COLISTIN

MONOTHERAPIE VS KOMBINATIONSTHERAPIE

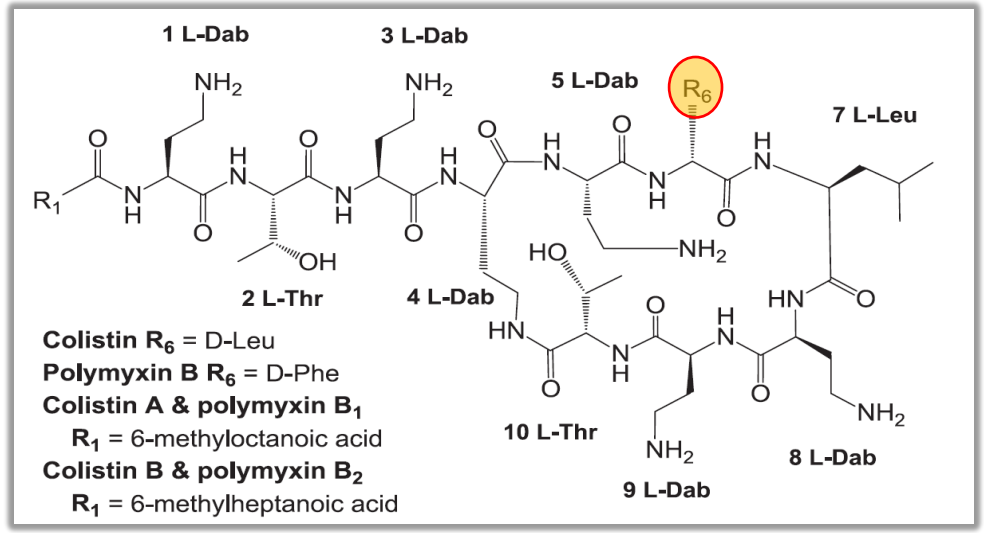
FLORIAN THALHAMMER
KLINISCHE ABTEILUNG FÜR INFEKTIONEN UND TROPENMEDIZIN
UNIVERSITÄTSKLINIK FÜR INNERE MEDIZIN – MEDIZINISCHE UNIVERSITÄT WIEN
www.antibiotika-app.eu – florian.thalhammer@meduniwien.ac.at

DIE WILL-HABEN-APP

COLISTIN – MONO ODER KOMBI

Struktur der Polymyxine

- **Polymyxine**
  - kationisch, verzweigte, zyklische Peptidantibiotika
  - Erstbeschreibung 1947
- **Colistin**
  - entspr. Polymyxin E
  - stammt von *Bacillus colistinus*
  - Lipopeptidmischung aus Colistin A & B
- **Polymyxin B1 & B2**
  - stammt von *Paenibacillus polymyxa*
  - Unterschied zu Colistin durch EINE Aminosäure (D-Leucin)



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Stock, Arzneimitteltherapie 2011 – Couet, Clin Microbiol Infect 2012 – Bergen, Diag Microbiol Infect Dis 2012

COLISTIN – MONO ODER KOMBI
Sulfat – Base – Methansulfonat

COLISTIN

- entspr.
  - Colistinsulfat
  - Colistinbase
- aktive Substanz
- tubuläre Reabsorption
- lange Halbwertszeit
- nicht-renale Elimination
- nephrotoxisch
- Bindung an α-1-saures Glykoprotein

COLISTINMETHANSULFONAT

- entspr. Colistinmethansulfonat
  - "CMS" in der Literatur
- Prodrug
  - *in vivo* Umwandlung von CMS in Colistinbase kaum vorhersagbar
- instabil
- inaktive Substanz
- kurze Halbwertszeit
- renale Elimination
- geringe Nephrotoxizität

COLISTIN – MONO ODER KOMBI
Von Milligramm und Units

- **1.000.000 I.U. Colistin**
  - **33.3 mg Colistinbase (CBA)**
  - **50.0 mg Colistinsulfat**
  - **80.0 mg Colistinmethanesulfonat (CMS)**

CMS ► COLISTIN

- **Colistinbase-Aktivität (CBA)**
  - 1 mg CBA ~ 33.250 IU
  - 5 mg/kg KG (bei 70 kg KG = 350 mg CBA/Tag) ~ 11.5 Mio IU/Tag

COLISTIN – MONO ODER KOMBI
Serumkonzentration von Colistin

- **Renale Clearance von CMS bei Nieren-gesunden Patienten größer als die Konversion von CMS zu Colistin**
- **Max. 20% der CMS-Dosis wird in Colistin umgewandelt**

Li, Lancet Infect Dis 2006 – Nation, Clin Infect Dis 2014

COLISTIN – MONO ODER KOMBI

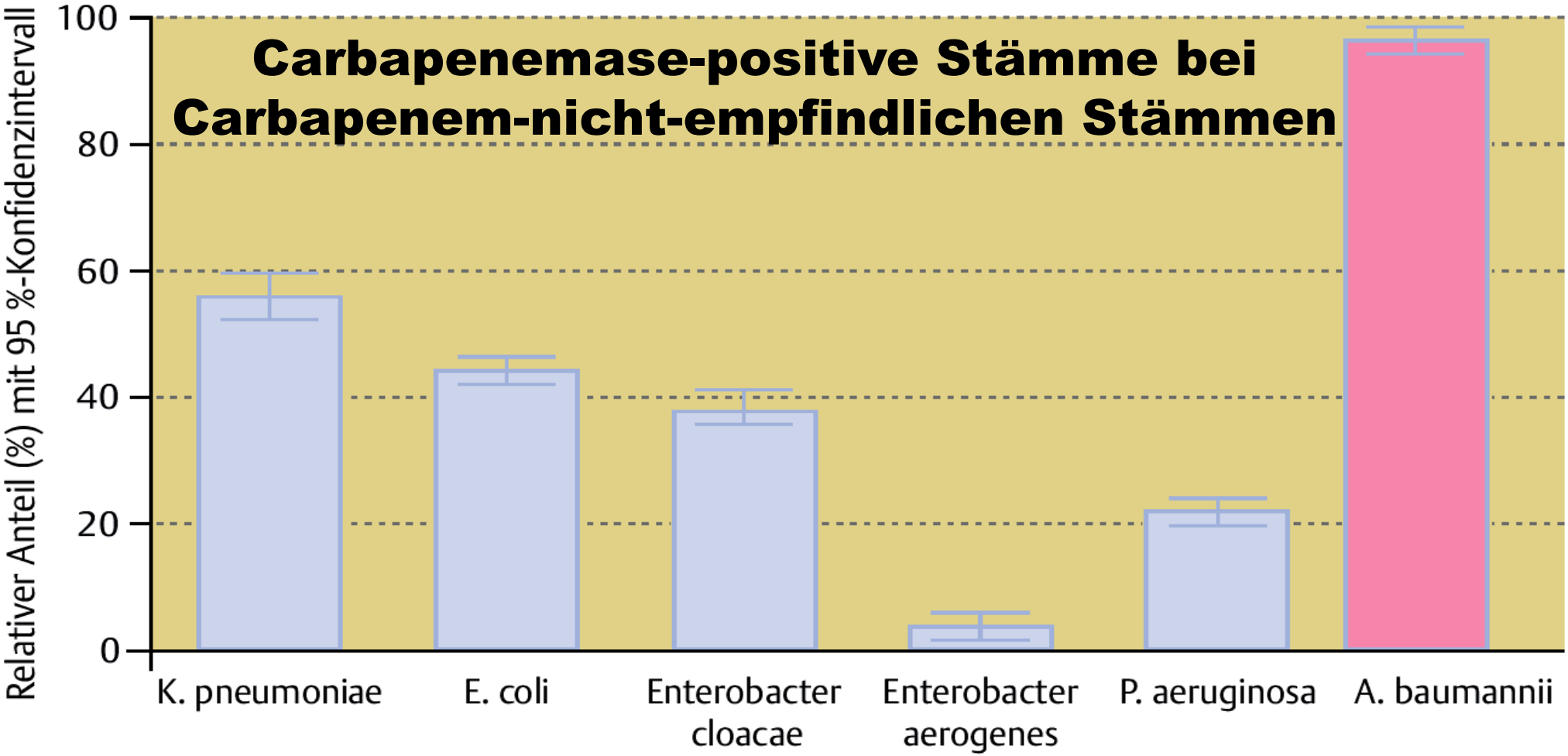
Keimspektrum

	Pseudomonas	Acinetobacter	AmpC	ESBL (MDR-GNR)	Carbapenem-resistant
Cefepim	■		■		
Imi/Mero/Doripenem	■	■	■	■	
Ertapenem			■	■	
Sulbactam		■			
Tigecyclin*		■	■	■	■
Polymixin/Colistin*	■	■	■	■	■

*keine *Proteus spp.*-Aktivität

Gurjar, J Intensive Care 2014

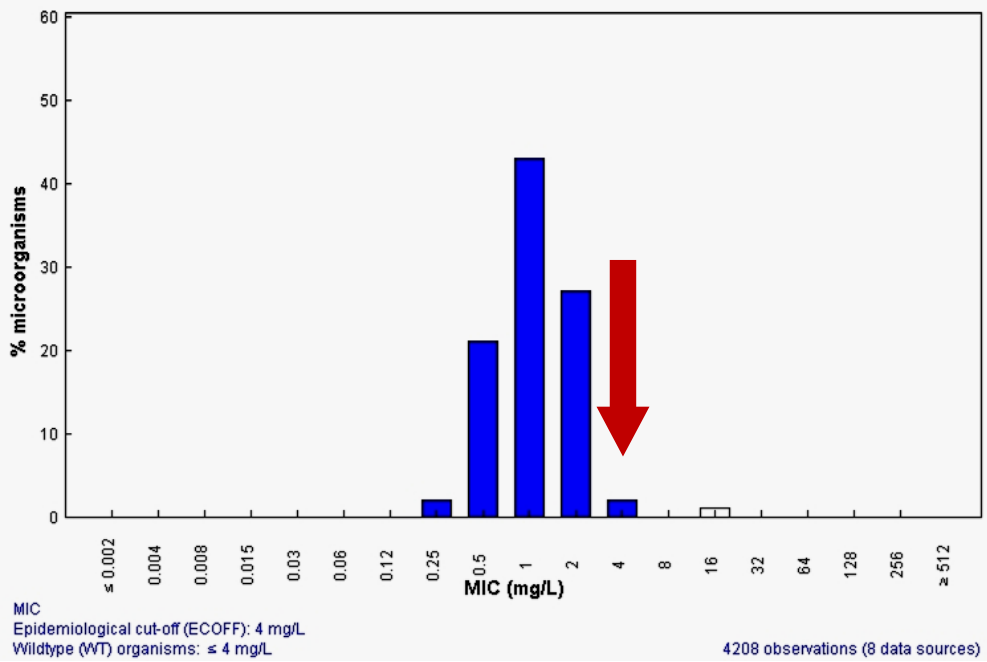
COLISTIN – MONO ODER KOMBI
Carbapenemase-positive Stämme



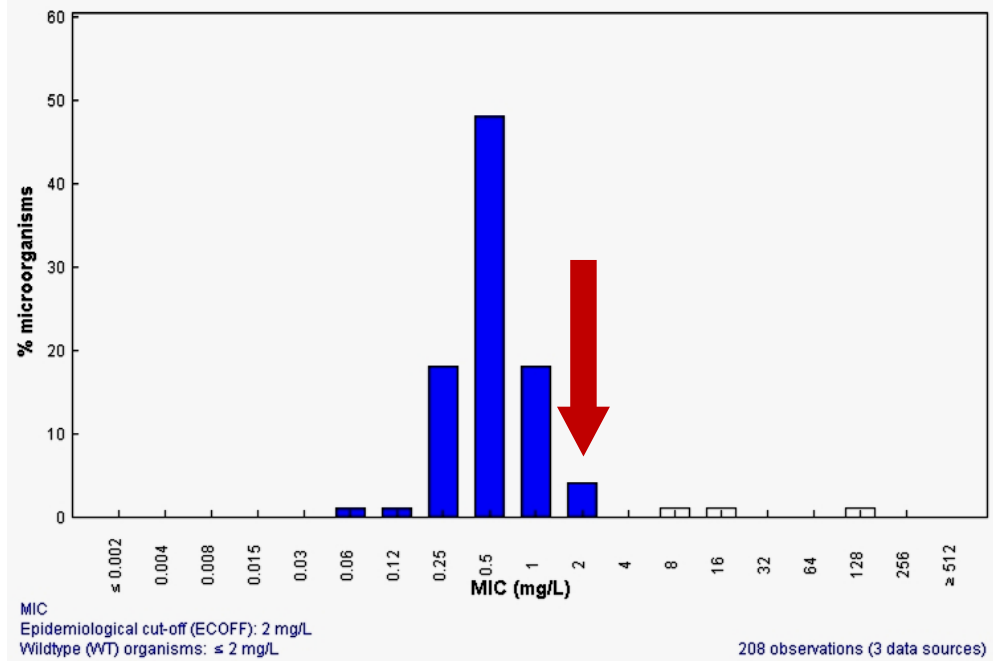
Mischnik, Dtsch Med Wochenschr 2015

COLISTIN – MONO ODER KOMBI
MHK-Verteilung

Pseudomonas aeroginosa



Enterobacter aerogenes

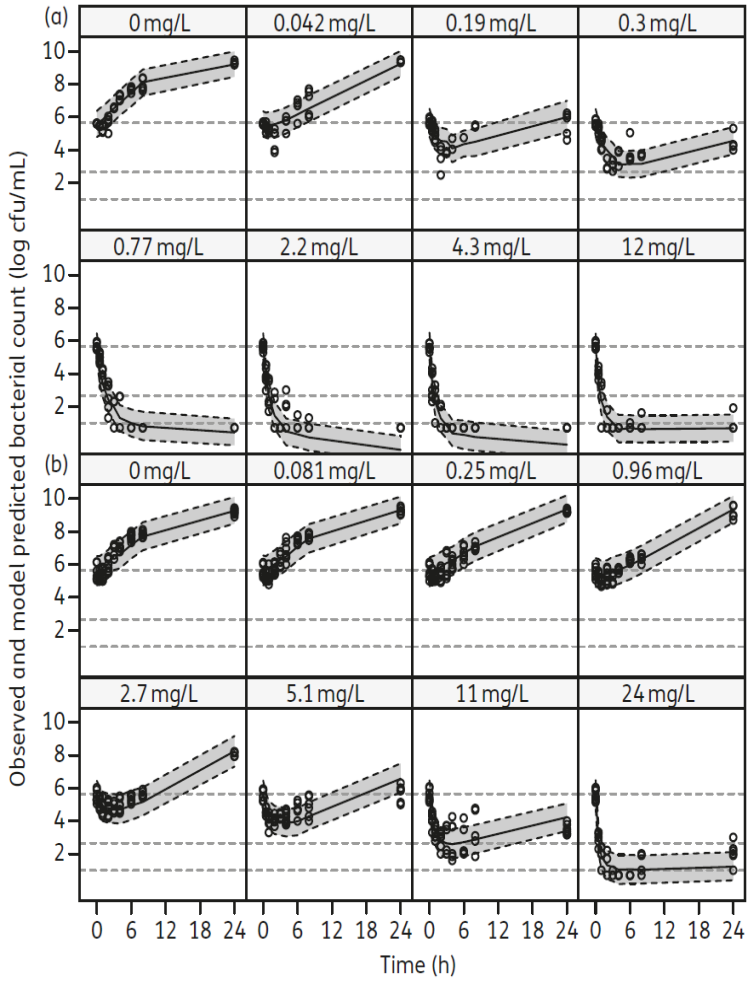


COLISTIN – MONO ODER KOMBI
Dosierungsoptionen

	Polymyxin B	Colistimethate sodium (CMS) Colomycin® injection	Colistimethate sodium (CMS) Coly-Mycin® M Parenteral
Composition of vials	500 000 units (*c.* 50 mg)	500 000 IU (40 mg) 1 000 000 IU (80 mg) 2 000 000 IU (120 mg)	150 mg colistin base activity (400 mg CMS)
Recommended dose for patients with normal renal function	15 000–25 000 IU/kg/day in one daily or two divided doses (equivalent to 1.5–2.5 g)	≤60 kg, 50 000–75 000 IU/kg/day in three divided doses (equivalent to 4–6 mg/kg/day CMS) 60 kg, 1–2 million IU three times a day (equivalent to 80–160 mg CMS three times per day) Maximum dose of 6 million IU in 24 h	2.5–5.0 mg/kg/day colistin base activity in 2–4 doses (equivalent to *c.* 6.67–13.3 mg/kg/day CMS)
Recommended dose adjustment in patients with renal impairment	According to creatinine clearance (CLCR): • CLCR of 30–80 mL/min, loading dose of 2.5 mg/kg/day on the first day and then 1.0–1.5 mg/kg/day • CLCR <30 mL/min, loading dose of 2.5 mg/kg/day on the first day and then 1.0–1.5 mg/kg/day every 2–3 days • Anuric patients, loading dose of 2.5 mg/kg/day on the first day and then 1.0–1.5 mg/kg/day every 5–7 days	According to creatinine clearance (CL_{CR}) and over 60 kg bodyweight: • CL_{CR} 20–50 mL/min, 1–2 million IU every 12 h • CL_{CR} 10–20 mL/min, 1 million IU every 12–18 h • CL_{CR} <10 mL/min, 1 million IU every 18–24 h	According to creatinine clearance (CL_{CR}) and over 60 kg bodyweight: • CL_{CR} 50–80 mL/min, 75–115 mg every 12 h • CL_{CR} 30–50 mL/min, 66–150 every 12–24 h • CL_{CR} 10–30 mL/min, 100–150 every 36 h
Recommended dose for inhalation therapy	2.5 mg/kg daily in divided doses every 6 h (respiratory infections) to 500 000 IU twice a day (pneumonia)	1–2 million units twice daily, dissolved in 2–4 mL of water for injections or 0.9% sodium chloride intravenous infusion for use in a nebuliser	1–2 million IU, 2 or 3 times daily, diluting the appropriate dose in 2–4 mL of preservative-free 0.9% sodium chloride injection, sterile water, or a mixture of 0.9% sodium chloride injection and sterile water for use in a nebuliser

Cervera, Clin Microbiol Infect 2014

COLISTIN – MONO ODER KOMBI
Dosisempfehlung 2014



- **LD: 12 Mio IU** – KG-unabhängig
  - killing-rate 12 Mio: 75%
  - killing-rate 9 Mio: 55%
  - killing-rate 6 Mio: 45%
- **Infusionsdauer bis zu 2 Std**
  - Abtötungsrate nicht niedriger zu 15 oder 30 min Infusionsdauer
- **ED: 4.5 Mio IU 2 x tgl.**
  - Aufteilung auf 3 x tgl möglich

Mohamed, J Antimicrob Chemother 2014

COLISTIN – MONO ODER KOMBI
Pharmakodynamik

C_{ss} 2 mg/L

MHK < 1 mg/L

Bergen, Antimicrob Agents Chemother 2010 – Dudhani, Antimicrob Agents Chemother 2010 – Dudhani, J Antimicrob Chemother 2010

COLISTIN – MONO ODER KOMBI

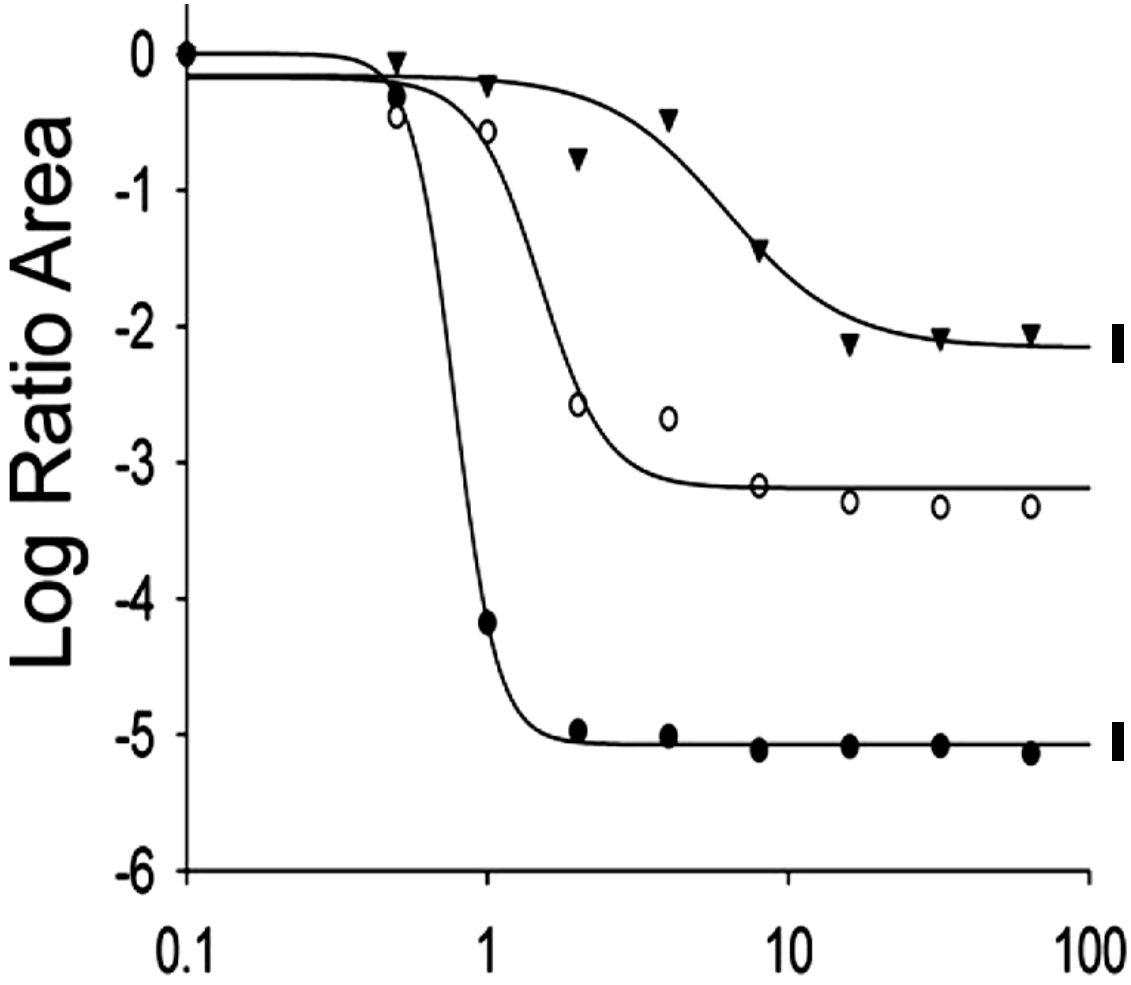
Inoculum Effekt

Antibiotic	Control organism	Inoculum concn. (CFU)			
		10^4	10^5	10^6	10^7
Ampicillin	*E. coli* WHO-5 $p < 0.05$	8.71[a]	8.57	8.71	10.00
Cephalothin	*E. coli* WHO-5 $p < 0.01$	10.28	10.28	11.00	12.00
Chloramphenicol	*E. coli* WHO-5 $p < 0.05$	8.76	8.58	8.91	9.54
Kanamycin	*E. coli* WHO-5 $p < 0.01$	8.77	9.25	10.08	10.77
Tetracycline	*E. coli* WHO-16 n.s.	7.40	7.50	7.29	7.86
Gentamicin	*E. coli* 4883 $p < 0.001$	6.50	7.67	8.75	10.00
Colistin	*E. coli* WHO-5 $p < 0.001$	6.00	8.50	9.00	9.75

Antibiotic	Control organism	Inoculum concn. (CFU)			
		10^4	10^5	10^6	10^7
Gentamicin	*P. aeruginosa* HC-2 $p < 0.001$	1.84[a]	1.84	3.30	7.19
Carbenicillin	*P. aeruginosa* HC-2 n.s.	14.60	15.00	14.90	15.90
Kanamycin	*P. aeruginosa* HC-2 $p < 0.01$	14.00	14.20	14.60	15.00
Colistin	*P. aeruginosa* HC-2 $p < 0.001$	8.49	9.60	11.20	13.00

Tilton, Appl Microbiol 1973

COLISTIN – MONO ODER KOMBI
Inoculum Effekt



Inoculum GROSS

Inoculum	E_0	Emax	EC_{50}	H
10^6 CFU/mL	-0.003	5.07	0.777	6.10
10^8 CFU/mL	-0.173	3.01	1.49	3.95
10^9 CFU/mL	-0.156	1.99	6.22	2.20

Inoculum KLEIN

- ▼ $CFU_0=10^9$ CFU/ml
- ○ $CFU_0=10^8$ CFU/ml
- ● $CFU_0=10^6$ CFU/ml

Bulitta, Antimicrob Agents Chemother 2010

COLISTIN – MONO ODER KOMBI
Heteroresistenz

- Subpopulationen Colistin-resistenter Stämme in einem Isolat
- MHK-Wert suggeriert Empfindlichkeit
- Eradikation der Colistin-empfindlichen Stämme führt zu unghemmten Wachstum Colistin-resistenter Stämme

Li, Antimicrobial Agents Chemother 2006 – Landersdorfer, Semin Resp Crit Care Med 2015

COLISTIN – MONO ODER KOMBI

Grenzwert für Kombinationstherapie

MINIMALE HEMMKONZENTRATION

1 mg/L

KOMBINATIONSTHERAPIE

Landersdorfer, Semin Respir Crit Care Med 2015

COLISTIN – MONO ODER KOMBI
Klebsiella pneumoniae Carbapenemase

30-Tagesmortalität

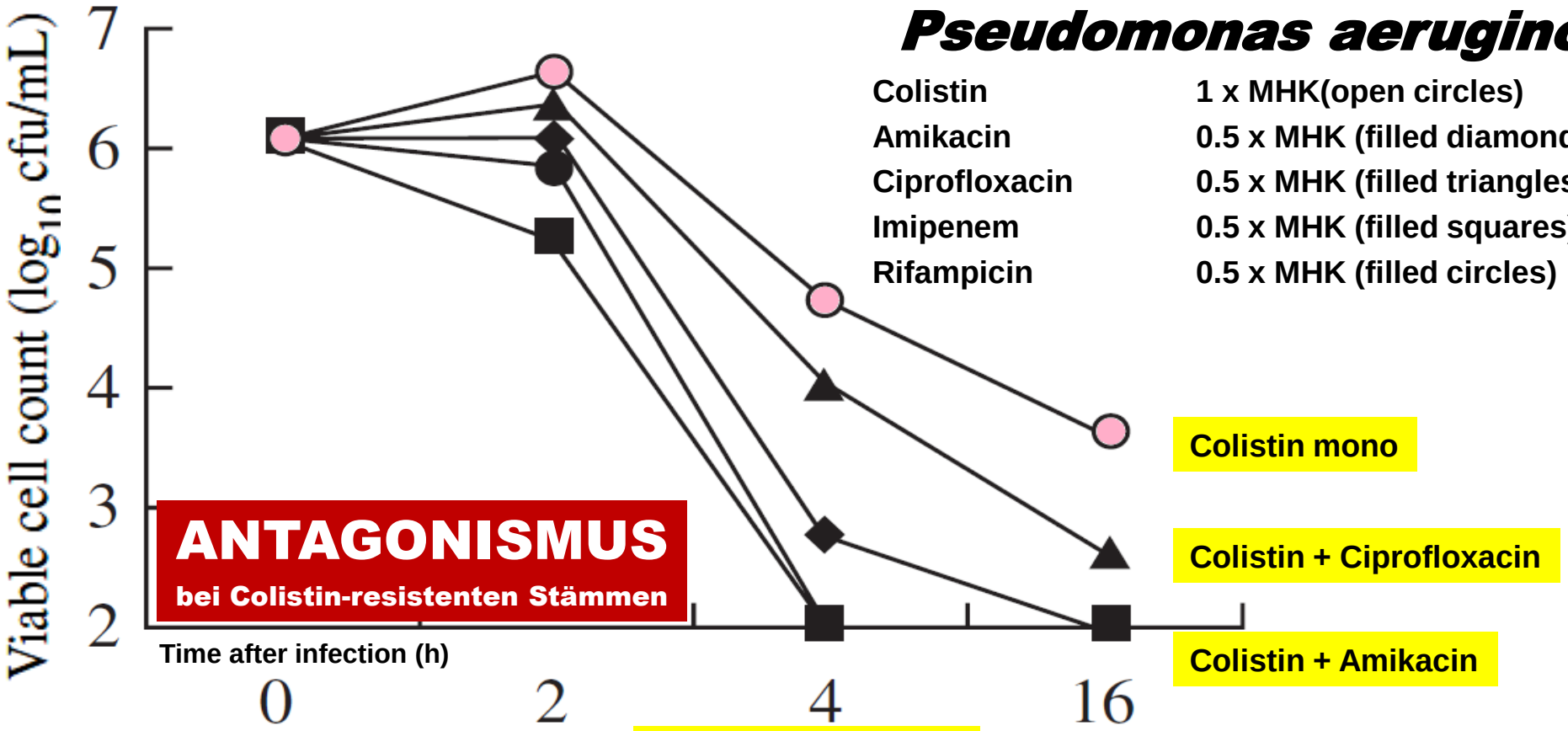
- **Monotherapie** **54.3%**
- **Kombinationstherapie** **34.1%**

p = 0.02

Tumbarello, Clin Infect Dis 2012

COLISTIN – MONO ODER KOMBI

Kombinationstherapie in vitro



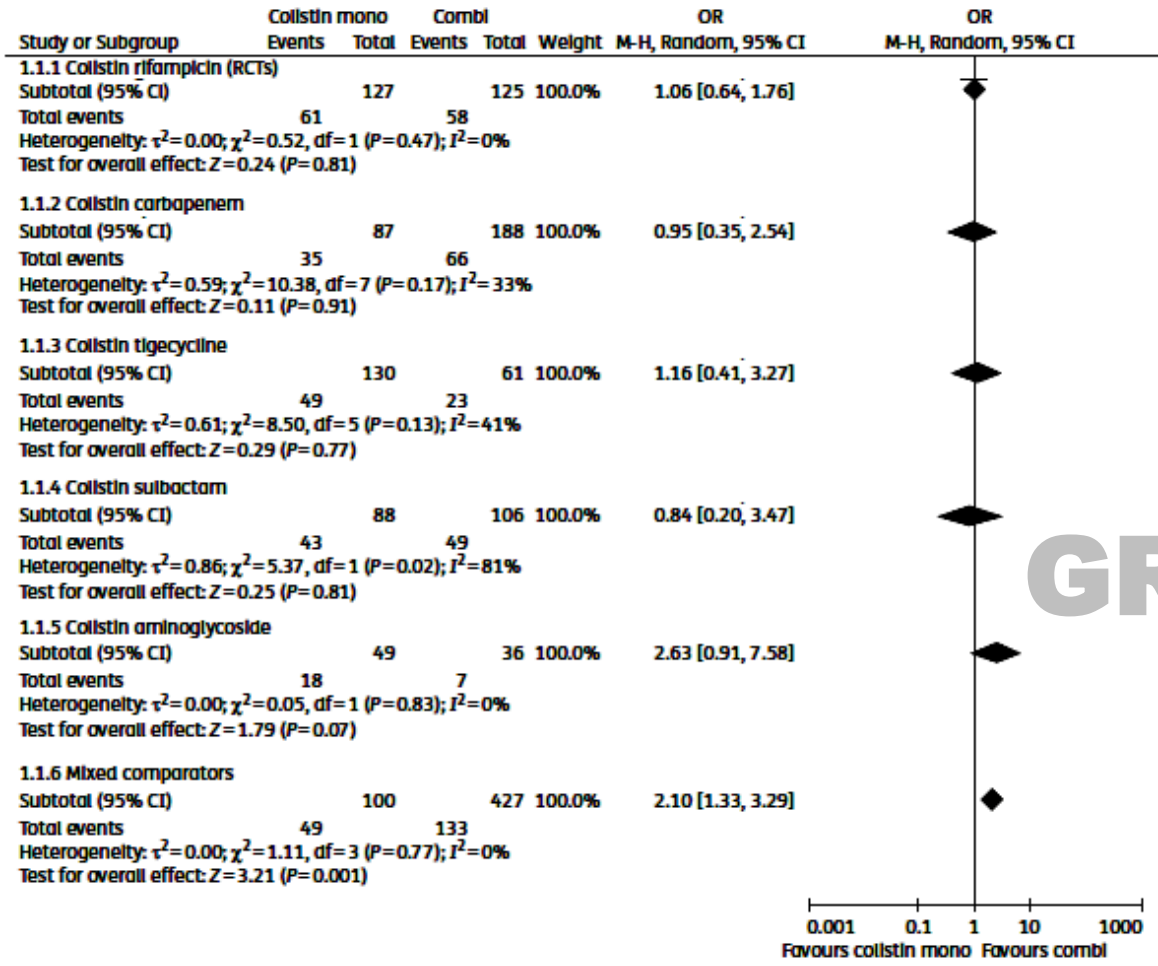
Aoki, J Antimicrob Chemother 2009 – Souli, Antimicrob Agents Chemother 2009

COLISTIN – MONO ODER KOMBI
Argumente für die Kombination

- **Heteroresistenz**
- **Resistenzinduktion**
- **MHK ≥ 1µg/mL**
- **MDR-Enterobakterien**
- **schnelleres Therapieansprechen**
- **Dosierung**
- **Nephrotoxizität**

COLISTIN – MONO ODER KOMBI

Kombinationstherapie



CARBAPENEM RESISTENTE GRAM-NEGATIVE BAKTERIEN

Paul, J Antimicrob Chemother 2014

COLISTIN – MONO ODER KOMBI

Der Vergleich macht Sie sicher …

Year	Country	Design	Infection type	Combination regimen	Monotherapy regimen	Microbiology	*n*	Endpoint	Combination vs. monotherapy, %
2010	Greece	Retrospective	PNA, BSI, UTI, IAI, SSI, SSTI, CNS	Colistin + carbapenem, piperacillin–tazobactam, sulbactam or other	Colistin	Ab (some XDR)	170	Clinical cure	80.3 vs. 87
2013	Turkey	Open label RCT	VAP	Colistin + rifampin	Colistin	CR-Ab	43	Mortality	61.9 vs. 72.7
2013	Italy	Open label RCT	PNA, BSI, IAI	Colistin + rifampin	Colistin	XDR-Ab	209	Mortality	43.4 vs. 42.9
2013	Spain	Retrospective	BSI, PNA	Colistin + vancomycin	Colistin	CR-Ab	57	Clinical cure	55.2 vs. 67.9
2014	Thailand	Open label RCT	PNA, BSI, UTI, SSTI, IAI	Colistin + fosfomycin	Colistin	CR-Ab	94	Mortality	46.8 vs. 57.4
2014	Italy	Retrospective	PNA, BSI, UTI, IAI, SSI	Colistin + vancomycin	Colistin	CR-Ab	166	Mortality	41.7 vs. 35.3
2014	Turkey	Retrospective	BSI	Colistin + carbapenem, sulbactam, tigecycline or other	Colistin	XDR-Ab	240	Mortality	52.3 vs. 72.2
2014	USA	Retrospective	PNA, BSI	Colistin + carbapenem, sulbactam, tigecycline or other	Tigecycline, carbapenem, cefepime	XDR-Ab	36	Mortality	47 vs. 100

Viehman, Drugs 2014

COLISTIN – MONO ODER KOMBI
Colistin plus Daptomycin

In vivo activity of daptomycin/colistin combination therapy in a Galleria mellonella model of Acinetobacter baumannii infection

Antimicrobial treatment of multidrug-resistant Acinetobacter baumannii (MDR-AB) infections continues to pose significant challenges. With limited options, clinicians have been pushed towards using unorthodox combinations of licensed antibiotics. Although daptomycin/colistin combination appears to be a promising treatment option based on in vitro data, further preclinical work is needed. In this study, the A. baumannii-Galleria mellonella system was employed to study the in vivo efficacy of this combination in order to determine whether it should be explored further for the treatment of MDR-AB infections. The antimicrobial activity of colistin alone and in combination with daptomycin was assessed versus an A. baumannii type strain (ATCC 19606) and a MDR-AB clinical strain (GN2231) isolated in Anhui, China. Synergy studies were performed using the microtitre plate chequerboard assay and time-kill methodology. The in vivo activity of daptomycin/colistin combination was assessed using a G. mellonella larvae model. The combination of daptomycin and colistin was bactericidal against both strains tested. In chequerboard assays, daptomycin was highly active against A. baumannii when combined with colistin [fractional inhibitory concentration index (FICI) of <0.5]. Treatment of G. mellonella larvae infected with lethal doses of A. baumannii resulted in significantly enhanced survival rates when daptomycin was given with colistin compared with colistin treatment alone (P<0.05). This work suggests that daptomycin/colistin combination is highly active against A. baumannii both in vitro and in a simple invertebrate model of infection.

Yang, Int J Antimicrob Agents 2015

COLISTIN – MONO ODER KOMBI

Colistin plus Daptomycin

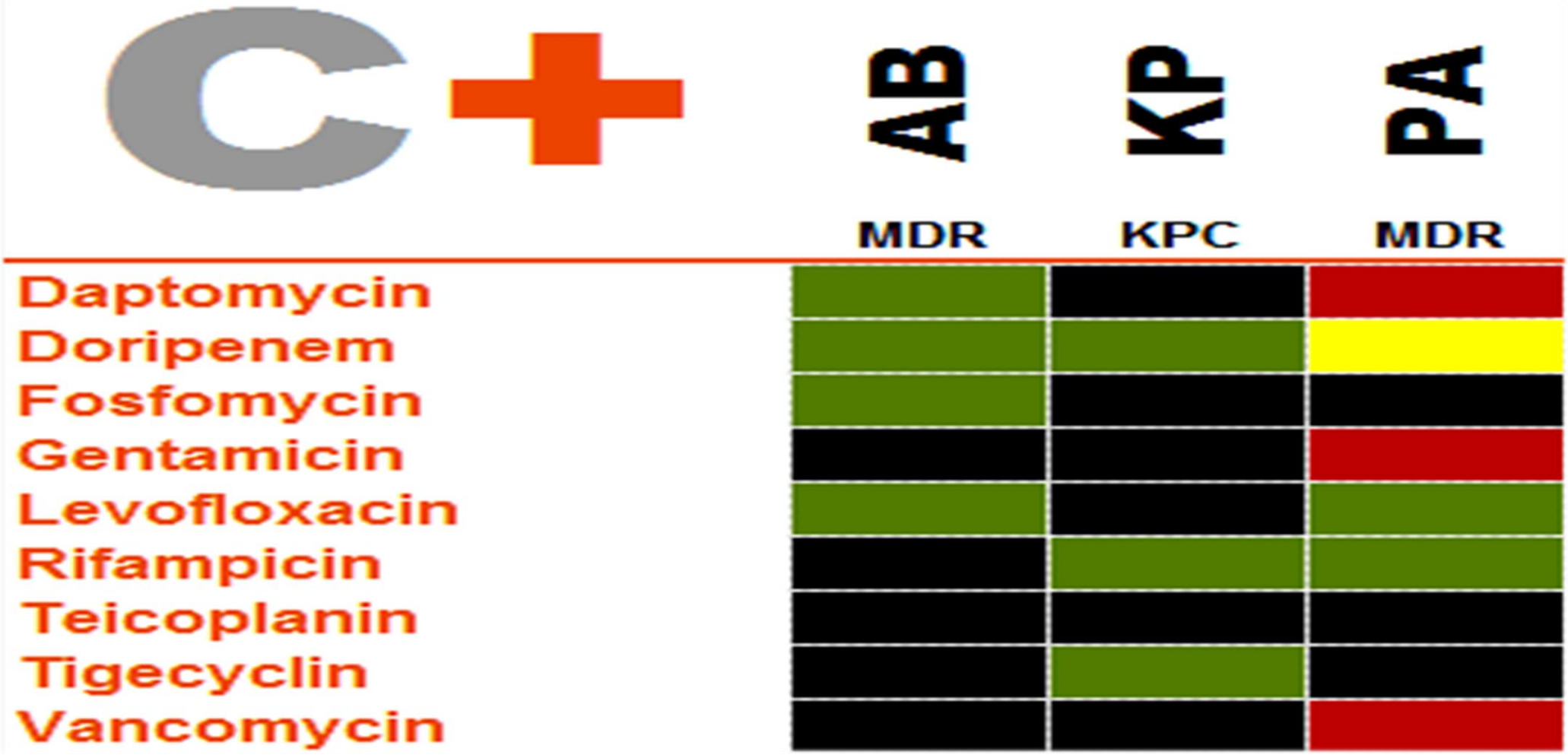
Colistin/daptomycin: an unconventional antimicrobial combination synergistic in vitro against multidrug-resistant Acinetobacter baumannii

The in vitro activity of the combination colistin/daptomycin was evaluated against multidrug-resistant Acinetobacter baumannii clinical isolates. Clonal relationships were assessed by pulsed-field gel electrophoresis. The following synergy studies were undertaken: (i) daptomycin MICs were determined by E-test on Mueller-Hinton agar plates supplemented with a subinhibitory concentration of colistin; and (ii) time-kill methodology using tubes containing an inoculum of 5×10(5)CFU/mL and subinhibitory concentrations of each antibiotic alone or in combination subcultured at 0, 5 and 24h for colony counting. Synergy was defined as ≥2log10CFU/mL decrease of viable colonies compared with colistin alone. Ten colistin-susceptible and four colistin-resistant A. baumannii isolates were tested. Isolates were assigned to nine different clonal types. Enhanced in vitro activity of the combination was detected only against colistin-susceptible isolates; using plates supplemented with colistin, the daptomycin MIC was reduced by 4- to 128-fold. From a total of 30 isolate-concentration combinations in time-kill studies, a synergistic interaction was detected in 16 (53.3%). The combination exhibited synergy against 8 and 12 of these combinations at 5h and 24h, respectively. No antagonism was detected. Colistin alone was bactericidal against two colistin-susceptible isolates at 24h, whereas the combination was bactericidal against 9 colistin-susceptible isolates at 24h. Against all colistin-resistant isolates, the combination exhibited a static effect and indifference in time-kill studies. Potent in vitro synergistic interactions between colistin and daptomycin provide evidence that this unorthodox combination may be beneficial in the treatment of colistin-susceptible multidrug-resistant A. baumannii.

Galani, Int J Antimicrob Agents 2014

COLISTIN – MONO ODER KOMBI

Ein Versuch …



COLISTIN – MONO ODER KOMBI
Argumente gegen die Kombination

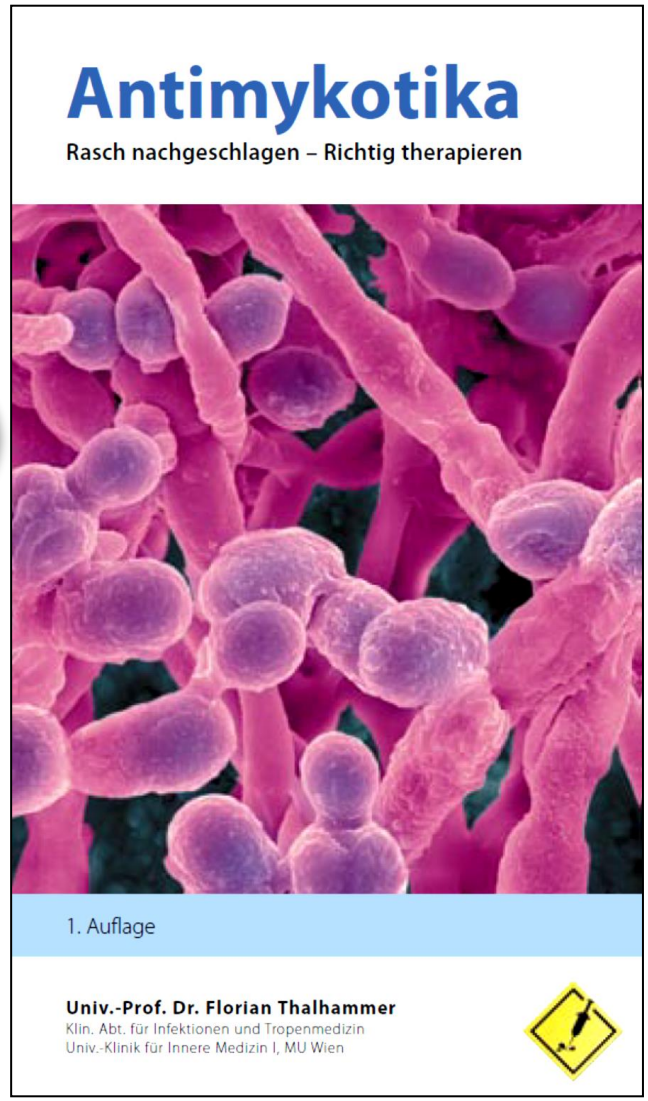
- **Monotherapie so gut wie Kombinationstherapie**
- **Retrospektive Studiendatenauswertung**
- **Colistin-Dosierung nicht ausreichend**
- ***in vitro* entspricht nicht *in vivo***
- **Heterogenität der Studienlage**

COLISTIN – MONO ODER KOMBI
Zusammenfassung

- **… not generally recommended …**
- **… further studies are needed …**

- **Stämme mit MHK > 1 mg/L**
- **Infektionen mit hohem Inoculum**
- **tiefe Infektionen (zB Lunge)**
- **Patienten mit moderater bis guter Nierenfunktion**

Landersdorfer, Semin Respir Crit Care Med 2015



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