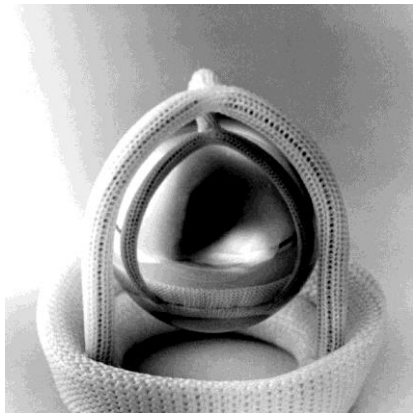
Universitätsklinikum
Hamburg-Eppendorf

Kombinationstherapien bei Fremdmaterial-assoziierten Infektionen

Prof. Dr. med. Holger Rohde
Institut für Medizinische Mikrobiologie, Virologie und Hygiene
UK Hamburg-Eppendorf

PEG Bad Honnef-Symposium
22.03.2016

(Endo-) Prothesen heute



Aortenklappen-Prothese

Impl. Defibrillator

ZVK

Künstliche Linse

Liquor-Shunt

Cochlea-Implantat

Brust-Implantat

Hüftendoprothese

Einsatz von Fremdmaterialien in Deutschland

Implantat	n/Jahr	Infektionsrate	Infektionen/Jahr
ZVK	~ 1,750,000	1 - 5 %	**17,500 - 87,000**
THE	160,000	< 2%	**~ 3500**
TKE	150,000	< 1 - 6 %	**1500 - 9000**
Herzklappen	18,000	0.8 - 5.7 %	**150 - 1000**
Schrittmacher	70,000	< 1 - 3 %	**700 - 2,100**
Linsen	~ 300,000	< 0.1 - 0.3 %	**< 300 - 900**
Liquor-Shunts	10,000	2 – 20 %	**200 – 2,000**

In Deutschland: bis zu 100.000 Infektionen jährlich

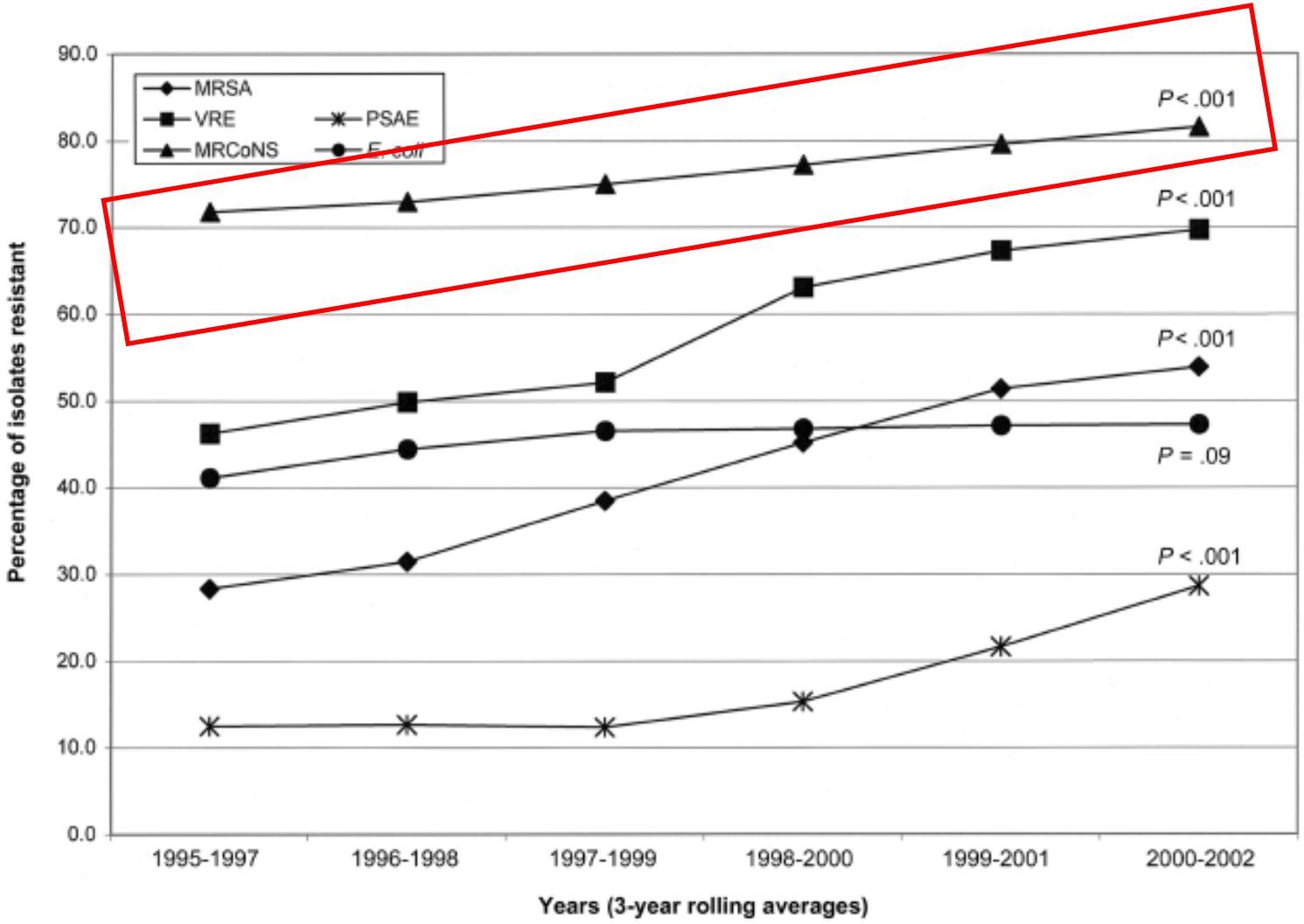
Mack, Rohde, 2006

Epidemiologie Fremdmaterial-assoziierter Infektionen

Erreger	Fremdmaterial				
	Gelenk-prothese[a]	Künstliche Herzklappe[b]	ZVK[c]	CAPD-Katheter[d]	Liquor-Shunt[e]
KNS	25 – 30	17	30-40	28	37
S. aureus	25	23	5-10	20	18
Gramnegative Stäbchen	20	3	4-10	28	4
Anaerobier	7-14	1-2	<1	n.a.	9
Candida	2	4	2-5	3	n.a.
Enterokokken	5	13	4-6	n.a.	1
Streptokokken	10-15	4	3	n.a.	4
Polymikrobiell	10-15	2	5	7	15

[a]Geipel, 2004; [b]Wang, 2007; [c]Trautner, 2004; [d]Troidle,1996; [e]Conen, 2008

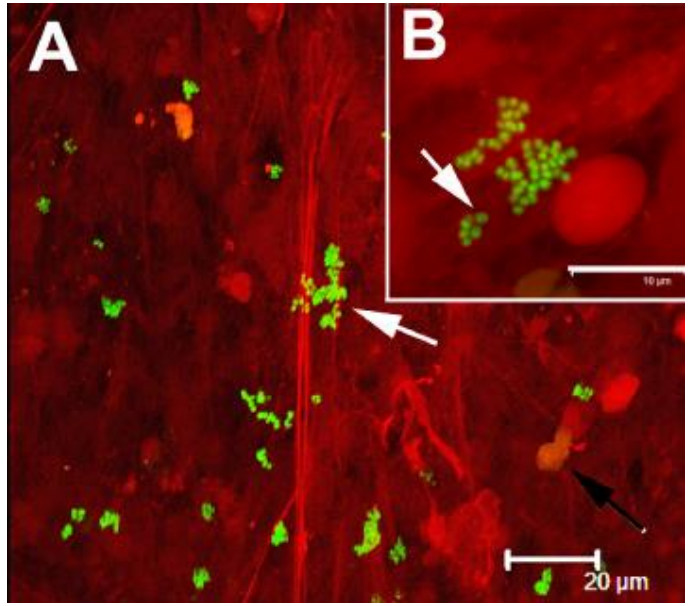
Entwicklung der Methicillinresistenz bei KNS



Wisplinghoff et al., CID 2004

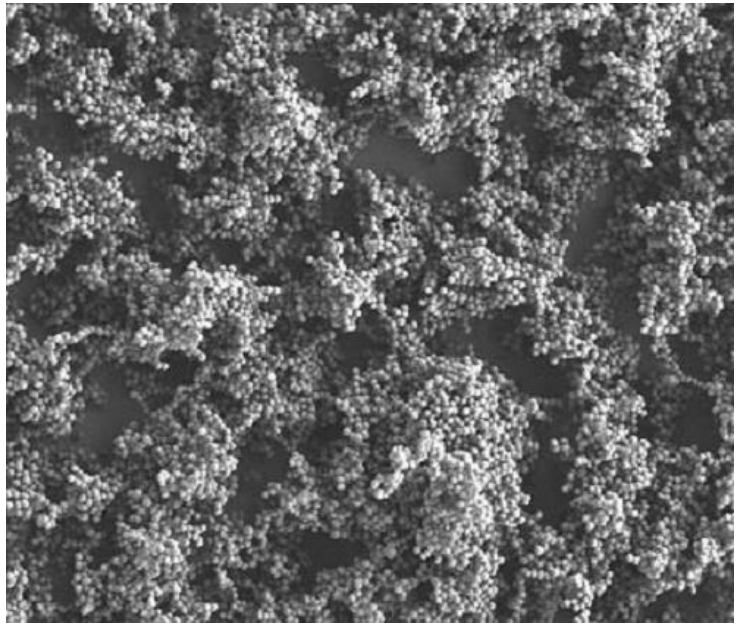
Biofilmbildung: Adhärenz und Akkumulation

Adhärenz und Mikrokolonien



Stoodley, 2008

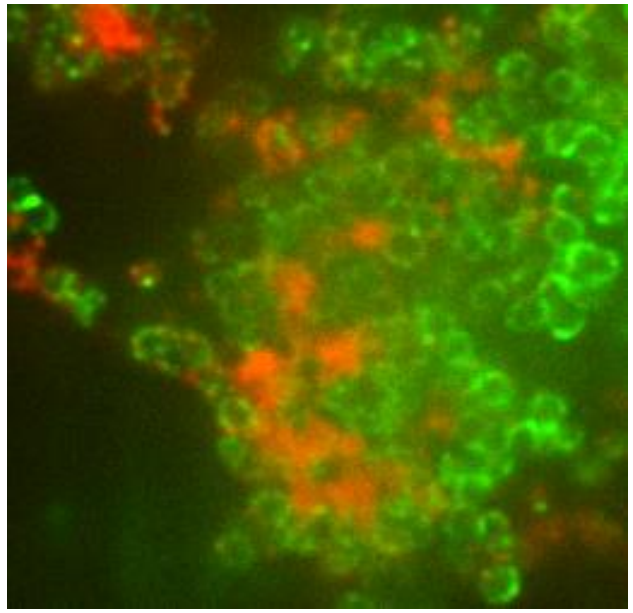
Biofilmbildung



Mack, Rohde, 2006

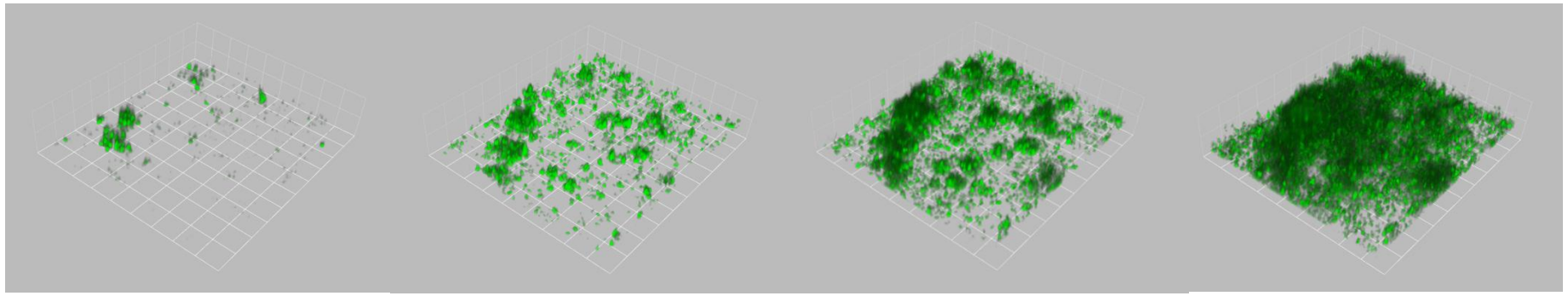
Dynamik der bakteriellen Biofilmbildung

Schommer, Rohde, unpublished.



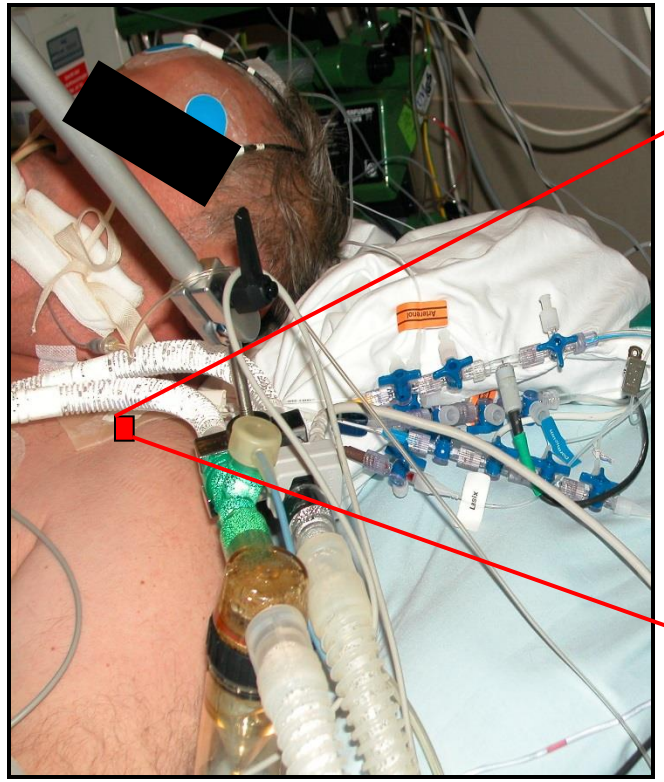
Ein selbstproduzierter Klebstoff verbindet Bakterien im Biofilm.

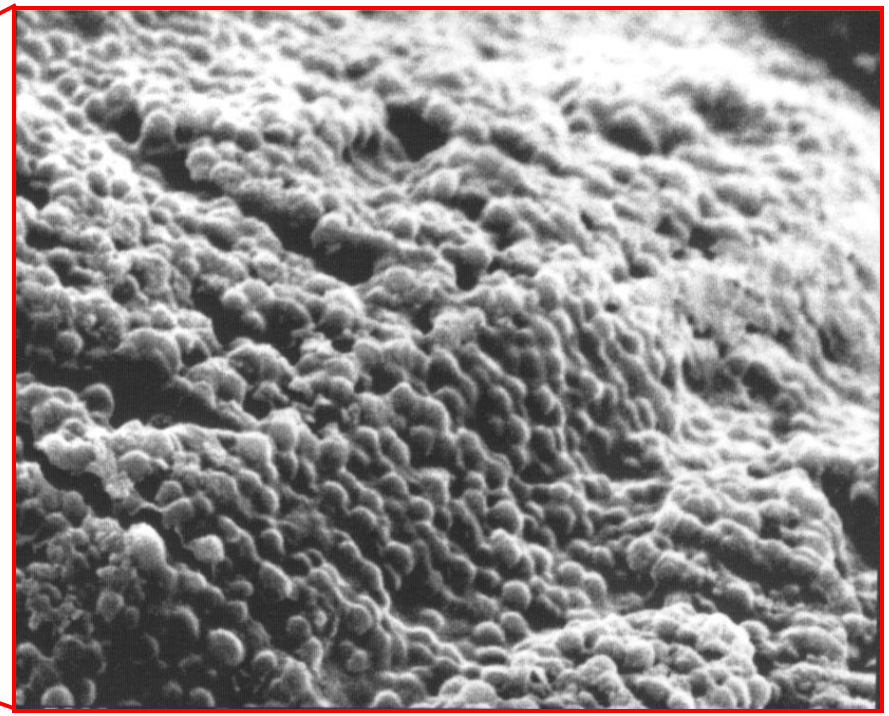
Dynamik bakterieller Biofilmbildung – das “race to the surface”



2h **4h** **6h** **10h**

Pathogenese von Fremdmaterial-assoziierten Infektionen





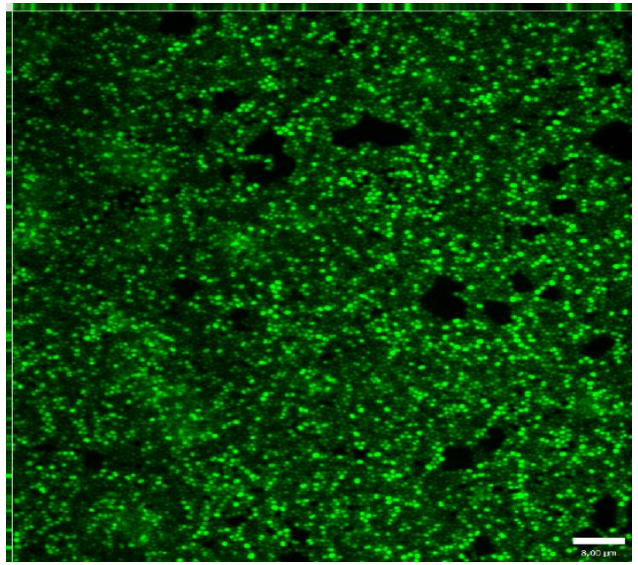
Persistierende Infektionen

Versagen von antibiotischen Therapien

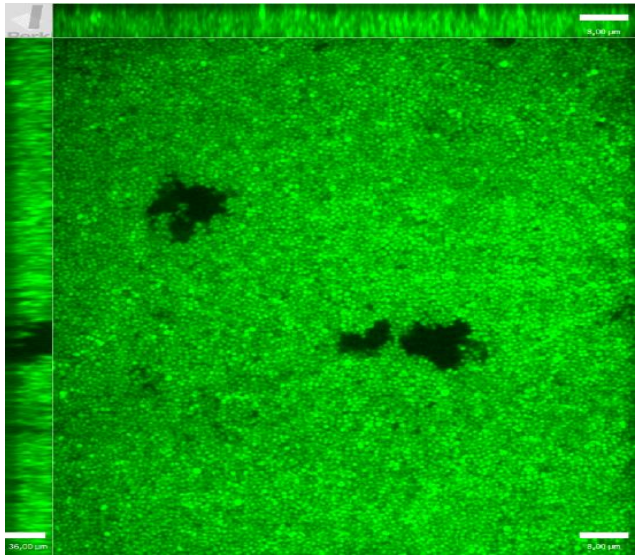
Wechselwirkung von Antibiotikum und bakteriellen Biofilmen: Biofilminduktion

S. epidermidis

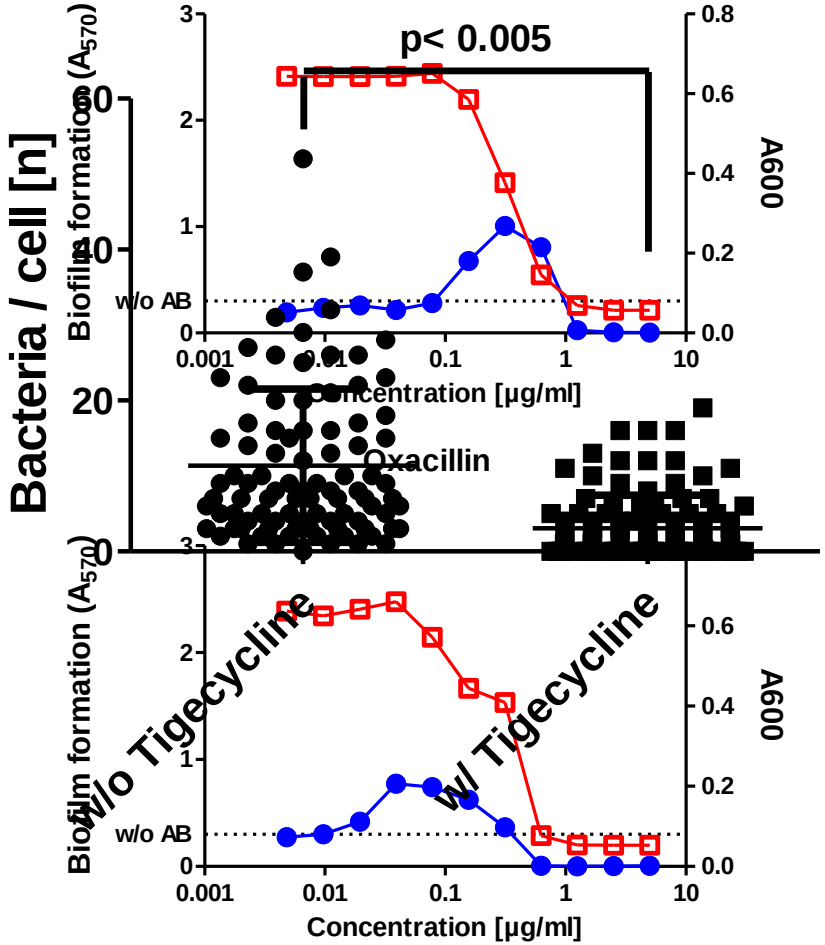
TSB



TSB + Tigecyclin



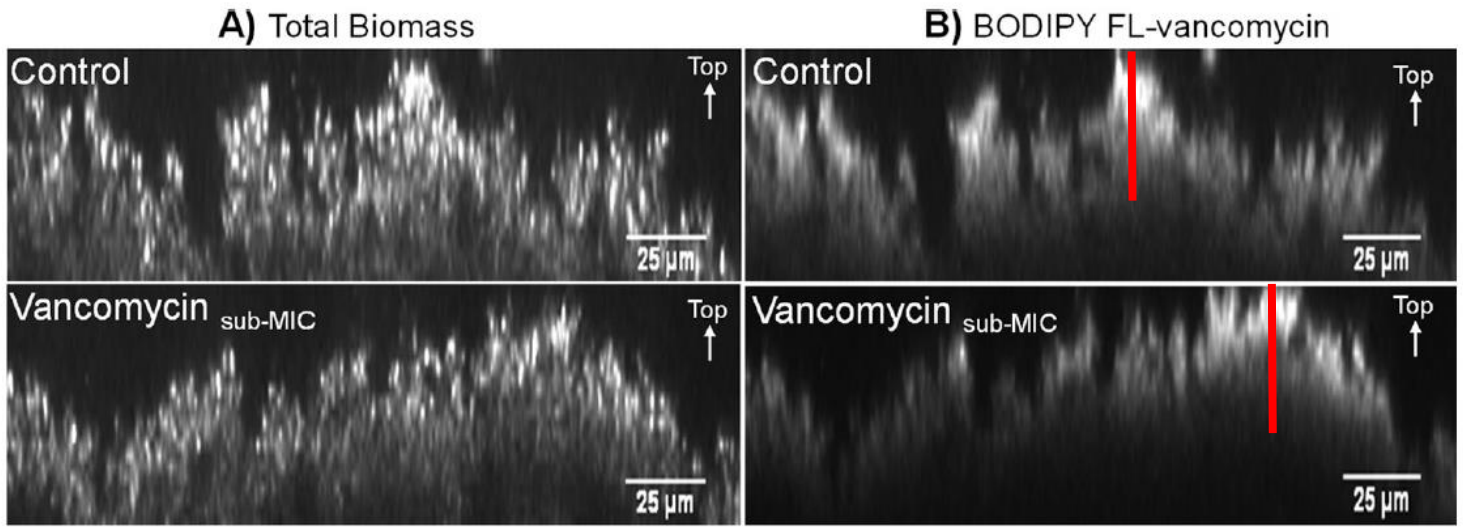
AB-induzierte Biofilmbildung interferiert mit Phagozytose



Rohde et al., unpublished

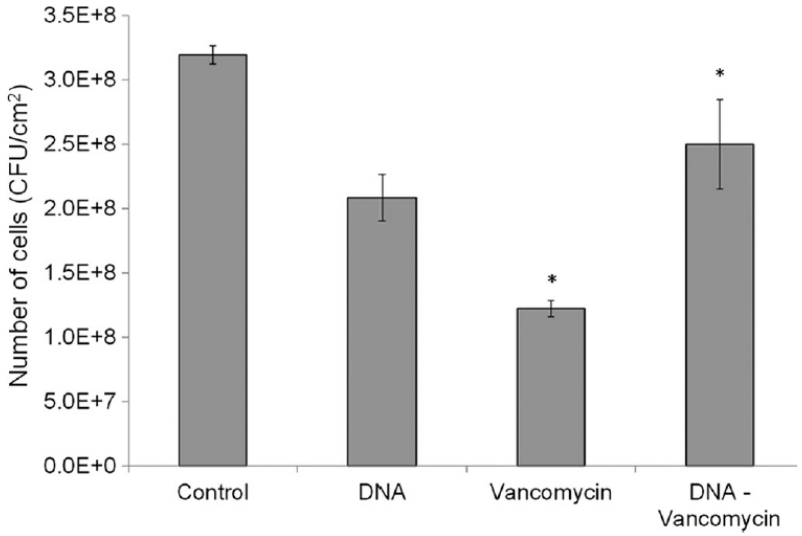
Komponenten der Biofilmmatrix wechselwirken mit Antibiotika

Sub-inhibitorische Vancomycinkonzentrationen induzieren eine Diffusionsstörung



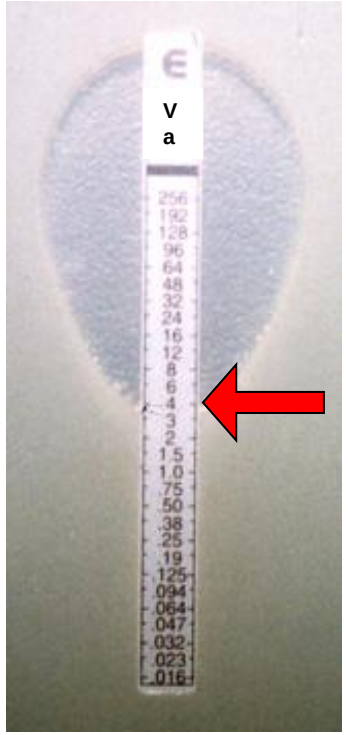
Doroshenko et al., 2014

eDNA bindet Vancomycin



Biofilmbildung als Ursache phänotypischer Resistenz

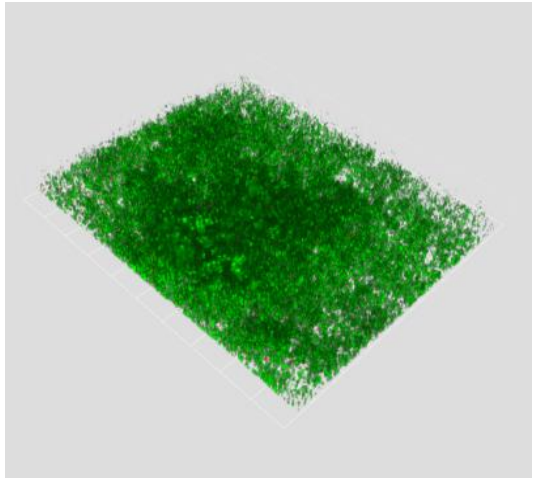
MHK unter Standardbedingungen



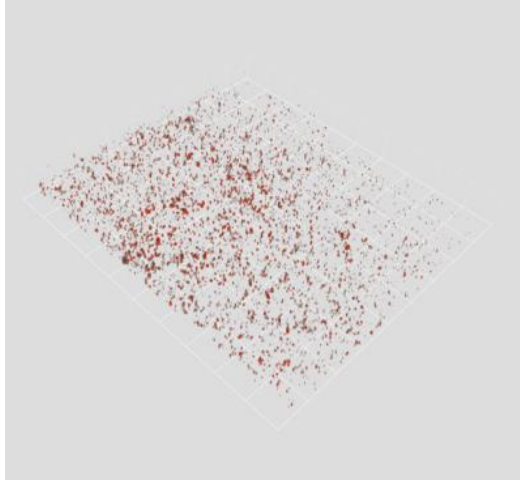
Abtötung von Biofilm-bildenden Bakterien

Vancomycin: 64 µg/ml

***S. epidermidis* (lebend)**



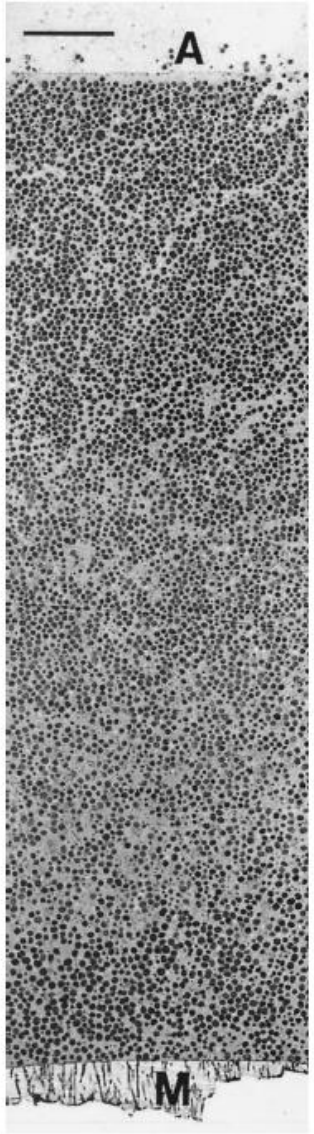
***S. epidermidis* (tot)**



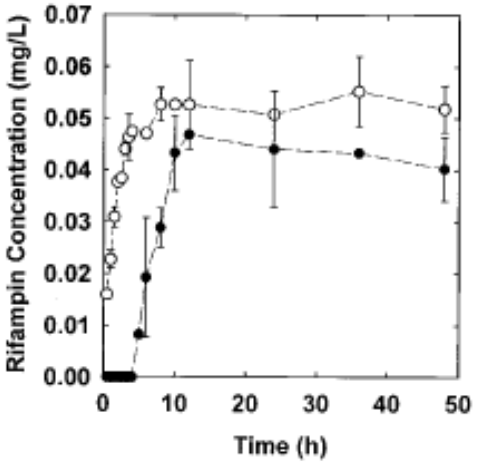
Grün: Lebend-Farbstoff

Rot: Tot-Farbstoff

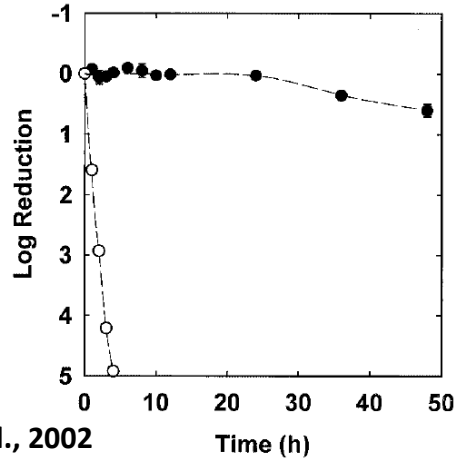
Stellt ein bakterieller Biofilm eine Diffusionsbarriere dar?



Diffusion durch den Biofilm

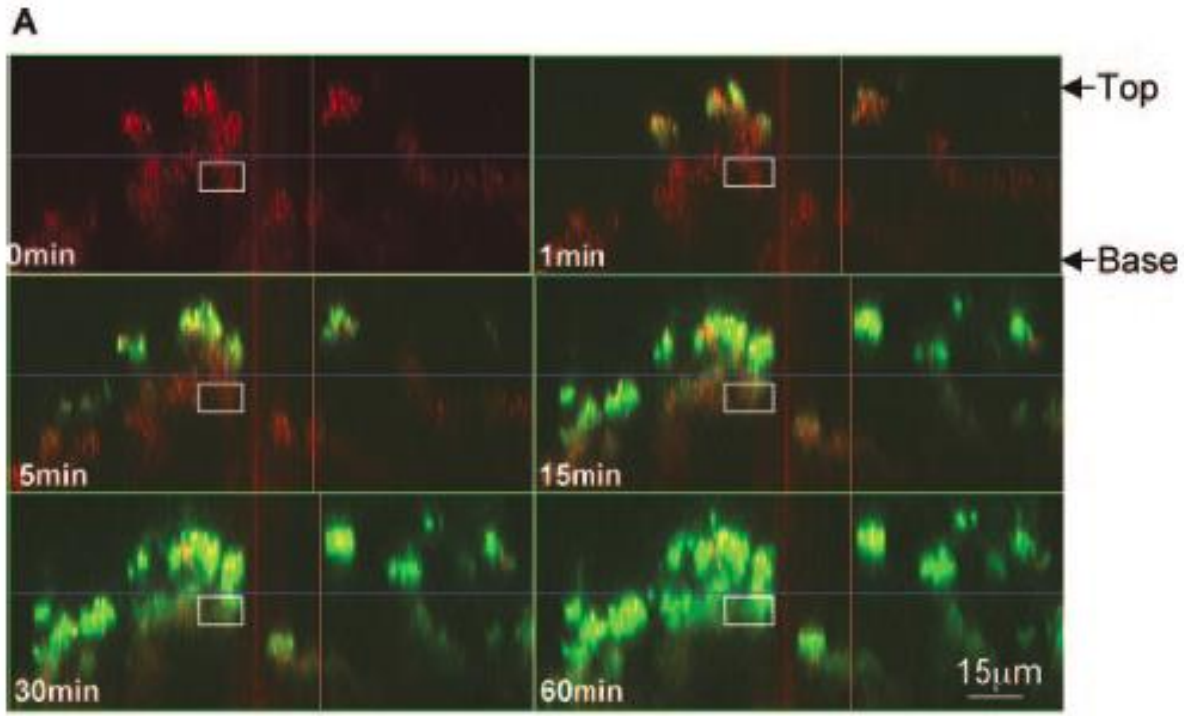


Rifampicinempfindlichkeit



Zheng et al., 2002

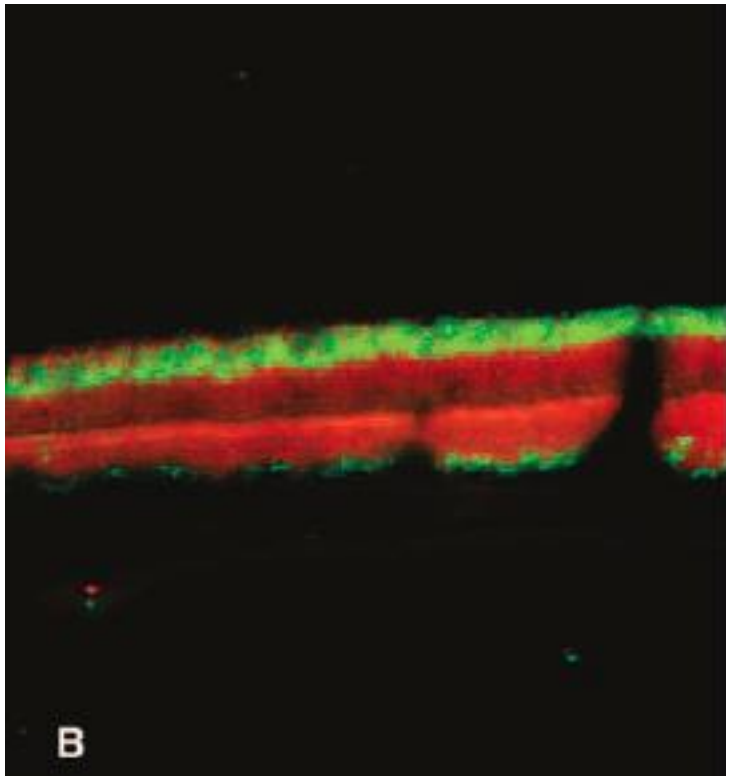
Vancomycindiffusion durch den Biofilm



Jefferson et al., 2005

Physiologische Heterogenität in Biofilmen

DNA Replikation im Biofilm

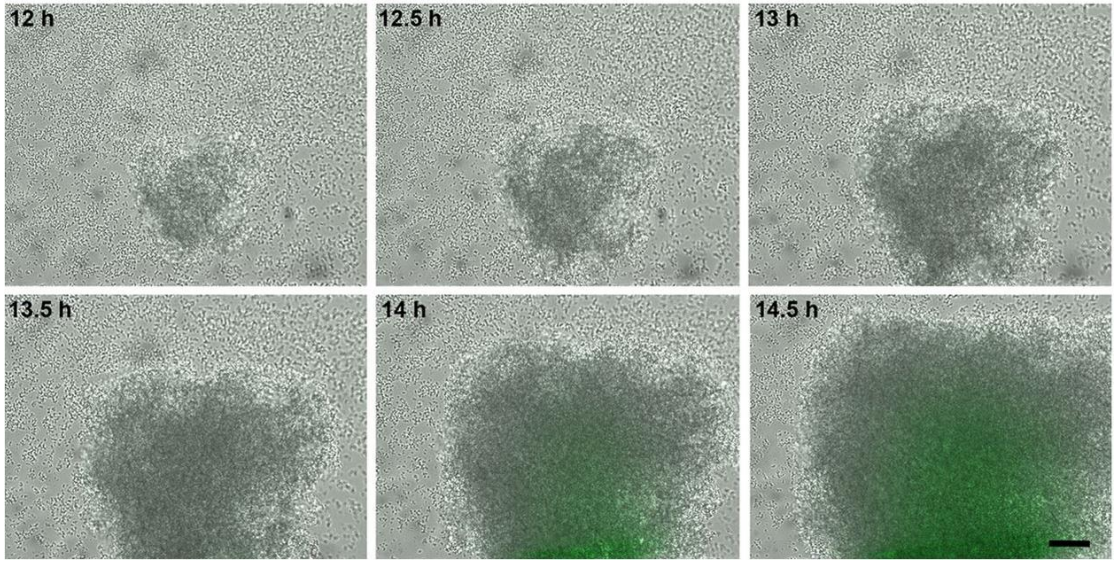


Aktiv

Inaktiv

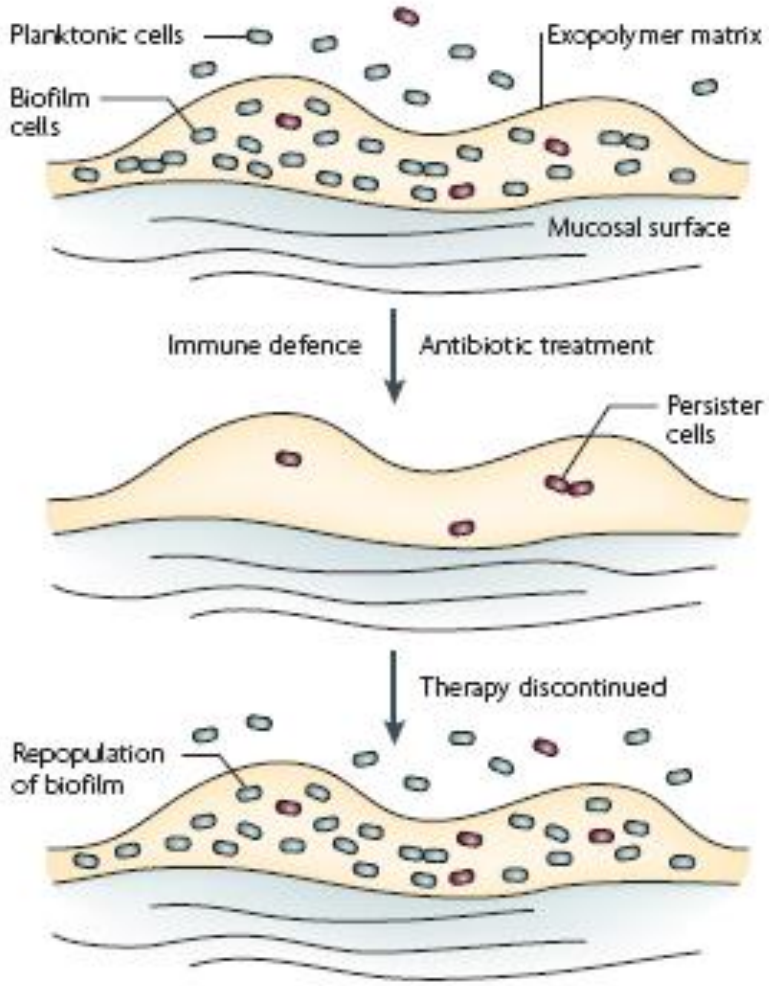
Rani et al., 2007

Differentielle Genexpression in *S. aureus* Biofilmen



Mooremeier et al., 2013

Resistenz im Biofilm: die mögliche Bedeutung von Persister-Zellen



Antibiotika töten Zellen im Biofilm

Einige Zellen überleben (=Persister); geschützt durch die Exomatrix widerstehen sie dem Immunsystem

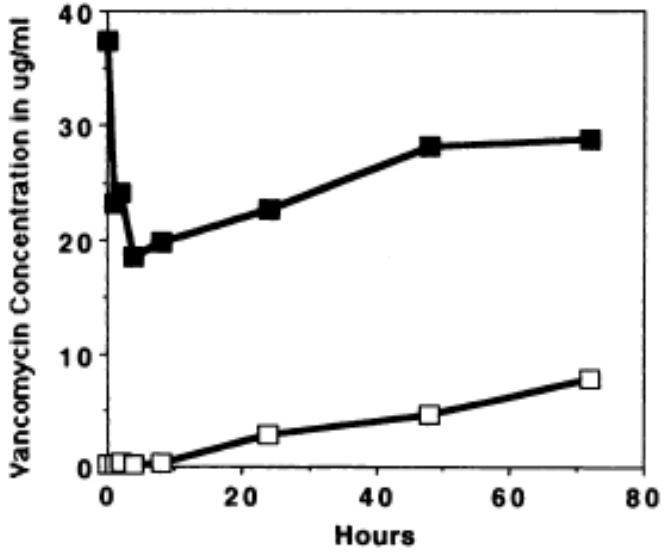
Persister sind Ausgangspunkt für Rekurrenz / Persistenz

Lewis, Nat. Rev. Micro. 2007

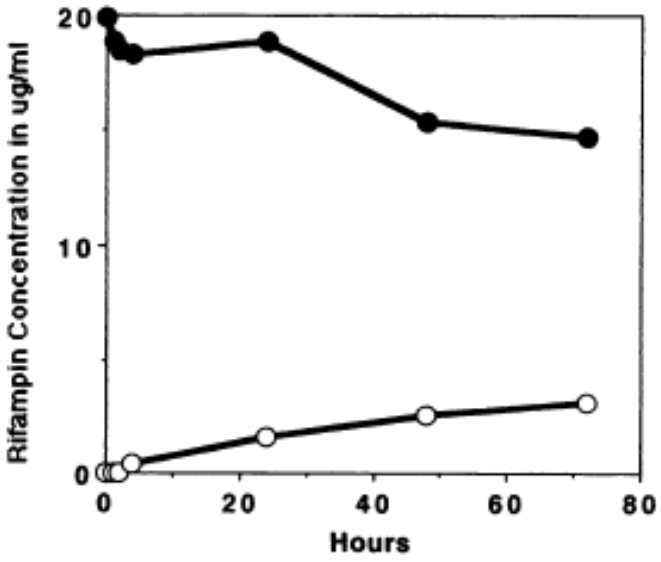
Ist die Kombination von Antibiotika ein geeignete Strategie, um Erreger im Biofilm zu bekämpfen?

Die Kombination von Vancomycin und Rifampicin moduliert die *S. aureus* Biofilmstruktur

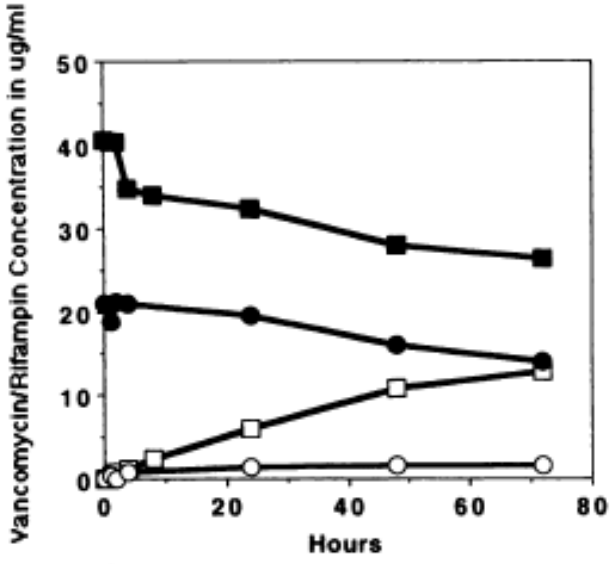
Vancomycin



Rifampicin

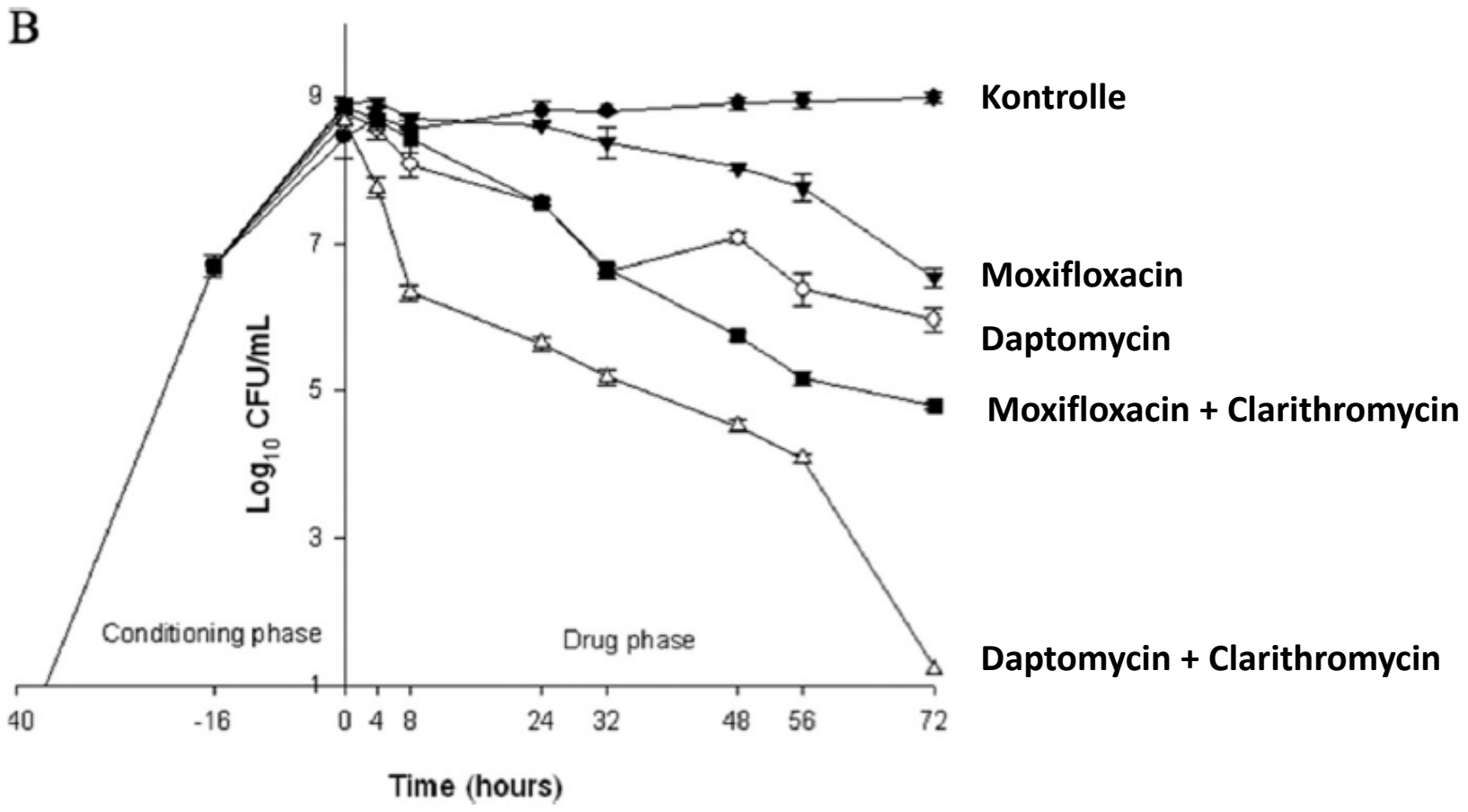


Vancomycin + Rifampicin



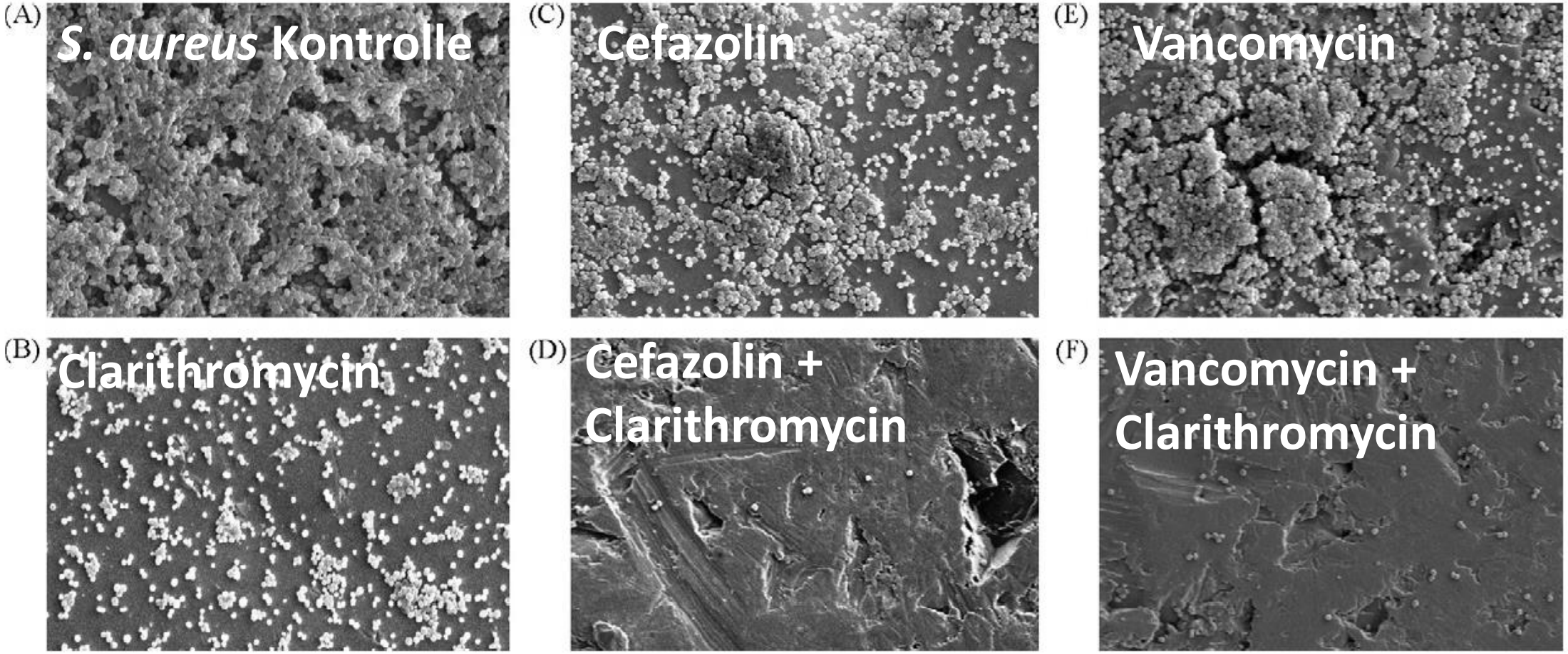
Dunne et al., 1993

Kombination von Antibiotika haben mögliche synergistische Effekte auf biofilmbildende *S. aureus*



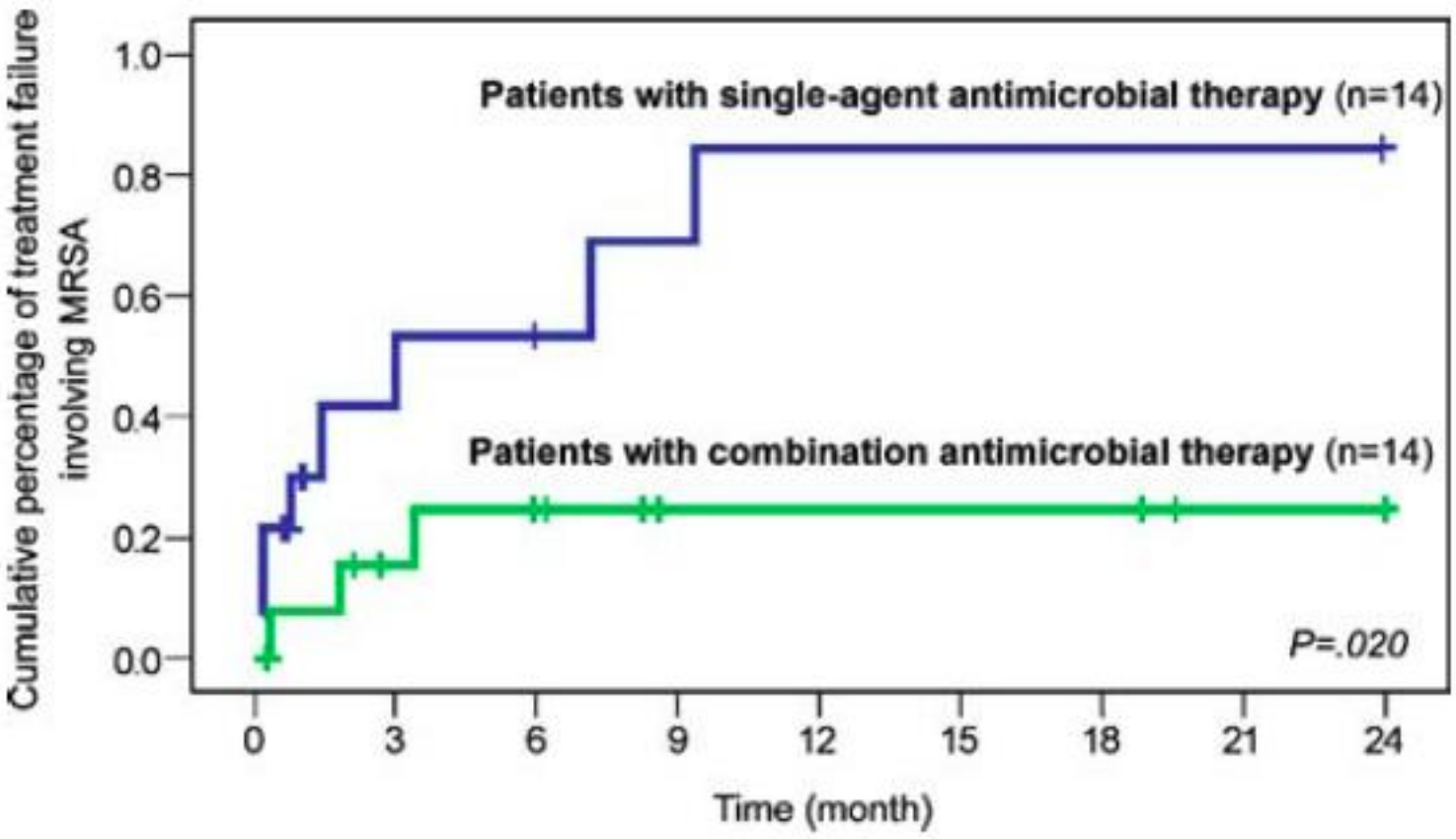
Parra-Ruiz et al., 2010

Kombination von Antibiotika haben mögliche synergistische Effekte auf biofilmbildende Bakterien



Fujimura et al., 2008

Kombination von Antibiotika zur Behandlung von PJI: klinische Evidenz



Ferry et al., 2010

Kombination von Antibiotika zur Therapie von *S. aureus* Biofilminfektionen: rationale Wahl der Partner

“Rifampin was a constituent of all the combinations active against *S. epidermidis* and MRSA and should be part of any antibiotic therapy directed against biofilms due to these organisms.”

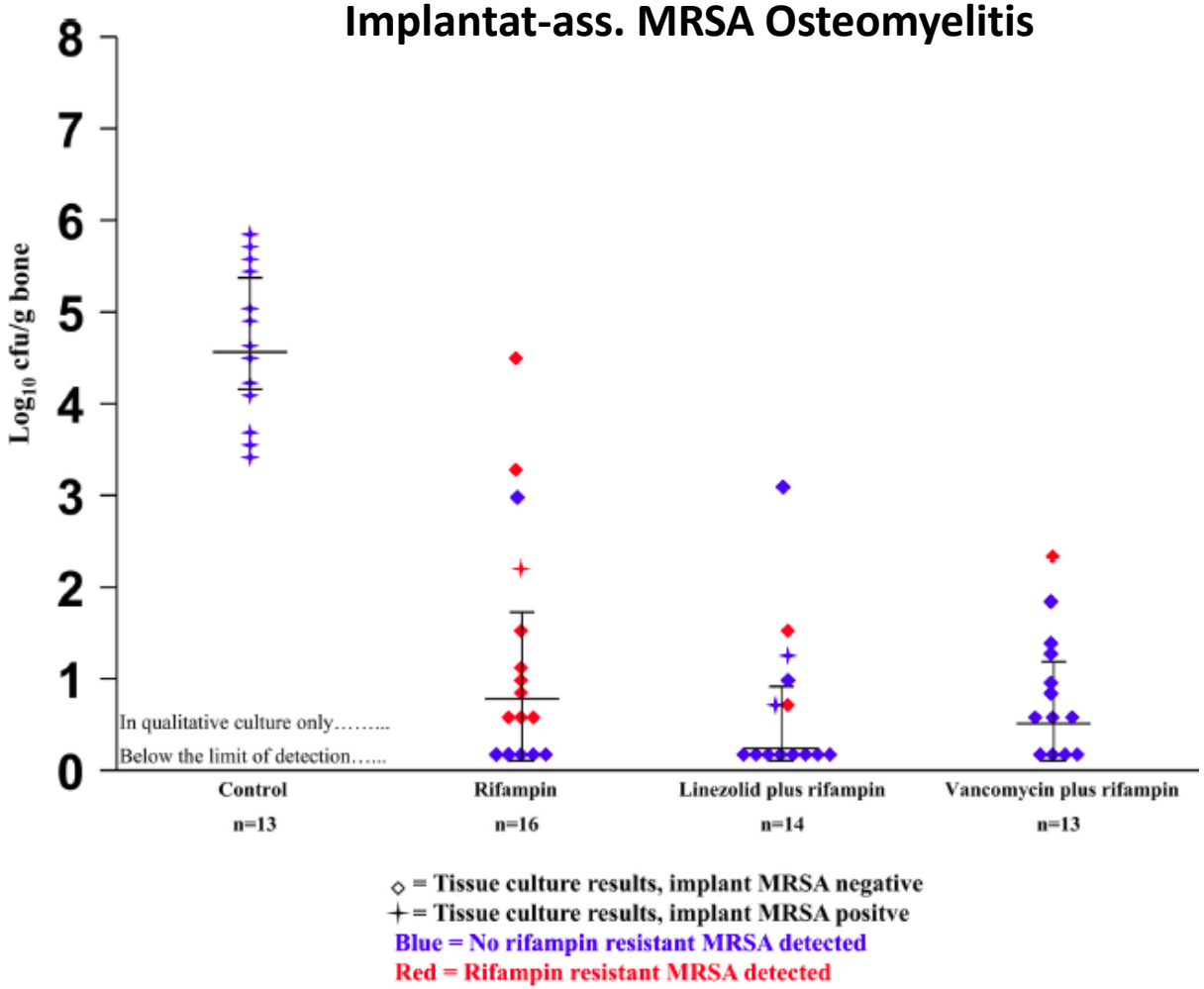
F	CFZ, CIP	CFZ, FA	CFZ, GEN, AZM	CFZ, GEN, CIP	CFZ, GEN, FA	CFZ, AZM, CIP	CFZ, AZM, FA	CFZ, CIP, FA	OXA, GEN	OXA, AZM	OXA, CIP	OXA, FA
	11 (0)	11 (4)	11 (1)	11 (0)	11 (7)	11 (0)	11 (10)	11 (10)	11 (6)	11 (0)	11 (0)	11 (6)
	2 (0)	*12 (7)*	*7 (1)*	*9 (1)*	*11 (8)*	*3 (1)*	*11 (6)*	*12 (8)*	*7 (3)*	*1 (0)*	*2 (1)*	*11 (7)*
	10 (1)	**17 (8)**	**12 (0)**	**12 (3)**	**17 (10)**	**14 (2)**	**17 (11)**	**17 (8)**	**3 (1)**	**5 (0)**	**1 (0)**	**14 (10)**
G	OXA, GEN, AZM	OXA, GEN, CIP	OXA, GEN, FA	OXA, AZM, CIP	OXA, AZM, FA	OXA, CIP, FA	VAN, GEN	VAN, AZM	VAN, CIP	VAN, FA	VAN, GEN, AZM	VAN, GEN, CIP
	10 (0)	11 (0)	11 (11)	11 (0)	11 (11)	11 (8)	11 (5)	11 (2)	11 (1)	11 (10)	11 (5)	11 (1)
	5 (2)	*8 (2)*	*10 (8)*	*3 (1)*	*12 (9)*	*12 (8)*	*11 (6)*	*11 (5)*	*12 (5)*	*12 (10)*	*11 (3)*	*12 (2)*
	6 (2)	**5 (0)**	**14 (14)**	**4 (2)**	**14 (12)**	**14 (9)**	**17 (5)**	**17 (6)**	**17 (8)**	**16 (13)**	**16 (3)**	**17 (7)**
H	VAN, GEN, FA	VAN, AZM, CIP	VAN, AZM, FA	VAN, CIP, FA	GEN, AZM	GEN, CIP	GEN, FA	AZM, CIP	AZM, FA	AZM, CIP, FA	Growth control	Sterility control
	10 (9)	11 (1)	11 (10)	11 (8)	11 (1)	11 (3)	11 (10)	11 (0)	11 (9)	11 (10)		
	11 (8)	*11 (2)*	*12 (10)*	*12 (8)*	*5 (1)*	*7 (1)*	*11 (10)*	*3 (1)*	*11 (8)*	*11 (9)*		
	17 (13)	**17 (5)**	**17 (14)**	**17 (12)**	**6 (1)**	**4 (0)**	**13 (12)**	**3 (5)**	**13 (13)**	**14 (13)**		

[a] MSSA, $n = 11$; MRSA, $n = 12$; *S. epidermidis*, $n = 17$. Results in italics are for MRSA; those in boldface are for *S. epidermidis*; those in regular font are for MSSA. See the footnote to Table 2 for drug abbreviations.

Saginur et al., 2006

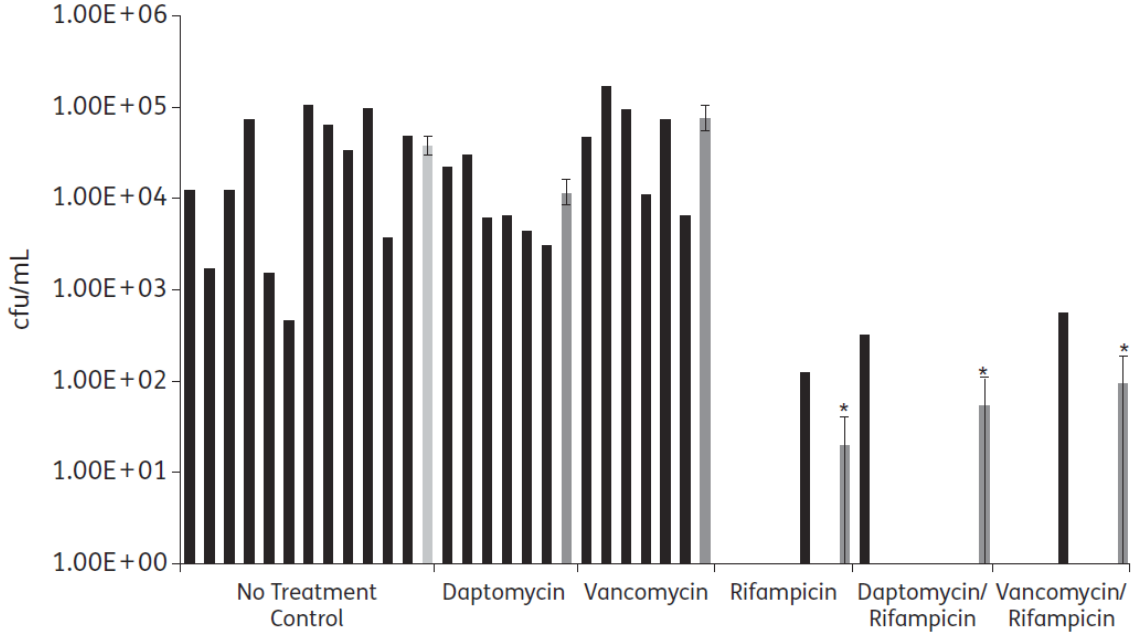
Kombinationstherapie von Biofilm-assoziierten Infektionen: Effektivität in Tiermodellen

Implantat-ass. MRSA Osteomyelitis



Vergidis et al., 2011

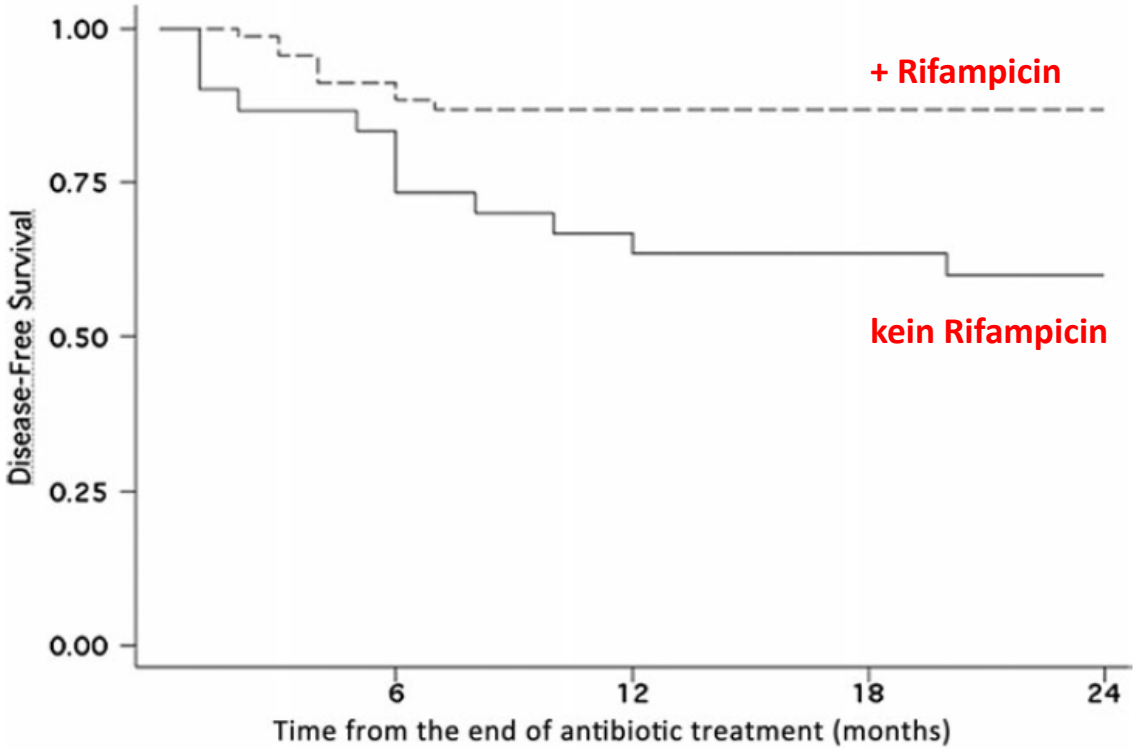
Fremdmaterial-ass. *S. epidermidis* Infektion



Olson et al., 2010

Rifampicin-Kombinationen erhöhen die Chancen einer erfolgreichen *S. aureus* PJI Behandlung

***S. aureus* PJI: Behandlungsversagen**



Aboltins et al., CMI 2007

Laffer et al., CMI 2006

Rebse et al. J Bone Joint Surg 2005

Berdal et al., CMI 2005

Zimmerli et al., JAMA 1998

Widmer et al., CID 1992

Senneville et al., 2011

Rifampicin: womit kombinieren?

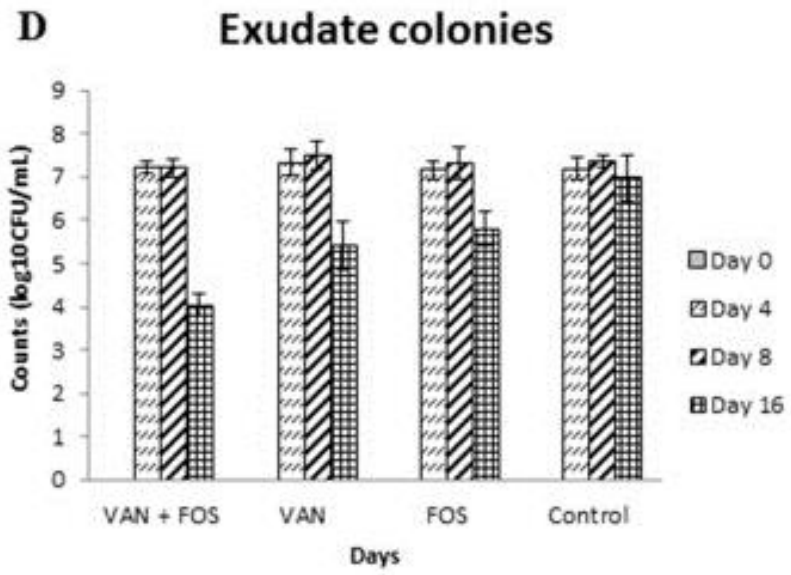
- Cotrimoxazol
- Tigecyclin
- Daptomycin
- Linezolid
- Chinolone
- ….

Flucloxacillin i.v. oder
Vancomycin i.v. oder
Daptomycin i.v.

Clinical Practice Guidelines by the Infectious Diseases Society of America, Osmon et al., CID 2013
ESCMID guideline for the diagnosis and treatment of biofilm infections 2014, Hoiby et al., CMI 2014

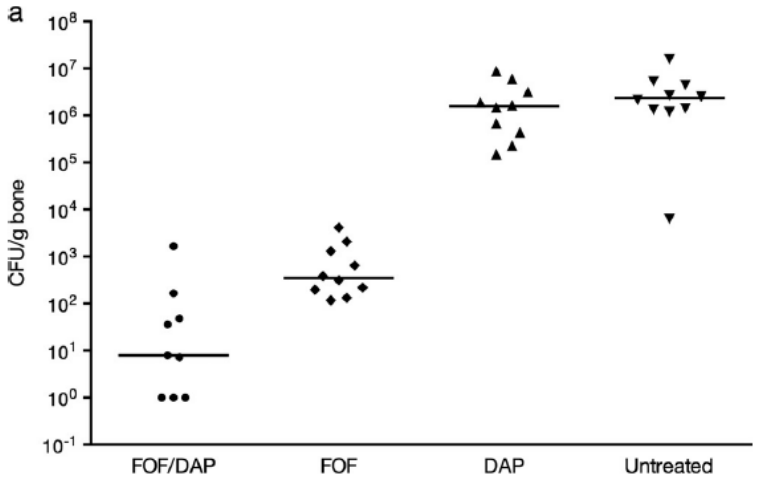
Kombinationenstherapie ein Staphylokokken Biofilminfektion: Alternativen zum Rifampicin?

Fosfomycin
Tissue cage Modell (Ratte)



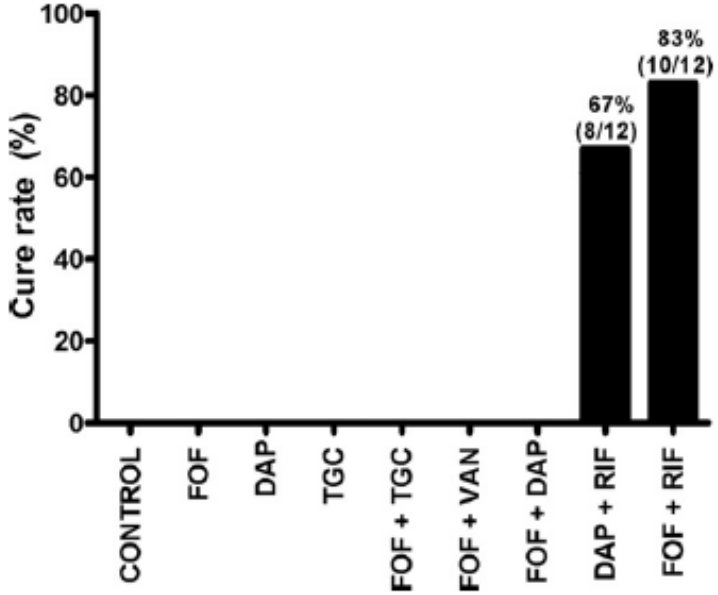
Shi et al., 2014

Fosfomycin
Implant-ass. Osteomyelitis (Ratte)



Lingscheid et al., 2015

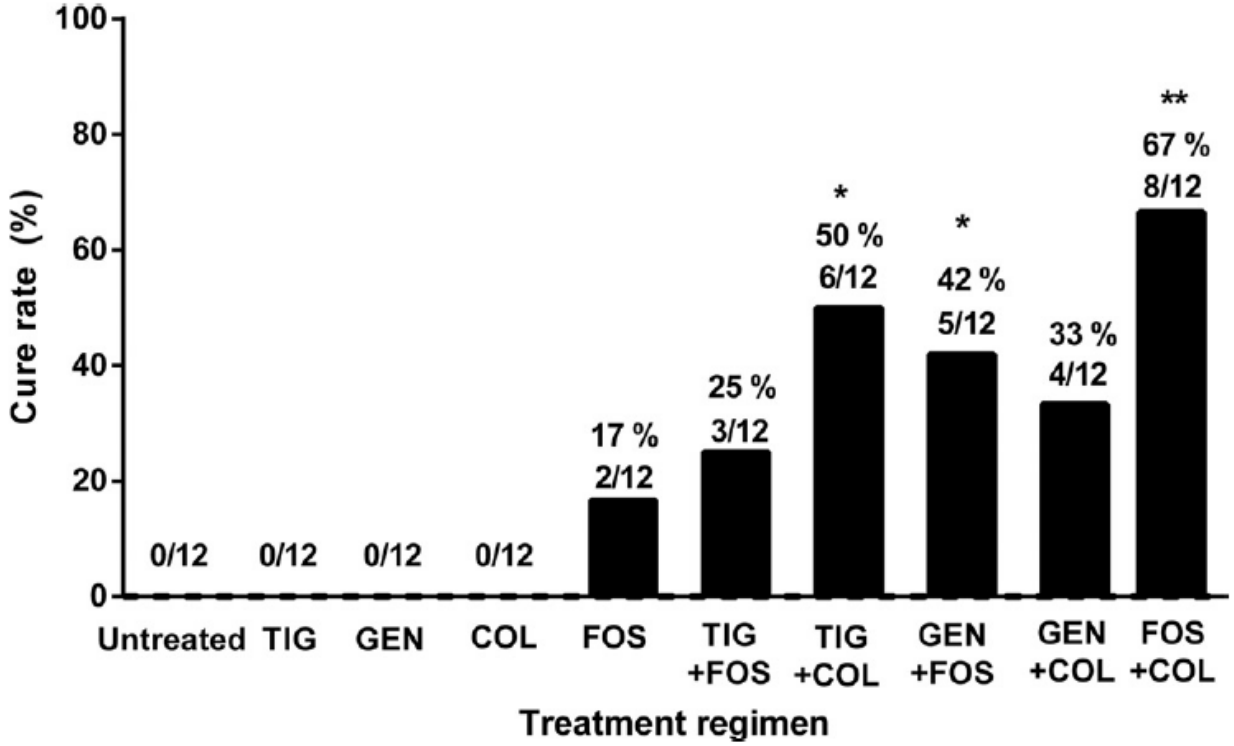
Fosfomycin
Tissue cage Modell (Meerschweinchen)



Mihailescu et al., 2014

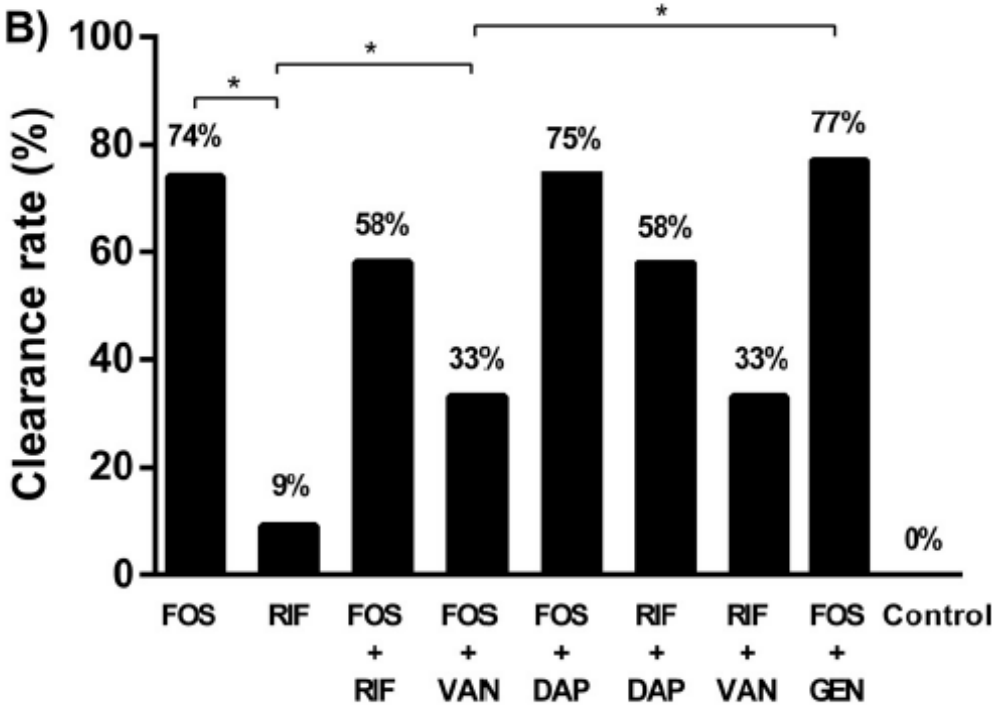
Müssen alle Biofilm-assoziierten Implantat-Infektionen mit Kombinationstherapien behandelt werden?

E. coli
Tissue cage Modell (Meerschweinchen)



Corvec et al., 2013

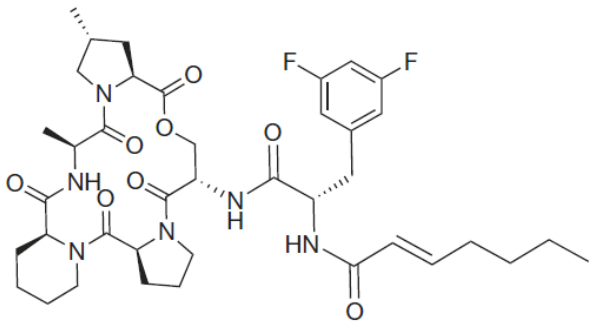
E. faecalis
Tissue cage Model (Meerschweinchen)



Oliva et al., 2014

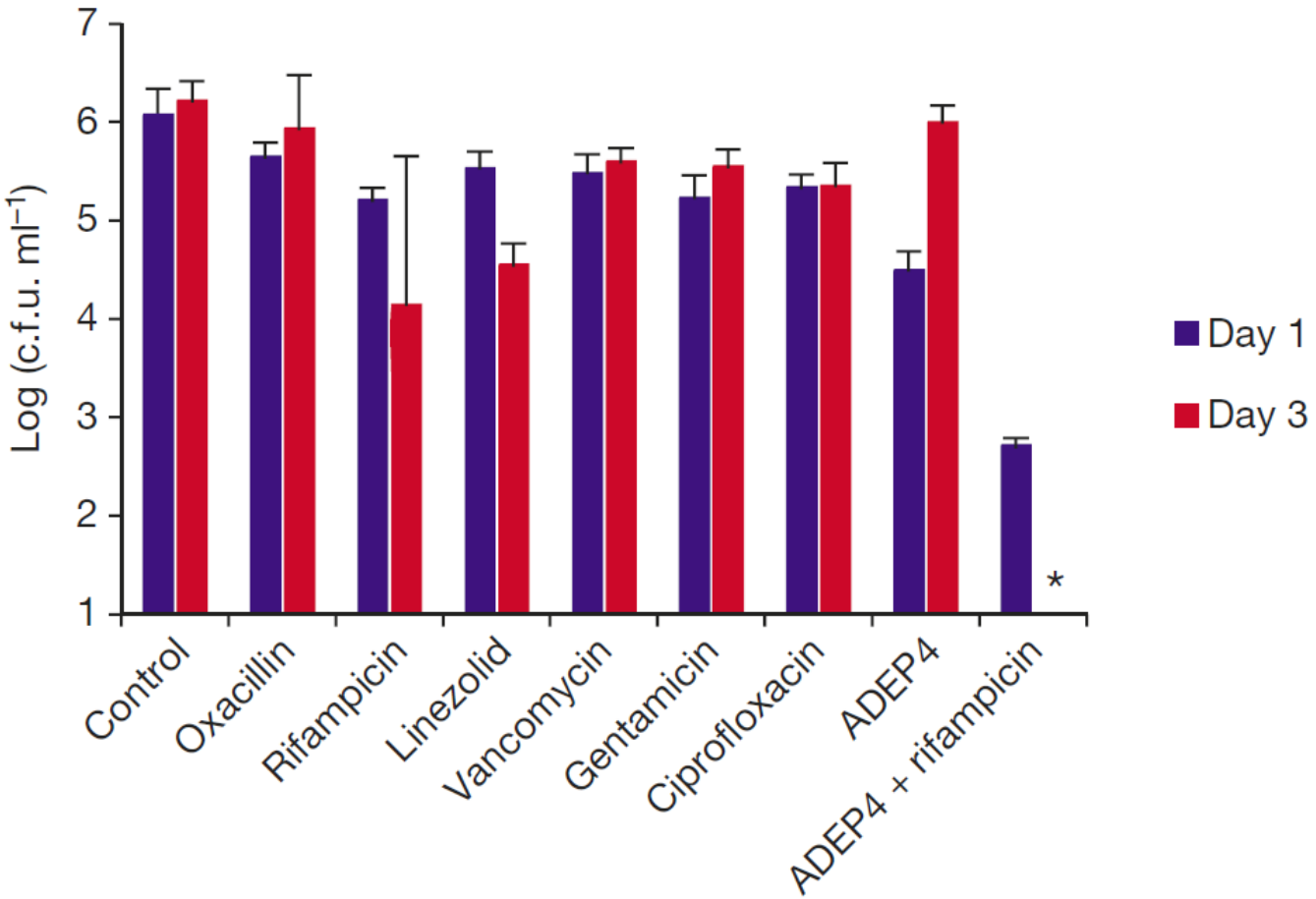
Neue Ansätze in der Therapie Biofilm-assoziierter Infektionen

Acyldepsipeptide 4

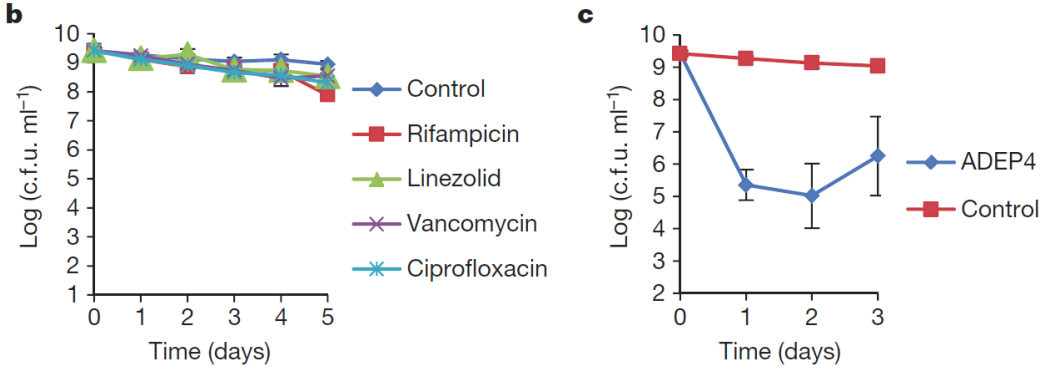


ADEP4

ADEP4 – Rifampicin eliminiert etablierte *S. aureus* Biofilme



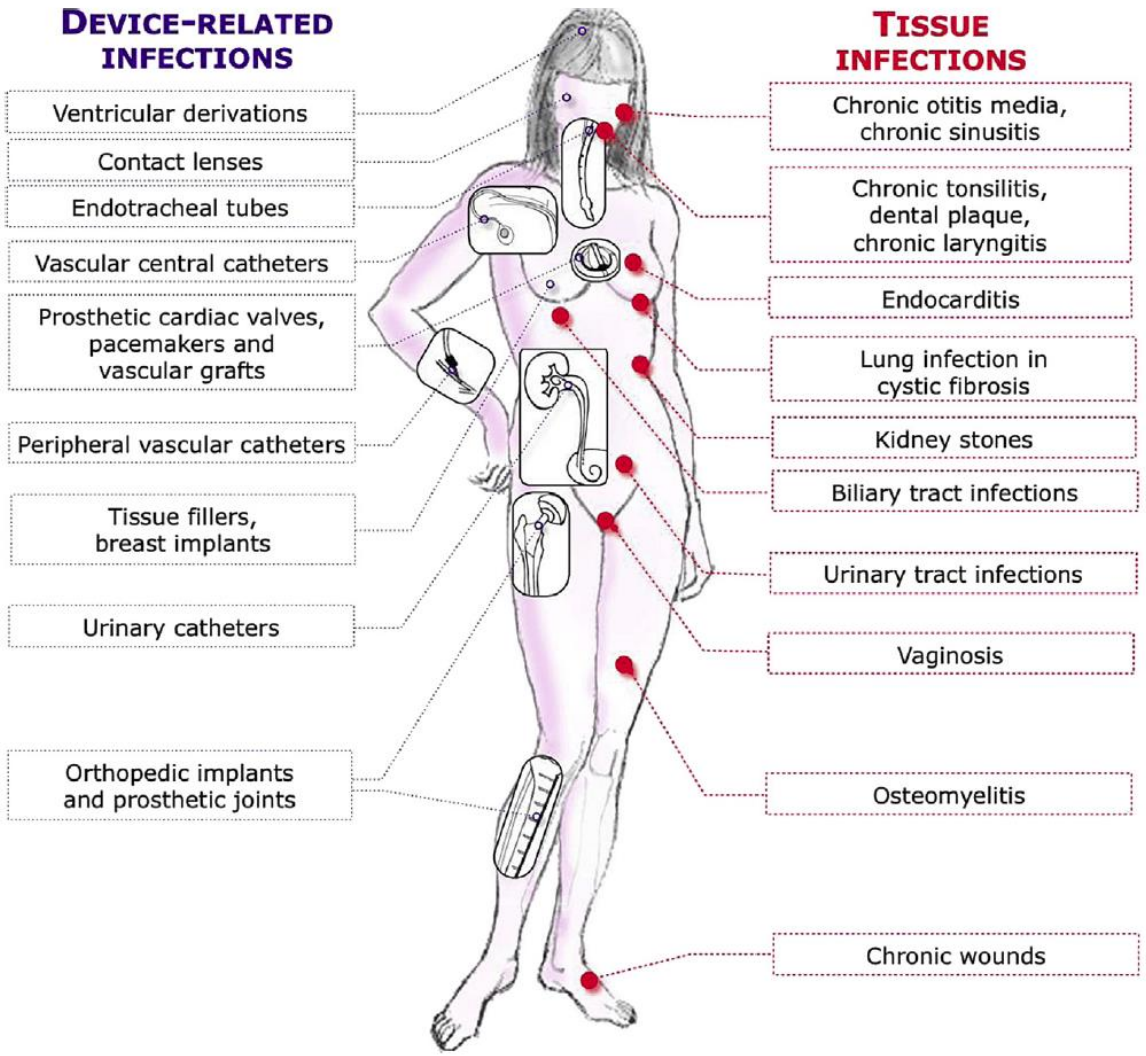
ADEP4 ist aktiv gegen *S. aureus* in der stationären Phase



Conlon et al., 2013

Zusammenfassung

- Der Biofilmphänotyp beeinflusst die Empfindlichkeit von bakteriellen Erregern.
- Experimentelle und klinische Evidenz unterstützen das Konzept der Kombinationstherapie bei **Endoprothesen-Infektionen durch Staphylokokken.**
- Rifampicin ist wesentliche Säule der Therapie
- Eine Bedeutung kann auf andere klinische Situationen übertagen werden.



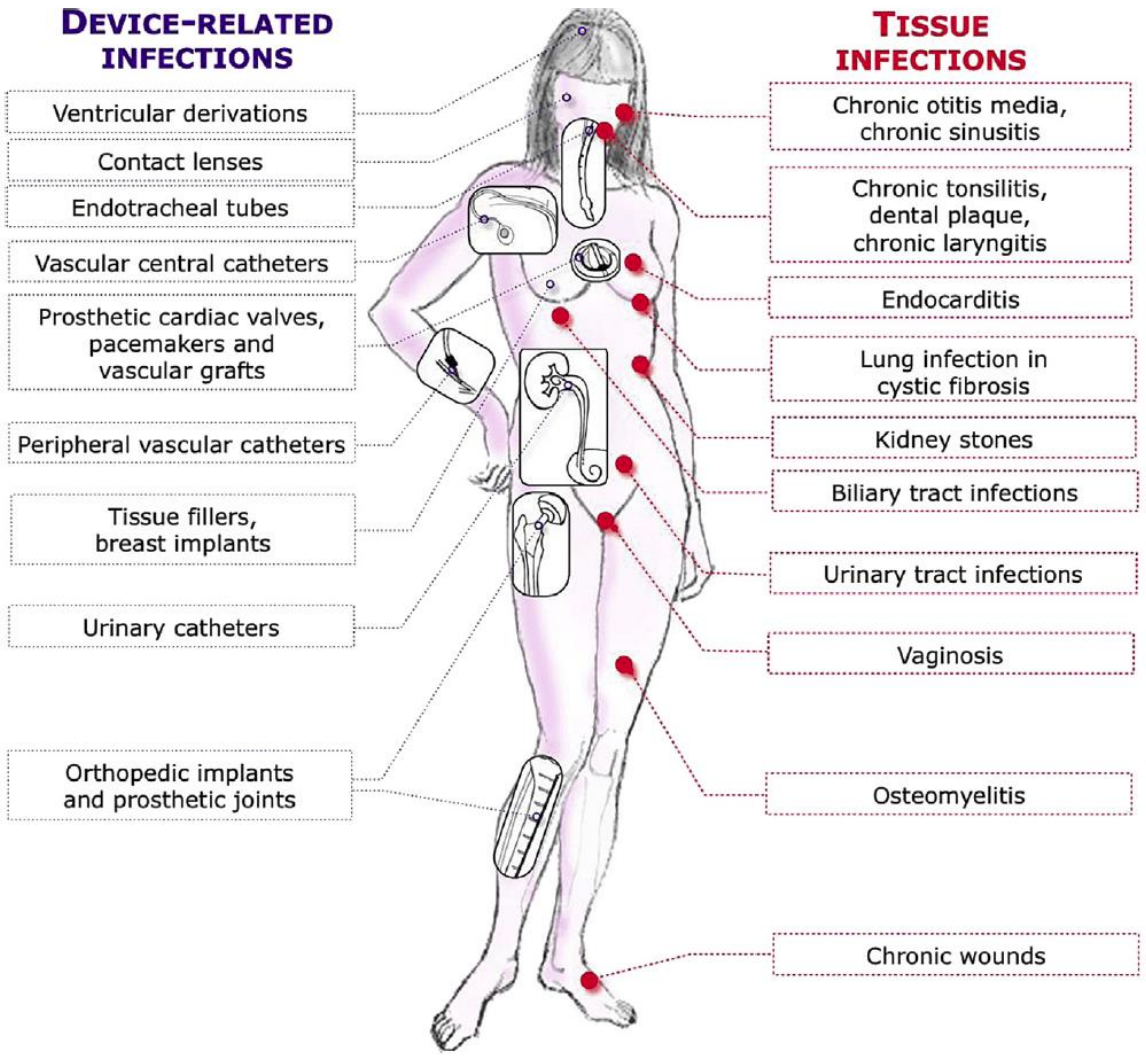
Zusammenfassung

Table I. Treatment protocol for device-associated infection, according to the pathogen and its antimicrobial susceptibility

Micro-organism	Initial treatment	Dose†	Duration	Follow-up treatment	Dose†
Staphylococcus sp. methicillin-susceptible	Cloxacillin or nafcillin‡ + rifampicin	2 g every 6 hrs IV 2 g every 6 hrs IV 450 mg every 12 hrs PO	2 weeks	Ciprofloxacin + rifampicin	750 mg every 12 hrs PO 450 mg every 12 hrs PO
Staphylococcus sp. methicillin-resistant	Vancomycin + rifampicin	1 g every 12 hrs IV 450 mg every 12 hrs PO	4 weeks	Fusidic acid or minocycline, + rifampicin	500 mg every 8 hrs PO 100 mg every 12 hrs PO 450 mg every 12 hrs PO
Streptococcus sp. (except *Streptococcus agalactiae)*	Penicillin G or ceftriaxone	5 million U every 6 hrs IV 2 g every 24 hrs IV	4 weeks	Amoxicillin	750 mg every 8 hrs PO
Enterococcus spp (and *Streptococcus agalactiae)*	Penicillin G§ + gentamicin	5 million U every 6 hrs IV 240 mg every 24 hrs IV	4 weeks	Amoxicillin	750 mg every 8 hrs PO
Enterobactenaceae (ciprofloxacin-susceptible)	Ceftriaxone	2 g every 24 hrs IV	3 to 5 days	Ciprofloxacin	750 mg every 12 hrs PO
Pseudomonas aeruginosa	Ceftazidime or cefepime, + gentamicin	2 g every 6 hrs IV 2 g every 6 hrs IV 240 mg every 24 hrs IV	4 weeks	Ciprofloxacin	750 mg every 12 hrs PO
Anaerobes	Clindamycin¶	600 mg every 6 hrs IV	4 weeks	Clindamycin¶	300 mg every 6 hrs PO
Mixed infections	Imipenem or meropenem	500 mg every 6 hrs IV 1 g every 8 hrs IV	4 weeks	According to pathogen	

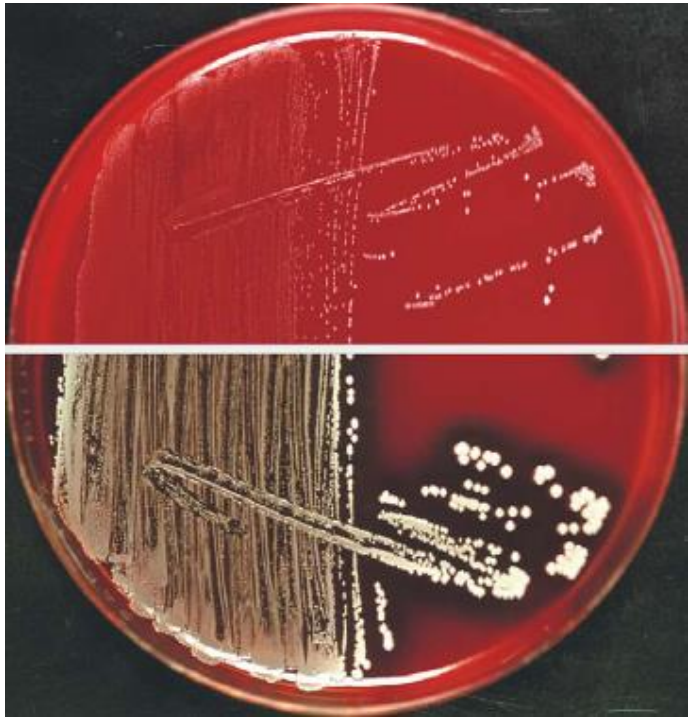
Zusammenfassung

- Der Biofilmphänotyp beeinflusst die Empfindlichkeit von bakteriellen Erregern.
- Experimentelle und klinische Evidenz unterstützen das Konzept der Kombinationstherapie bei **Endoprothesen-Infektionen durch Staphylokokken.**
- Eine Bedeutung kann auf andere klinische Situationen übertagen werden.
- Rifampicin ist wesentliche Säule der Therapie
- Nicht sicher belegt / empfohlen ist die Relevanz / Effektivität bei Infektionen durch andere Erreger (insbesondere Enterobakterien).



Small colony variants (SCV)

***S. aureus* SCV**



	Regulär	*Small colony variant*
Koloniegröße	2 mm	0,2 mm
Hämolyse	vorhanden	fehlt
Pigment	vorhanden	fehlt
Auxotrophie	keine	Hämin, Menandion
Aminoglykosid-empfindlichkeit	sensibel	resistent

Durch intrazelluläre Persistenz können SCV zum chronischen Charakter von Implantatinfektionen beitragen.