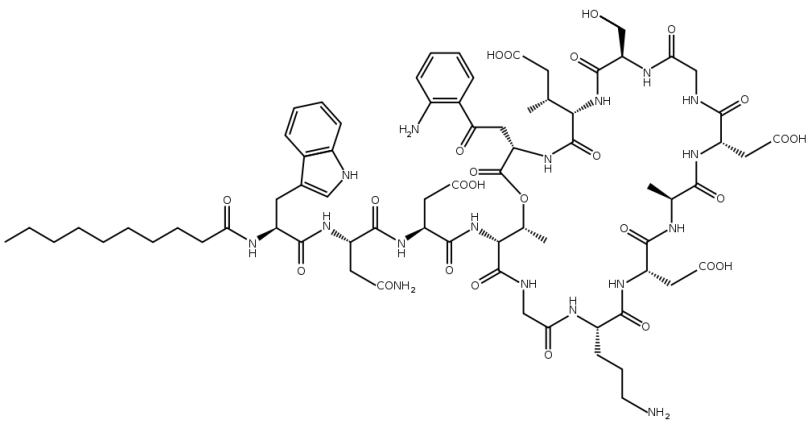
Bronchopulmonary disposition of intravenous voriconazole and anidulafungin given in combination to healthy adults.

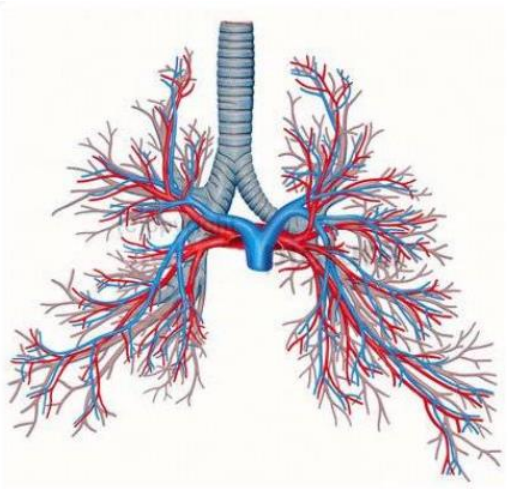
Crandon JL[1], Banevicius MA, Fang AF, Crownover PH, Knauft RF, Pope JS, Russomanno JH, Shore E, Nicolau DP, Kuti JL.

The mean total concentrations of both drugs in ELF and AM at 4, 8, 12, and 24 h remained above the MIC(90)/90% minimum effective concentration for most Aspergillus species.

Daptomycin

- Zugelassen für Haut und Weichteilinfekte
- Non-inferiority für Pneumonie (CAP) verfehlt
- Erste Beispiel für Organ spezifische Inhibierung eines Antibiotikums





Daptomycin Tiermodel

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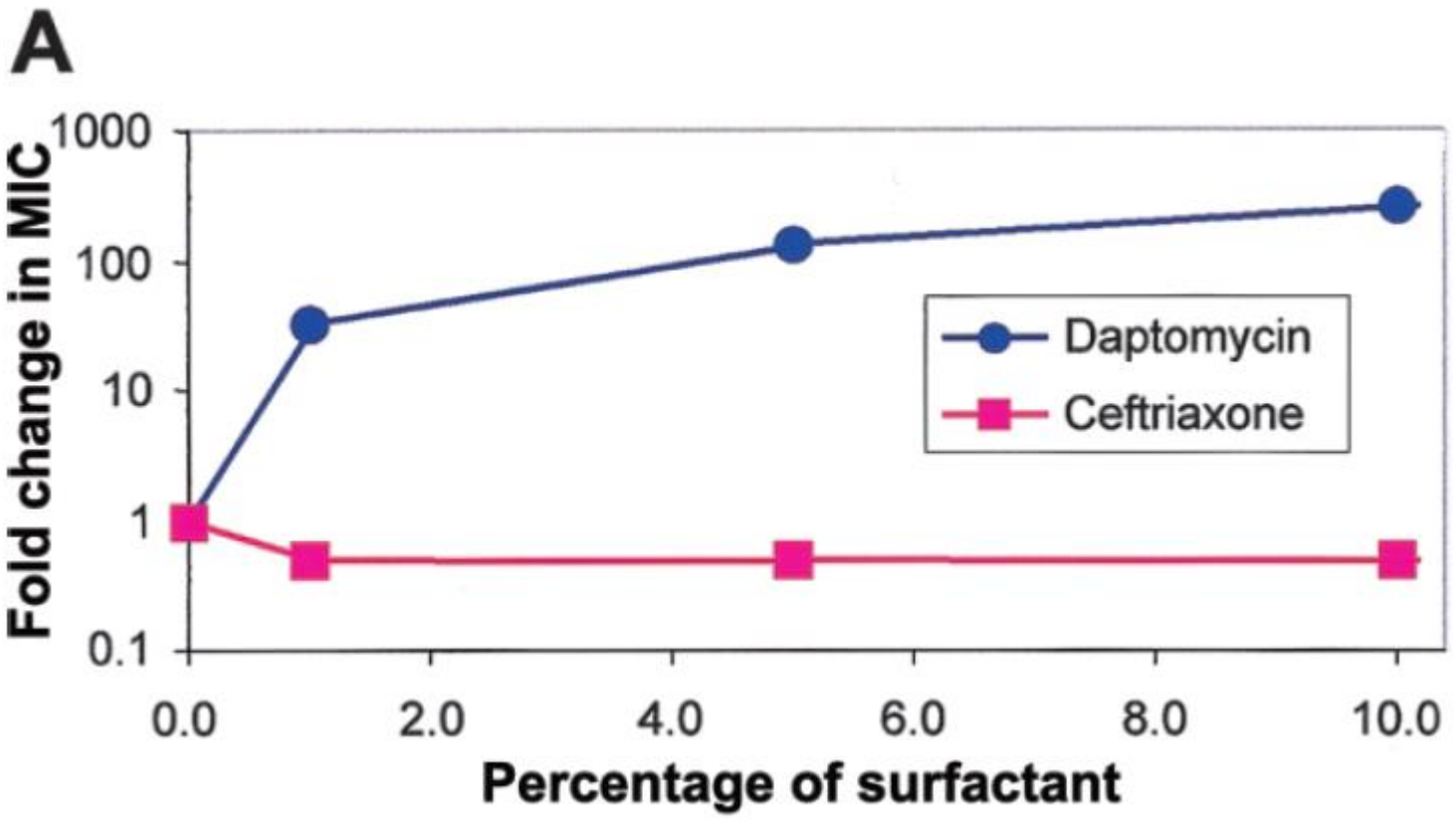
Table 1. Daptomycin efficacy in pulmonary infection models.

		Daptomycin		Comparator	
Model	Organism	Dose, mg/kg	Log reduction	Drug (dose, mg/kg)	Log reduction
Mouse BAP	*S. pneumoniae*	100	0.1 ± 0.13	Ceftriaxone (50)	4.5 ± 0.28
Mouse BAP	MRSA	100	0 ± 0.4	…	…
Rat HP	MRSA	50	2.1 ± 0.56	Vancomycin (100)	1.3 ± 1.19
Rat HP	*S. aureus*	75	2.2 ± 1.0	Nafcillin (150)	1.5 ± 0.62

NOTE. Data are expressed as reduction in bacterial burden in the infected organ, compared with that in untreated, infected controls. For bronchial-alveolar pneumonia (BAP), mice were treated at 1 and 4 h after infection, and lungs were harvested 24 h after infection. For hematogenous pneumonia (HP), rats were treated once daily (daptomycin and vancomycin) or twice daily (nafcillin) for 6 days after infection, and lungs were harvested on day 7. MRSA, methicillin-resistant *Staphylococcus aureus*; *S. pneumoniae, Staphylococcus pneumoniae*.

Silverman JA. JID 2005:191

In-vitro MIC



Silverman JA. JID 2005:191

Andere AB

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AAC Journals.ASM.org

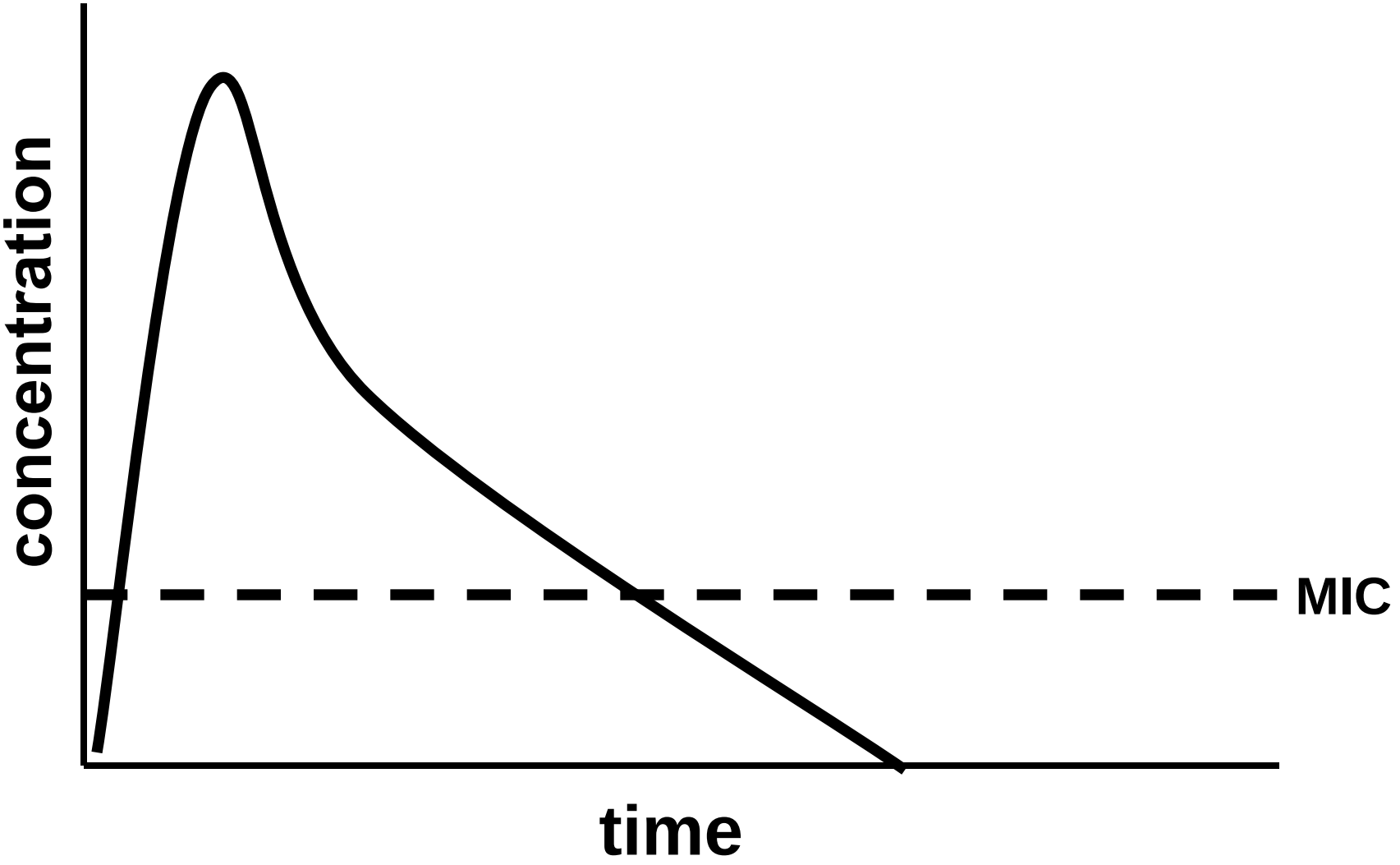
Effect of Pulmonary Surfactant on Antimicrobial Activity *In Vitro*

R. Schwameis,[a] Z. Erdogan-Yildirim,[a] M. Manafi,[b] M. A. Zeitlinger,[a] S. Strommer,[a] R. Sauermann[a,c]

Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria[a]; Institute of Hygiene and Applied Immunology, Medical University of Vienna, Vienna, Austria[b]; Main Association of Austrian Social Security Institutions, Vienna, Austria[c]

Time-kill curve experiments were performed with linezolid, doripenem, tigecycline, moxifloxacin, and daptomycin against *Staphylococcus aureus* and with colistin, moxifloxacin, and doripenem against *Pseudomonas aeruginosa* to evaluate the effect of porcine pulmonary surfactant on antimicrobial activity. Pulmonary surfactant significantly impaired the activities of moxifloxacin and colistin. When antibiotics are being developed for respiratory tract infections, the method described here might be used to preliminarily quantify the effect of pulmonary surfactant on antimicrobial activity.

Klinische Resistenz



Übersicht

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Materialien

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Antifungale Substanzen

Micafungin (MCF), Caspofungin (CPF), Anidulafungin (ANI)
Voriconazole (VCZ), Amphotericin B

Stämme

C. krusei ATCC 6258
C. albicans ATCC 90028
sowie jeweils 9 klinische Isolate

Medien

Roswell Park Memorial Institute (RPMI)
Sabouraud-dextrose broth (SDB)
Curosurf

Pulmonary Surfactant

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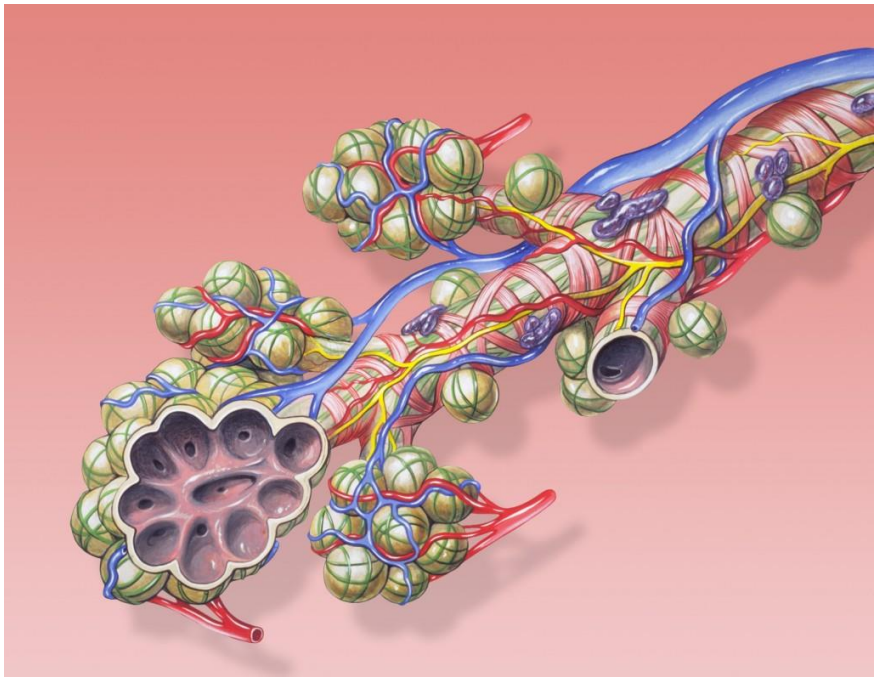
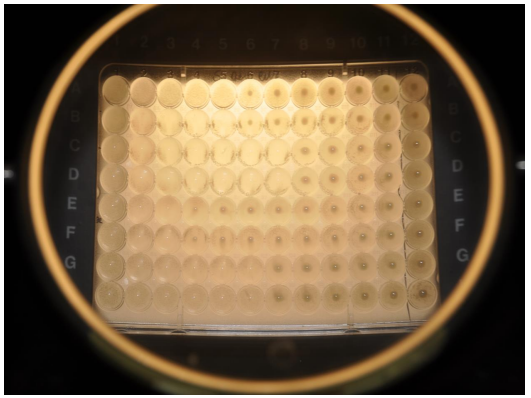
- 40% Dipalmitoylphosphatidylcholine (DPPC)
- 40% other phospholipids
- 5% surfactant associated proteins (SP-A,B,C and D)
- neutral lipids (cholesterol)



Methoden I

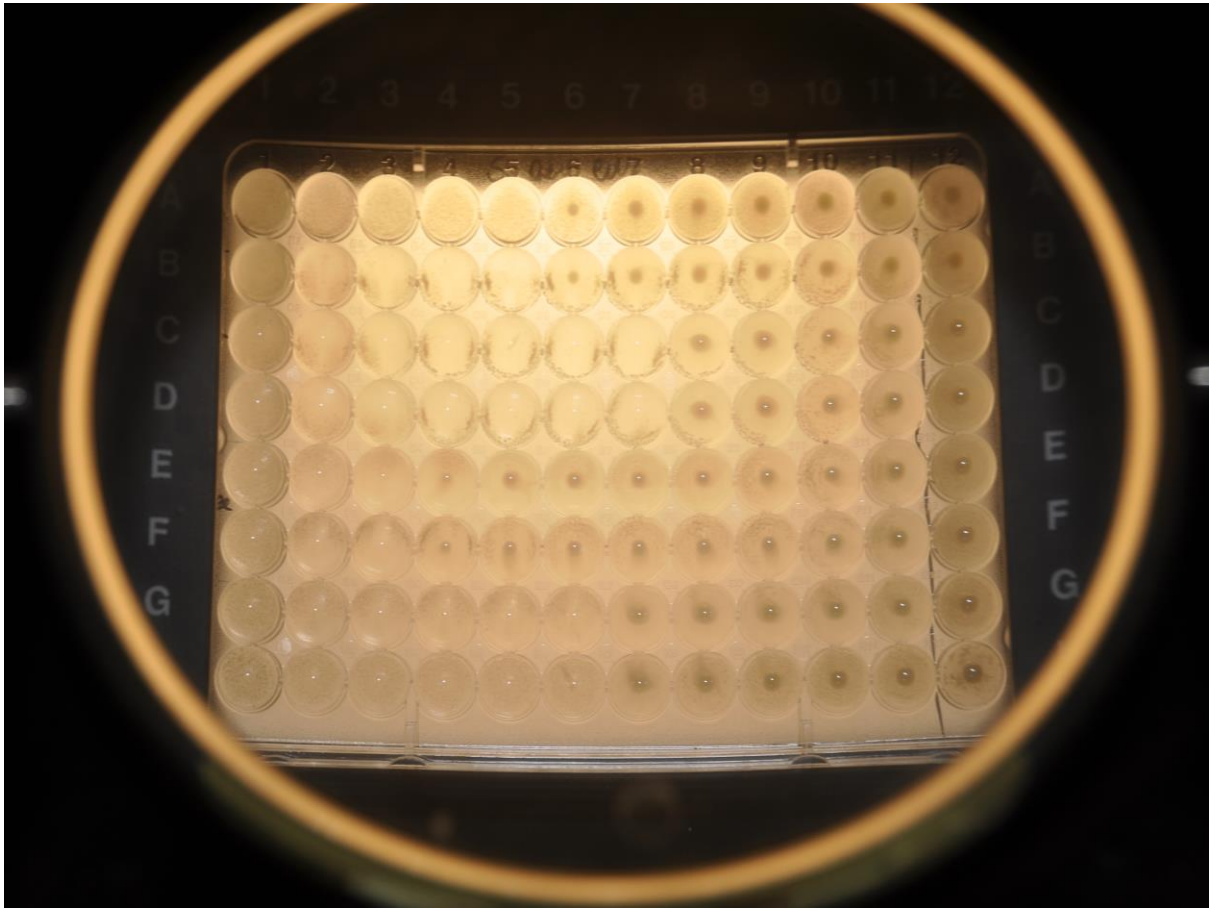
Mikrodilutionstest in
RPMI Medium
entsprechend EUCAST

MIC als 50% Reduction
in Pilzwachstum



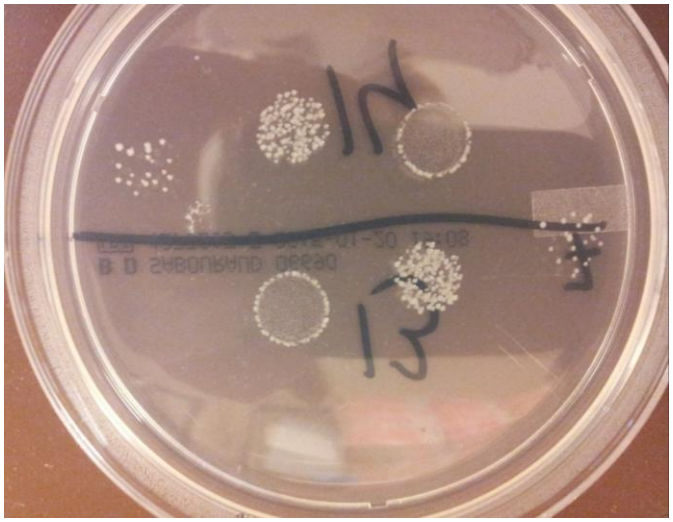
Minimal Inhibitory
Concentration (MIC)

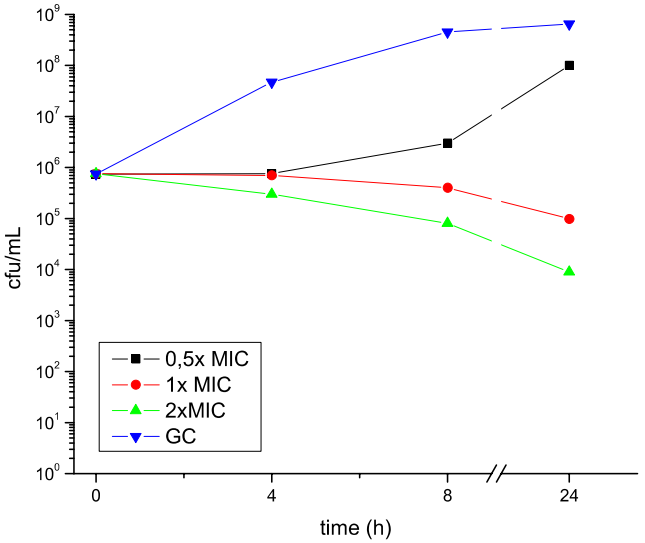
Nachteil MIC



Minimal Inhibitory Concentration (MIC)

Methode II





Time Kill Curves in Sabouraud-dextrose Medium

Konzentrationen entsprechend der jeweiligen MIC der Stämme

Voriconazol (*C. albicans*)

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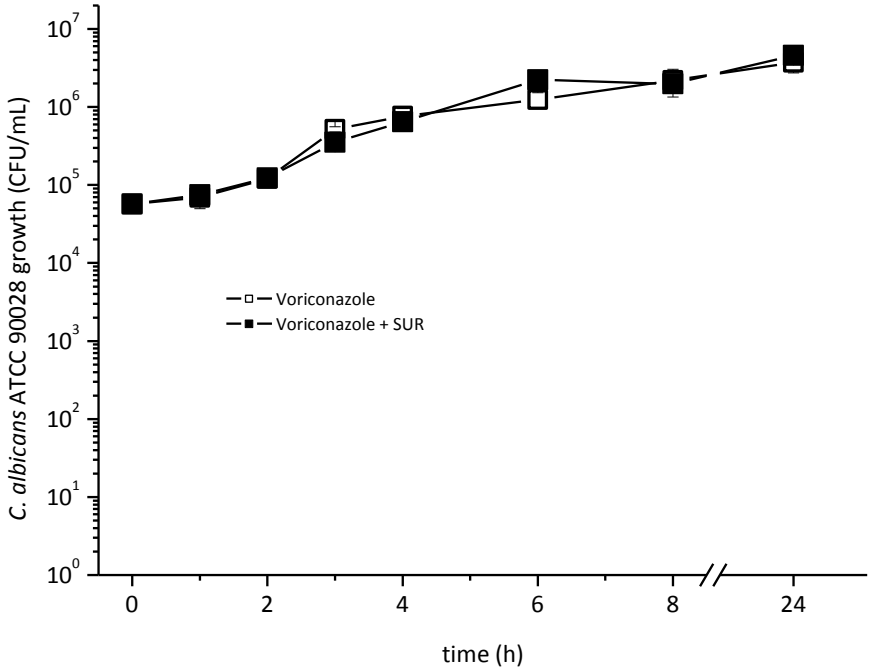
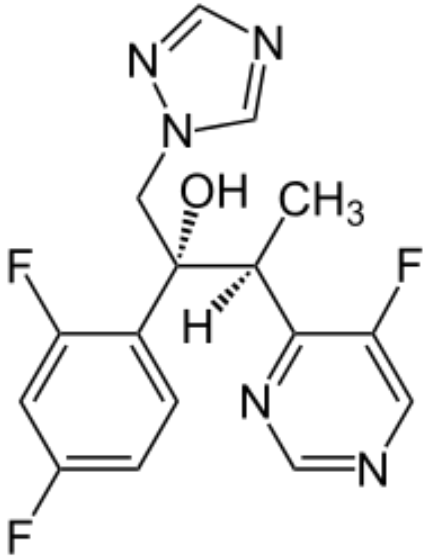
Voriconazol





Amphotericin B (*C. albicans*)

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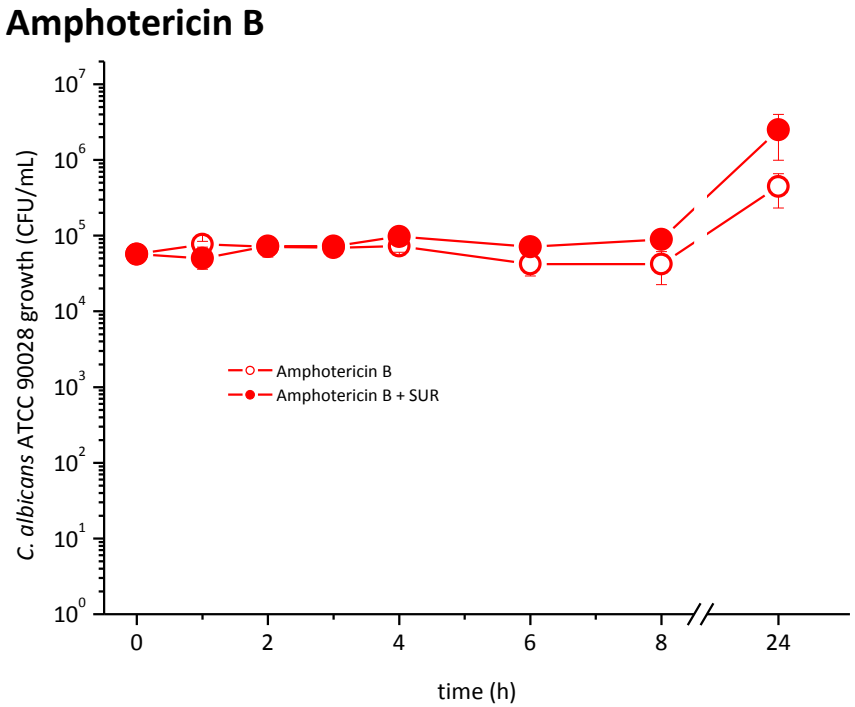

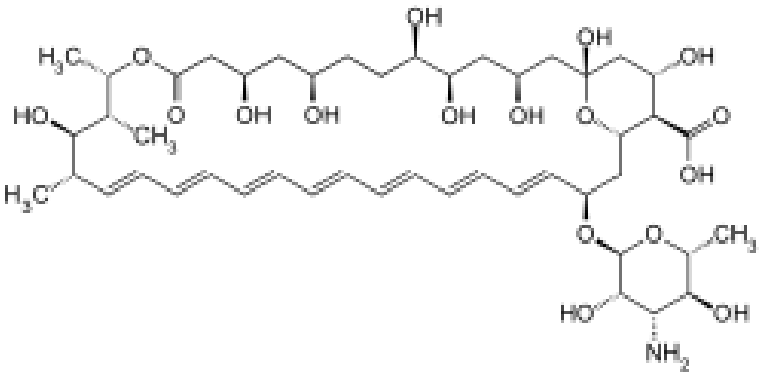

Micafungin (*C. albicans*)

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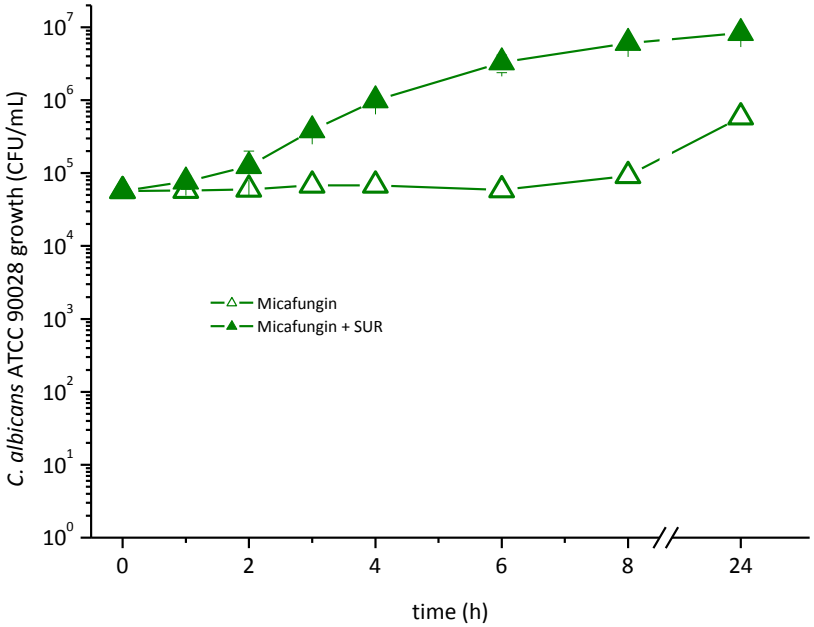
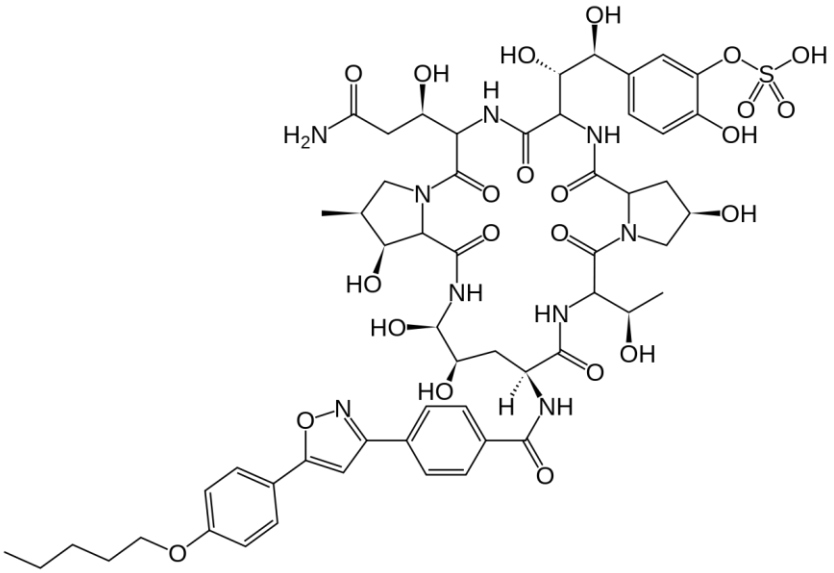
Micafungin





Anidulafungin (*C. albicans*)

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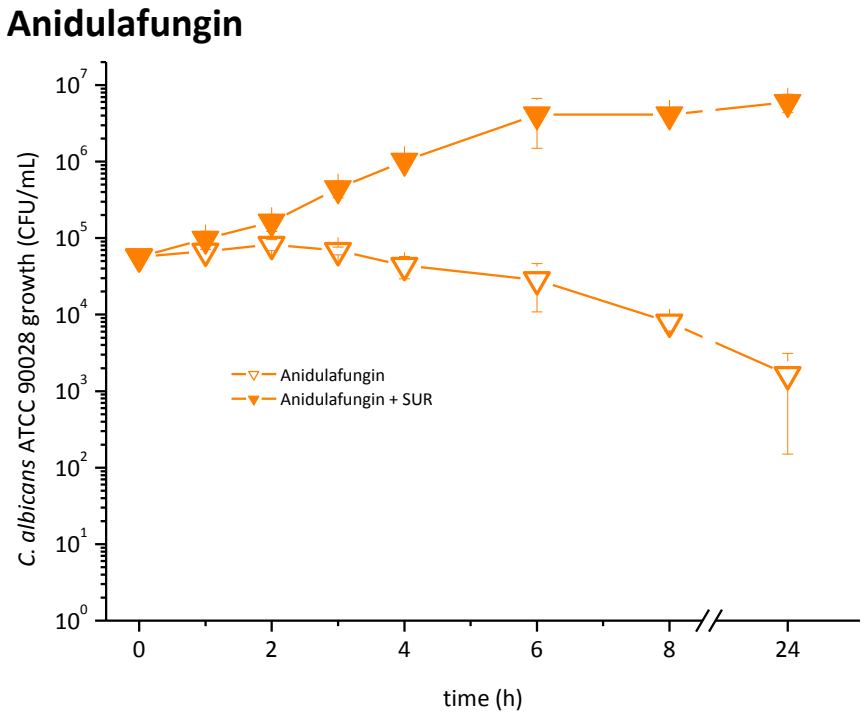

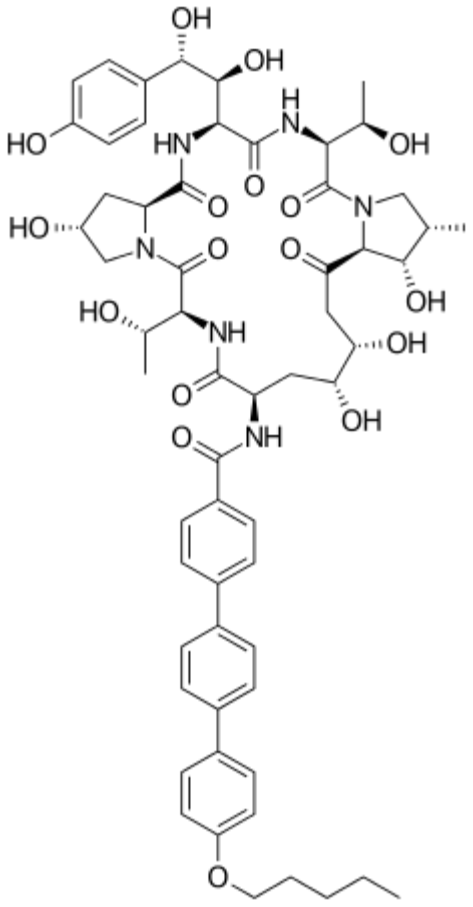

Caspofungin (*C. albicans*)

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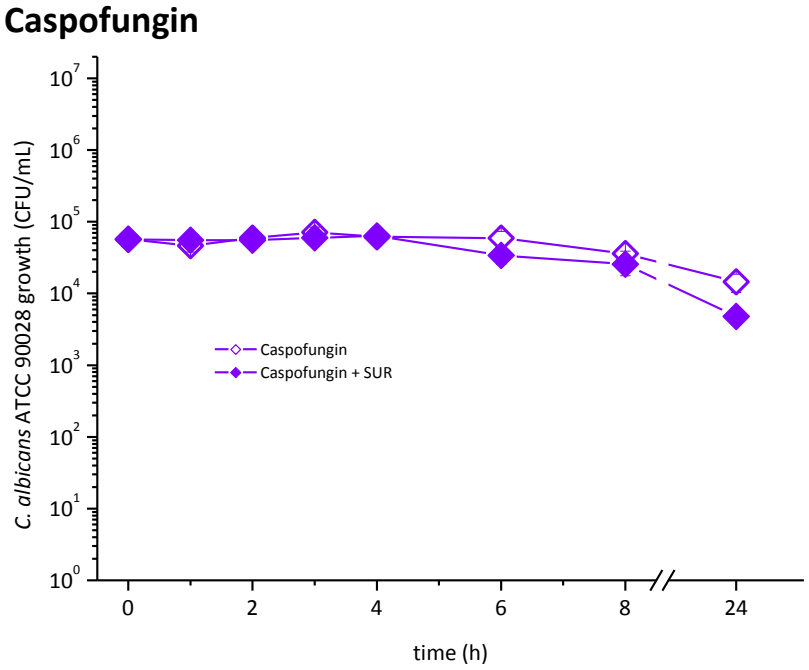
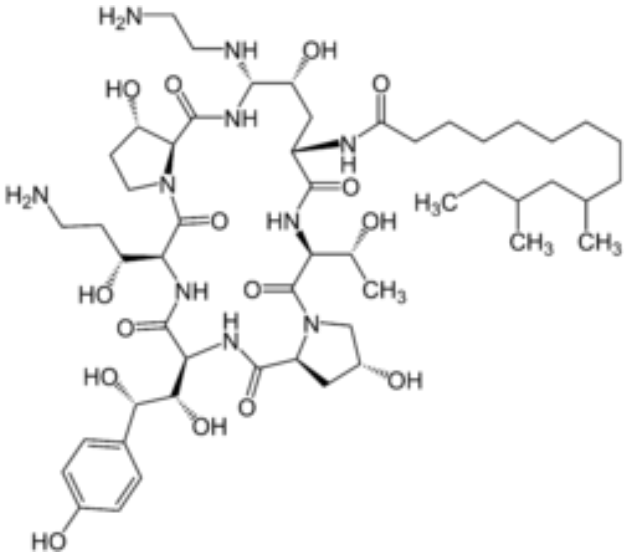
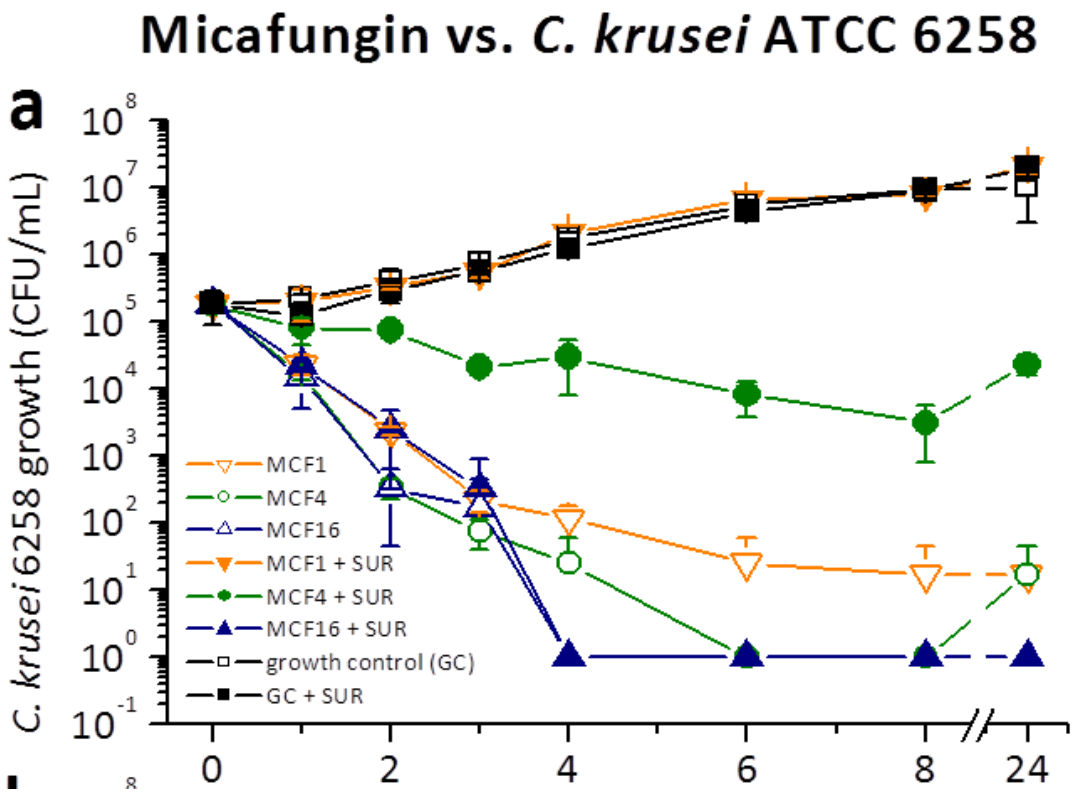




Abhängigkeit von AB Konzentration (Micafungin, *C. krusei*)



Konzentrationen entsprechend der 1, 4, 16x MIC des Stammes

Abhängigkeit von AB Konzentration (Anidulafungin, *C. krusei*)

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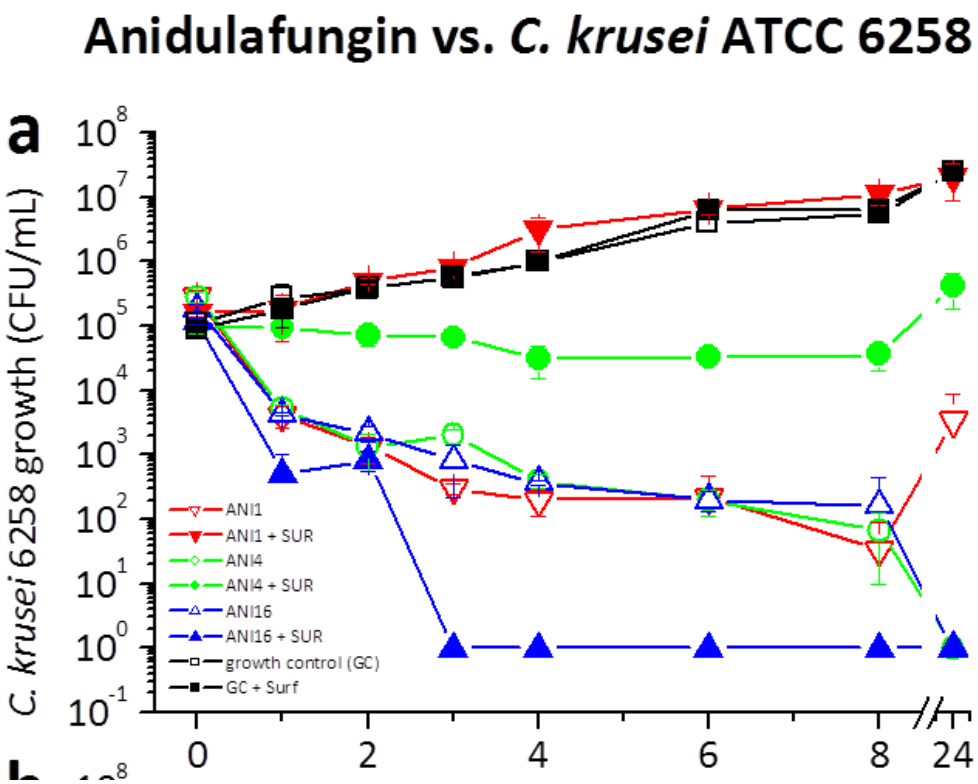
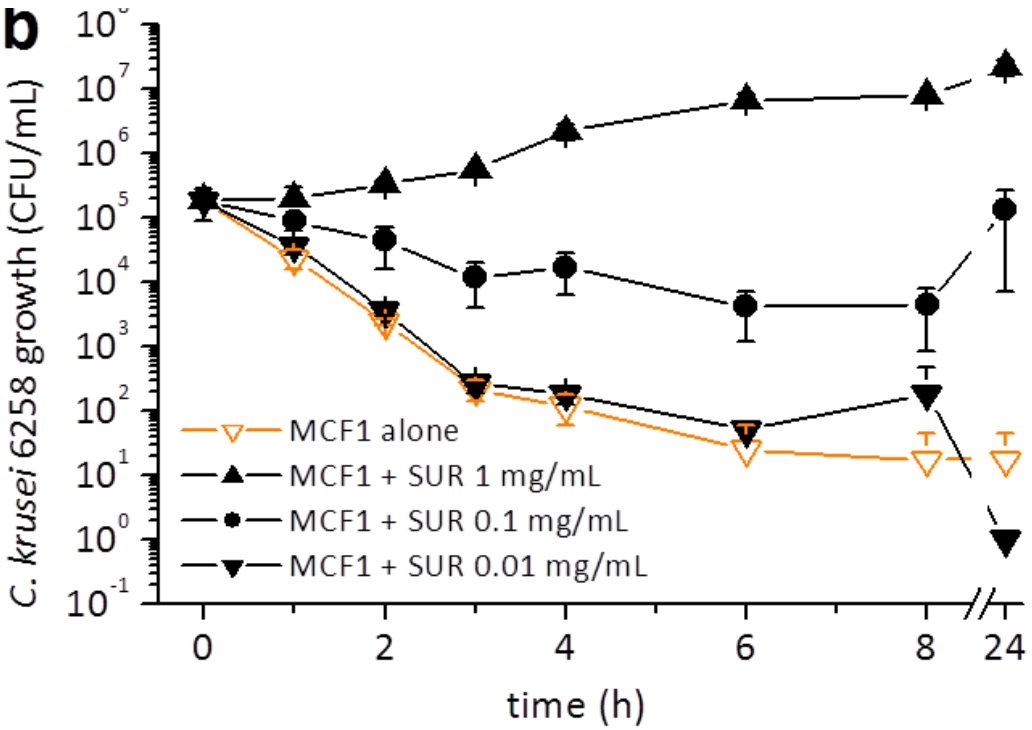


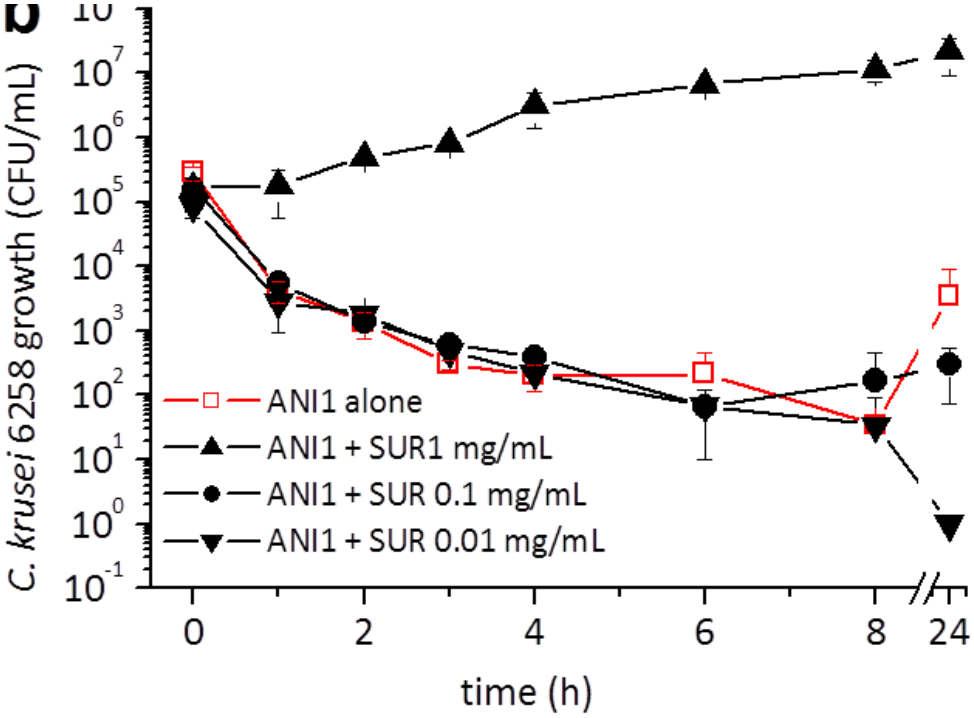
Konzentrationen entsprechend der 1, 4, 16x MIC des Stammes

Abhängigkeit Konz. Surfactant (Micafungin, *C. krusei*)



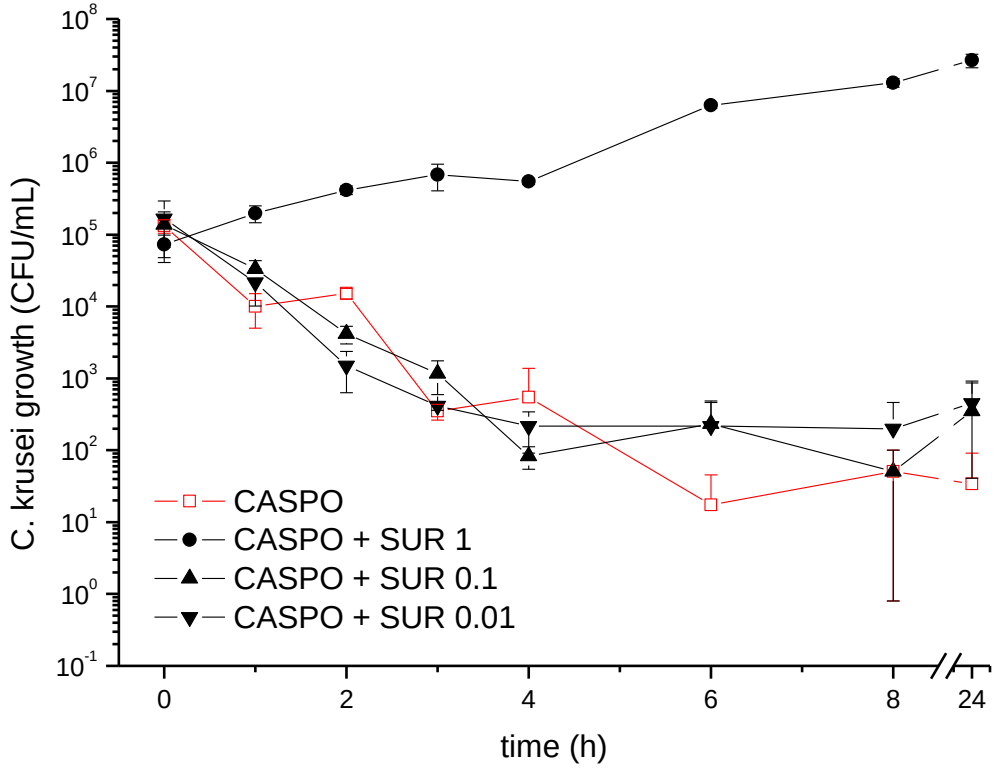
Konzentrationen entsprechend der 1x MIC des Stammes;
3 Surfactant Konzentrationen

Abhängigkeit Konz. Surfactant (Anidulafungin, *C. krusei*)



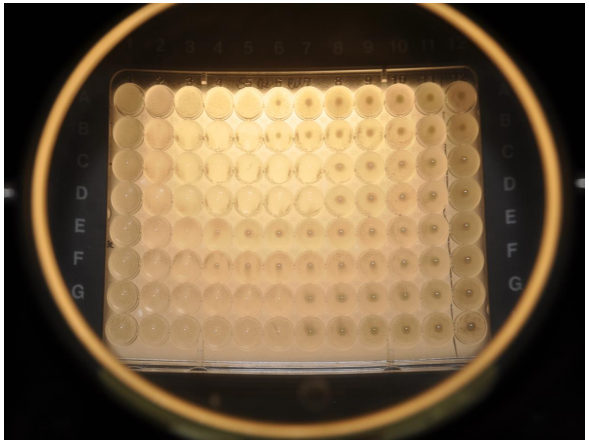
Konzentrationen entsprechend der 1x MIC des Stammes
3 Surfactant Konzentrationen

Abhängigkeit Konz. Surfactant (Caspofungin, *C. krusei*)



Konzentrationen entsprechend der 1x MIC des Stammes
3 Surfactant Konzentrationen

Methode III



24 Stunden statisches dynamisches Model in Sabouraud-dextrose Medium,
unterschiedliche Surfactant Konzentrationen,
Antifungale Konzentration entsprechend 4x MIC

Micafungin (*C. krusei*)

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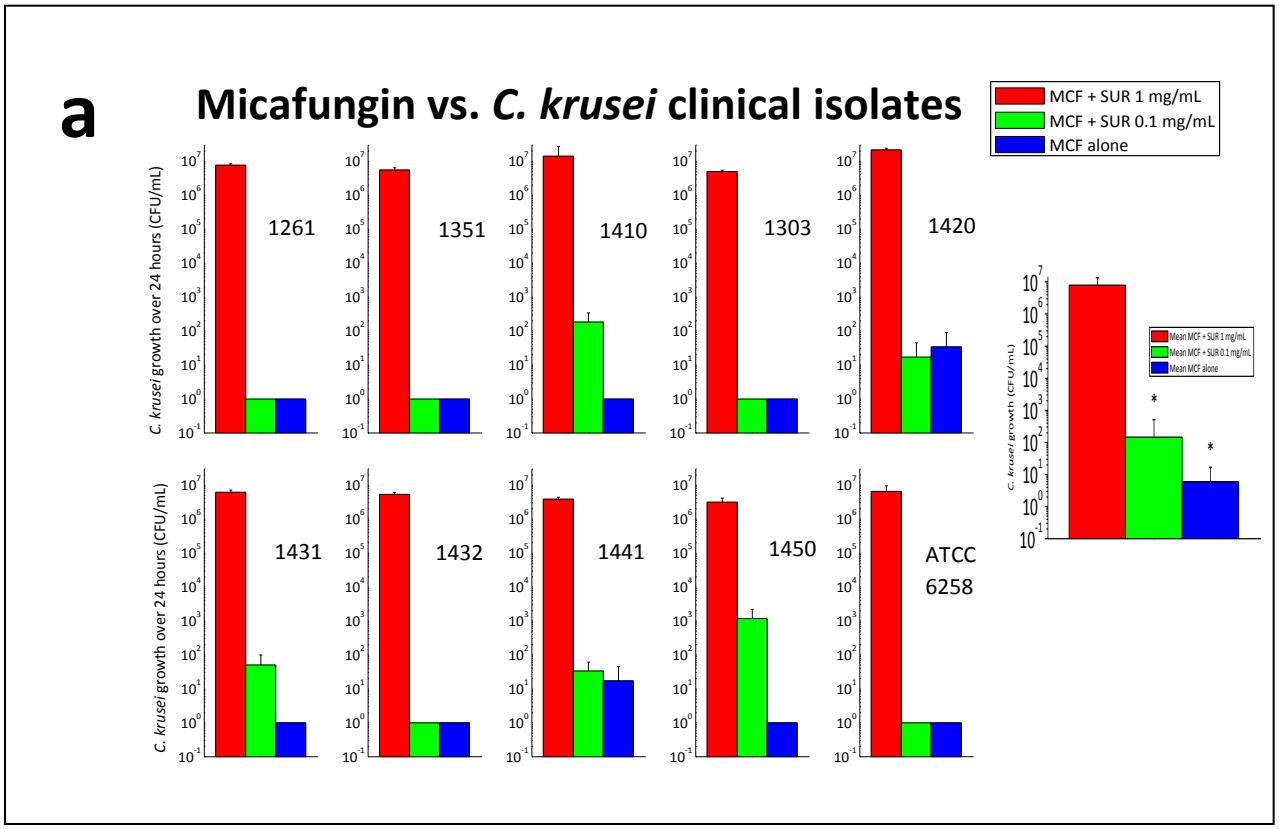

Anidulafungin (*C. krusei*)

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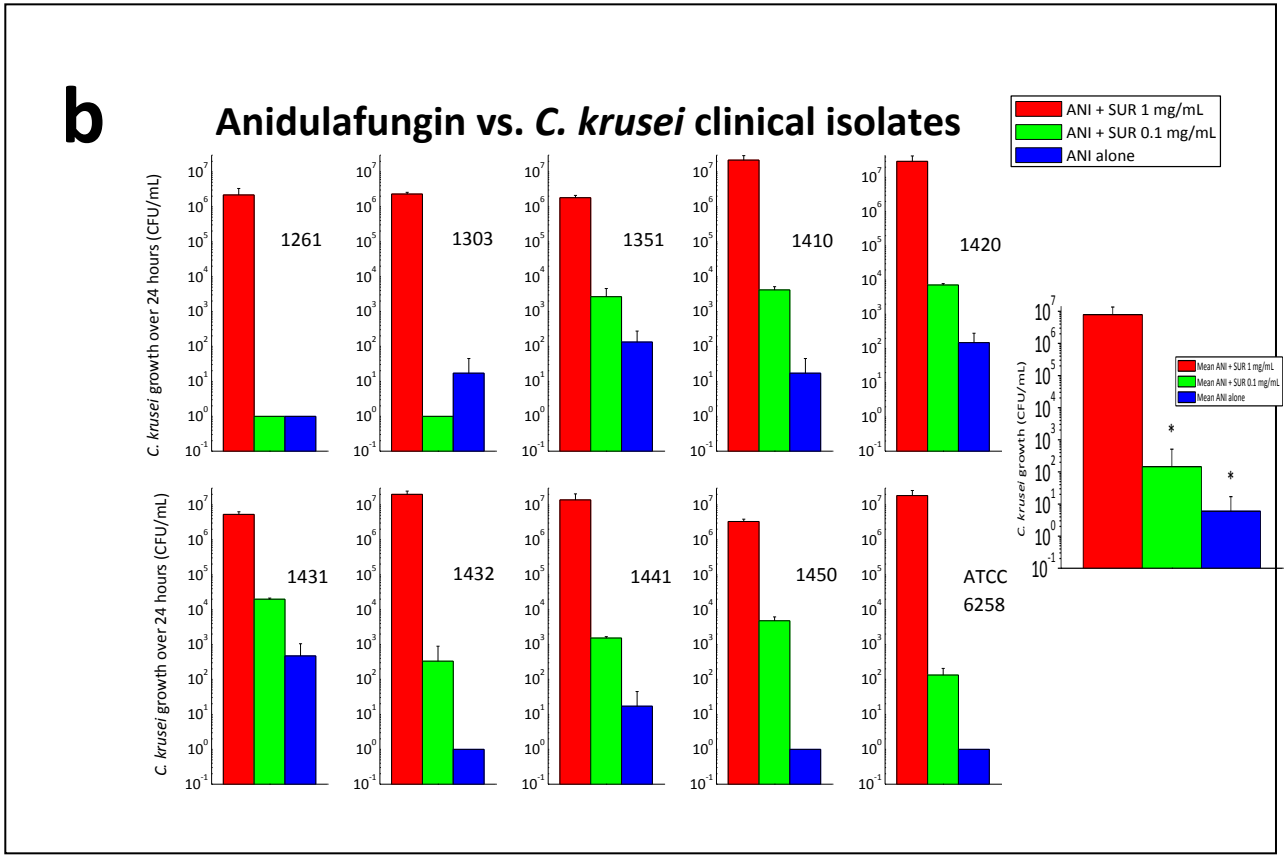

Caspofungin (*C. krusei*)

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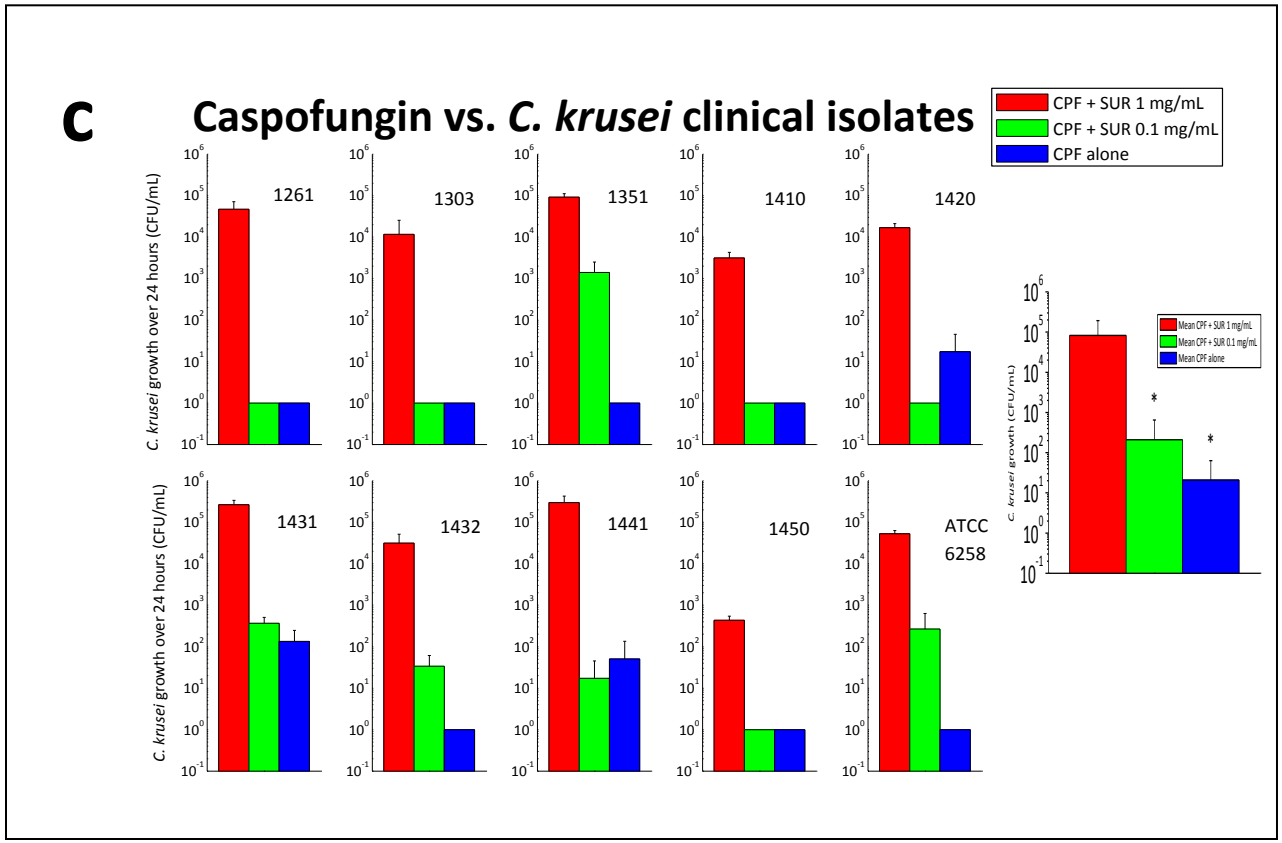

Übersicht

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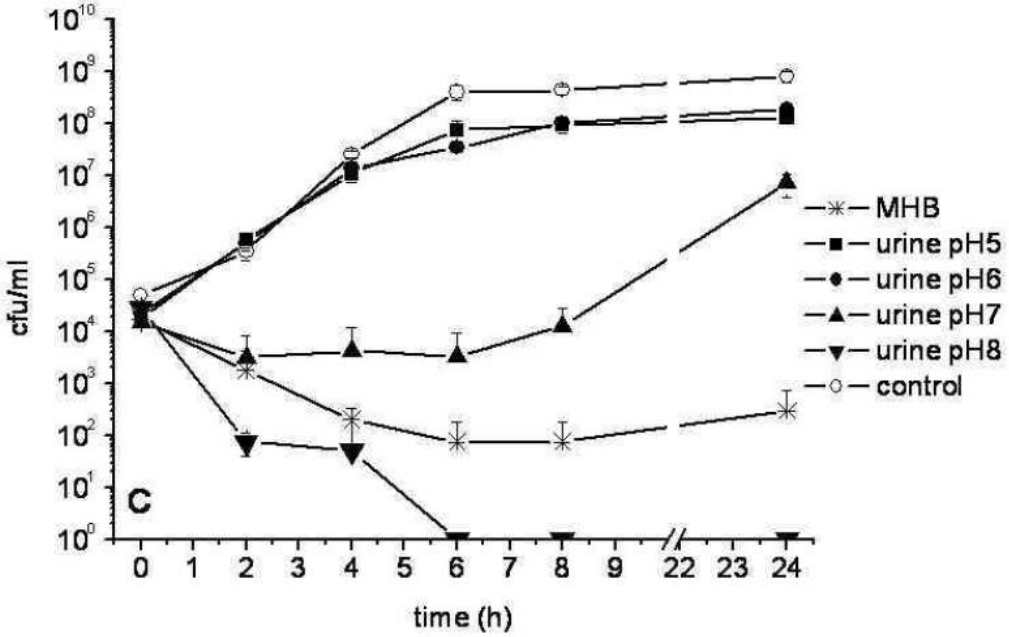
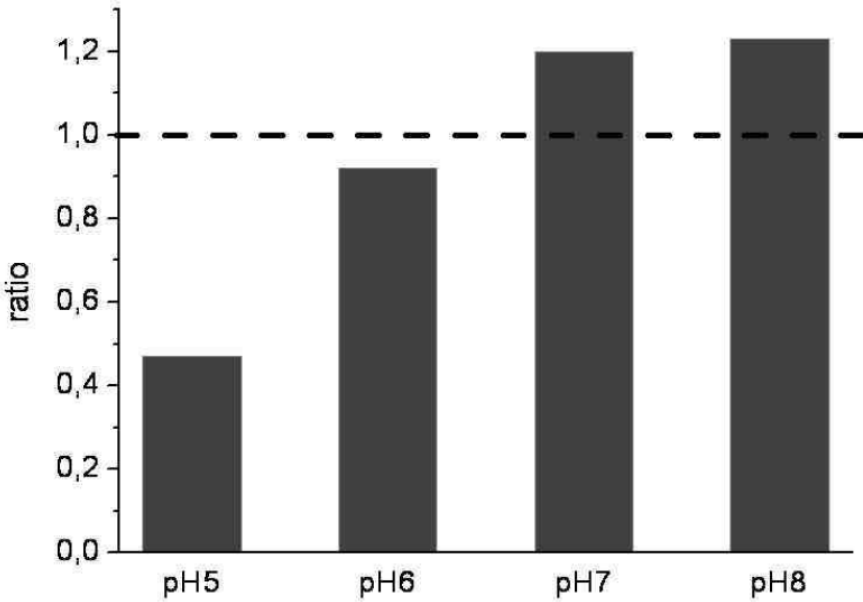
pH Einfluss (Moxifloxacin)





Erdogan Z. Research Microb. 2010

Protein Bindung

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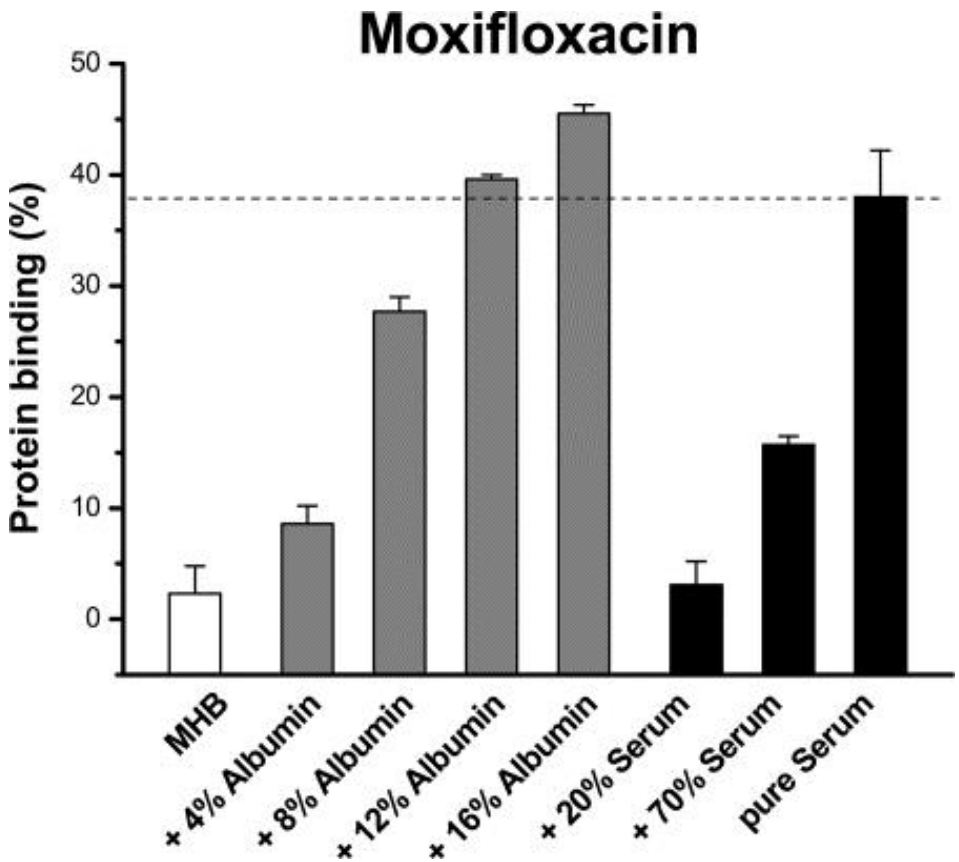
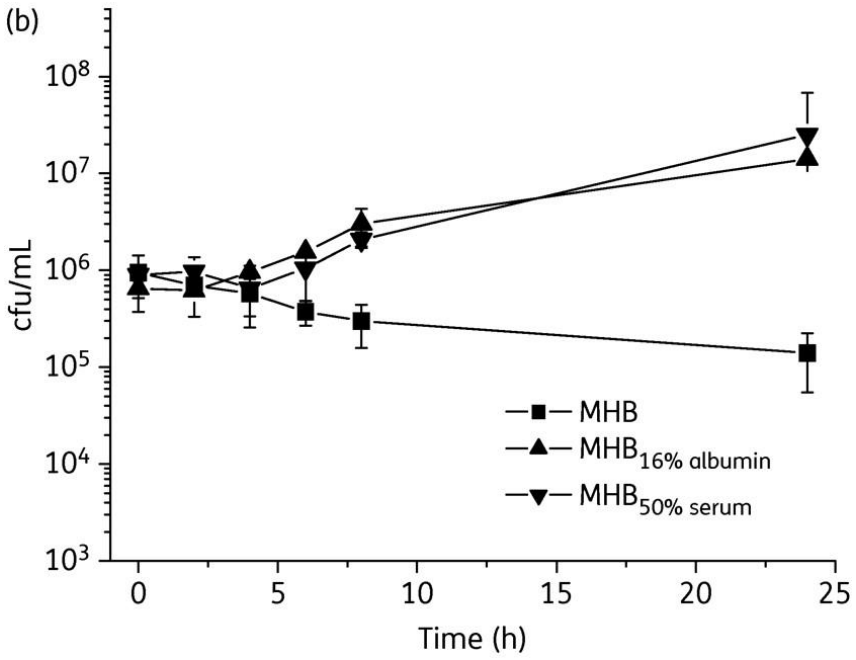
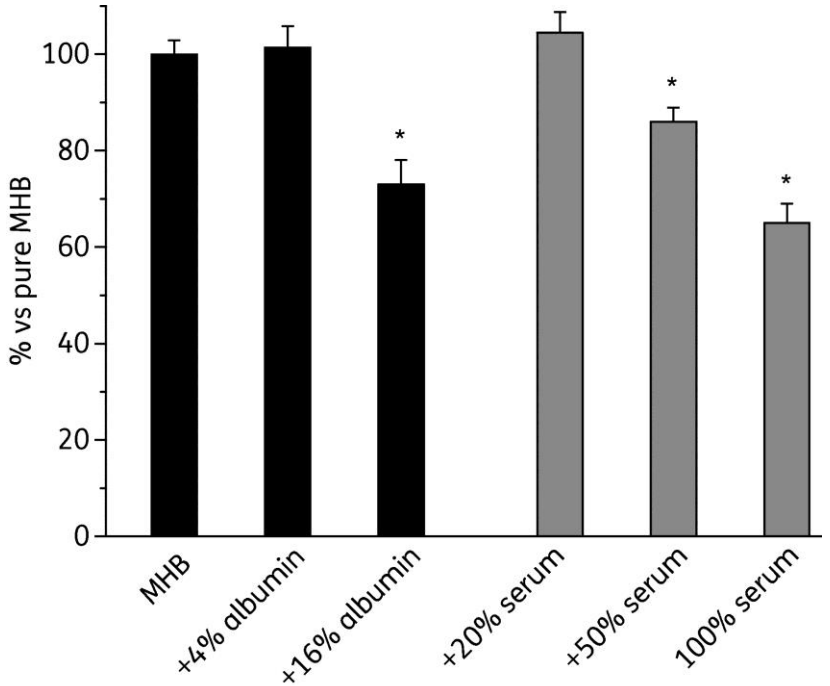


Zeitlinger M. J Antimicrob Chemother. 2008

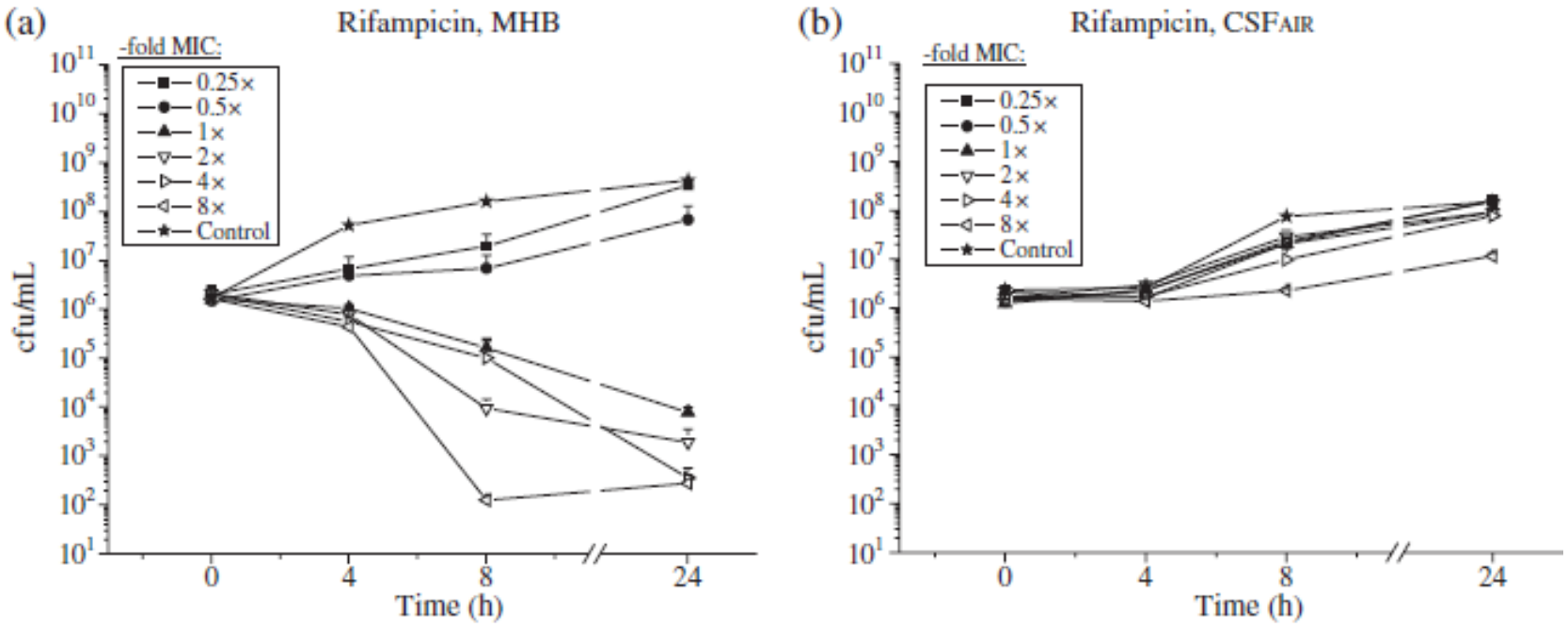
Einfluss Protein Bindung





Burian A. J Antimicrob Chemother. 2011

Cerebrospinal Flüssigkeit



Sauermann R. J Antimicrob Chemother. 2008

Zusammenfassung

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- Zugabe von Surfactant hatte signifikanten Effekt auf antifungale Wirksamkeit von Echinocandinen
- Abhängigkeit von Konz. des Echinocandins
- Abhändigkeit von Konz. von Surfactant
- Potentiell auch andere Einflusse im Körper

PK/PD

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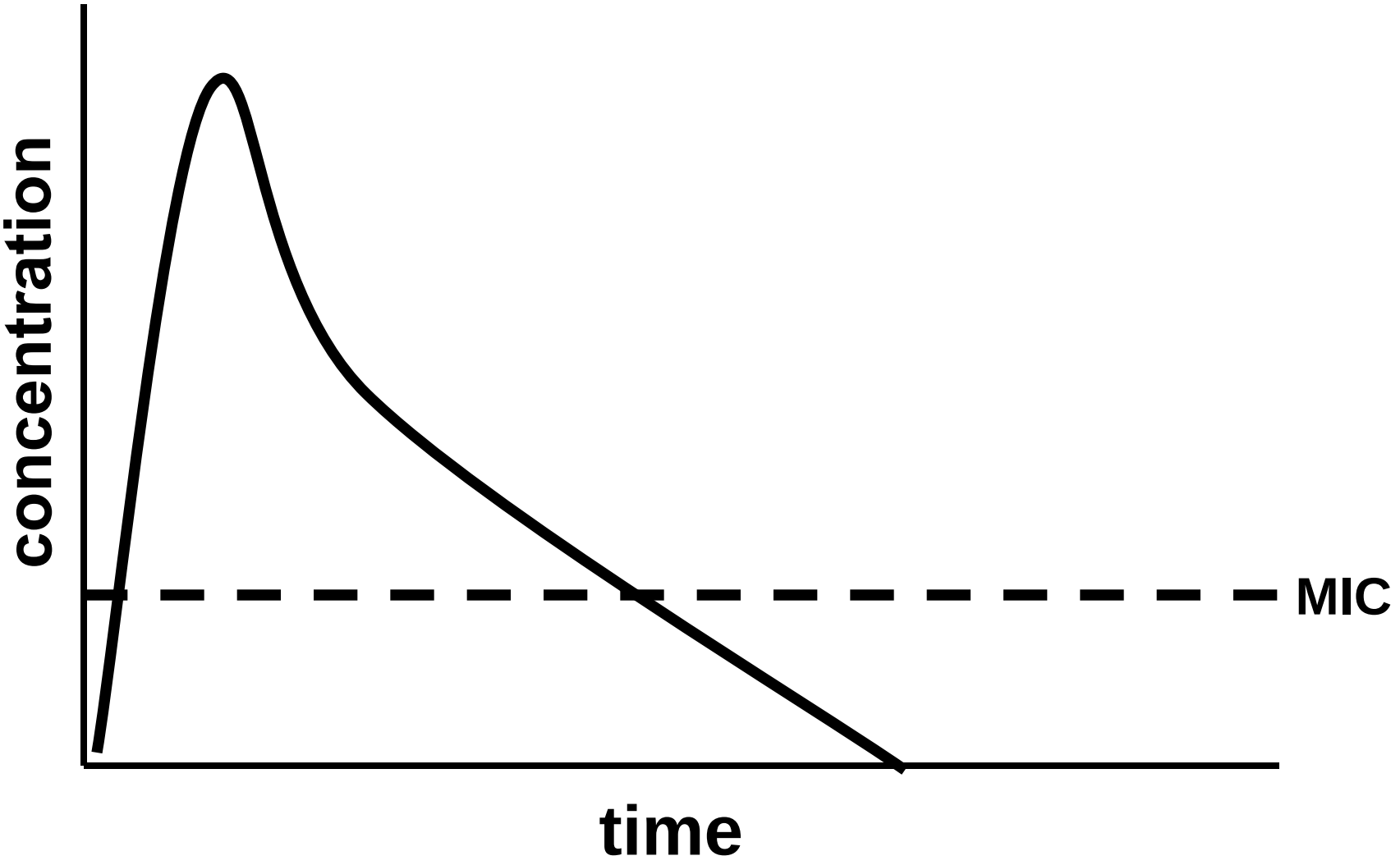

Department of Clinical Pharmacology

"Linking University Creativity to Industry Professionalism"

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