Infektionen durch CPE & Co therapieren

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CPE und Co

- „CPE“
  - Carbapenemase produzierende Enterobakterien
- „Co“
  - Pseudomonas aeruginosa
  - Acinetobacter baumannii
  - …

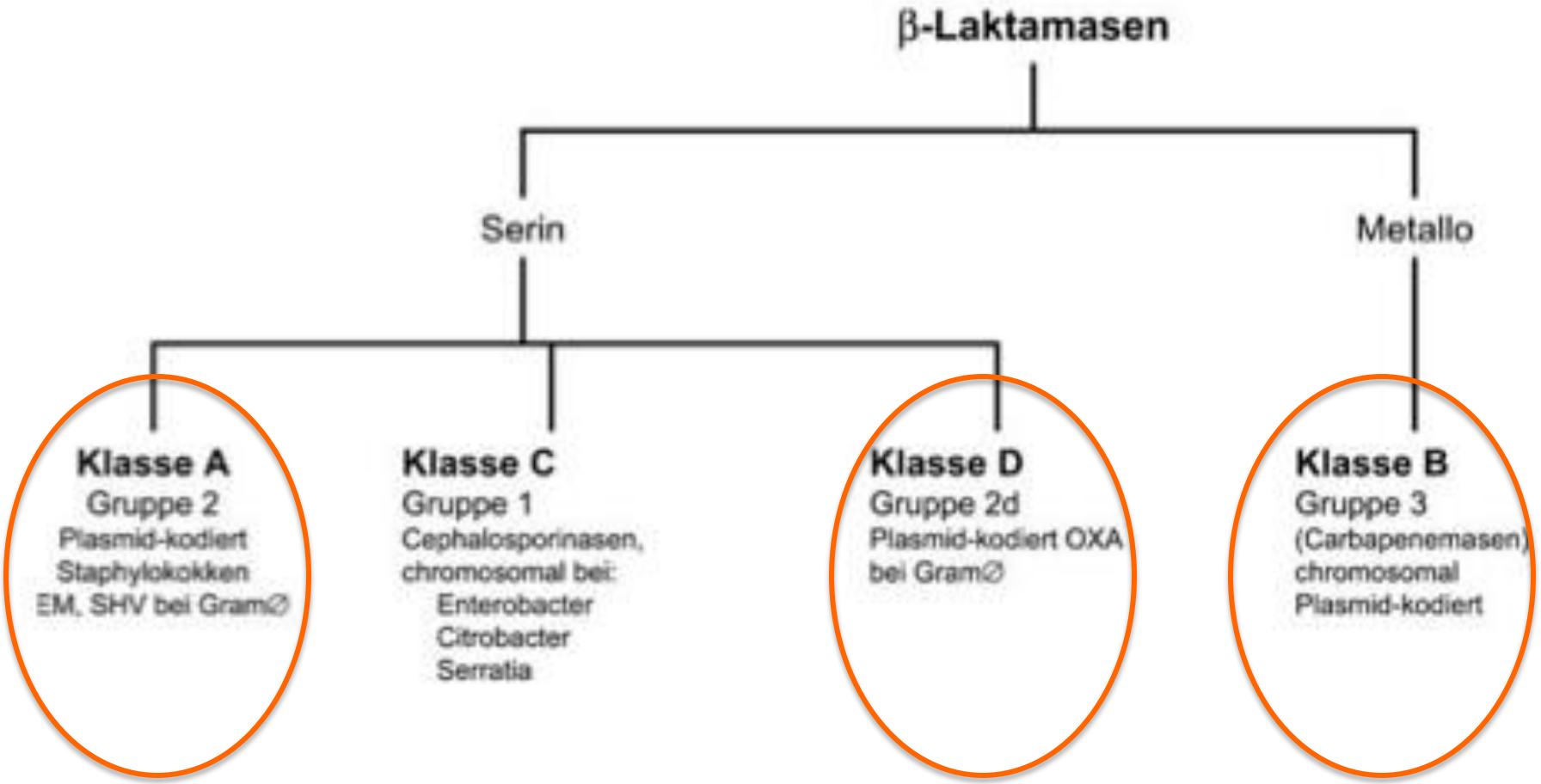
Carbapenem Resistenz

- Porinverlust
  - OprD
- Efflux
- Veränderte PBP
  - PBP2a bei MRSA

- Carbapenemasen (Betalaktamasen)

Beta Laktamasen

Carbapenemasen in Gruppe A,B,D (Ambler Klassif.)



Witte. Bundesgesundheitsblatt 2003;46:881

Carbapenem Resistenz

- Carbapenemasen (Betalaktamasen)
  - Oxa Beta-Laktamasen (Klasse D)
    - Acinetobacter, Kl. pneumoniae, E. coli...
  - Klebsiella pneumoniae Carbapenemasen KPC (Klasse A)
    - Kl. pneumoniae, E. coli, Enterobacter sp., Salmonella enterica, Proteus mirabilis, Citrobacter freundii, Pseudomonas aeruginaosa, Acinetobacter baumannii,...
    - Kl. oxytoca[Lit 2,3]

Lit 1: Witte. Bundesgesundheitsblatt 2003;46:881
Lit 2: Hirsch. JAC 2010;65;1119-25
Lit 3: Hönigl. AAC 2012, in press

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    - Kl. oxytoca[Lit 2,3]
  - Metallo Betalaktamasen (Klasse B)
    - Ps. aeruginosa, Acinetobacter spp. (chromosomal kodiert)
    - Kl. pneumoniae, andere Enterobacteriaceae (plasmid kodiert)
    - Acinetobacter spp. NDM 2 (plasmid kodiert) [Lit 4]

Lit 1: Witte. Bundesgesundheitsblatt 2003;46:881
Lit 2: Hirsch. JAC 2010;65;1119-25
Lit 3: Hönigl. AAC 2012, in press
Lit 4: Kaase. JAC 2011;66:1260-2

Metallo-Betalaktamasen

- IMP 1 (Japan) 1988
- VIM (Verona Imipenemase) 1999
- GIM (German Imipenemase) 2002

- SPM (Sao Paulo Metallo BL)
- AIM (Australien Imipenemase)
- KHM (Japan, Kyorin University Hospital Imipenemase)
- SIM (Seoul Imipenemase)

- NDM 1 (New Delhi) 2009
  - Plasmid kodiert
  - Übertragbar
  - importierte Pat. in Graz (2009-2010)

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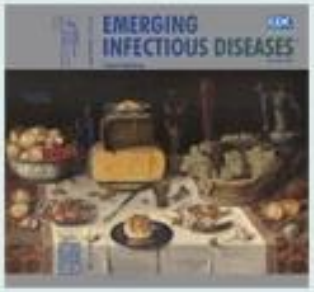

A Moveable Feast

A basket of grapes painted by Zeuxis more than 2,000 years ago was so realistic, the grapes so enticing, that birds flew down from the sky to peck at the picture, wrote Pliny the Elder in The Natural History... more

Expedited

- **Wild Chimpanzees Infected with 5 *Plasmodium* Species**
  M. Kaiser et al.
  (381 KB, 9 pages)
- **Alkhurma Hemorrhagic Fever in Travelers Returning from Egypt, 2010**
  F. Carletti et al.
  (210 KB, 8 pages)
- **New Delhi Metallo-β-Lactamase in *Klebsiella pneumoniae* and *Escherichia coli*, Canada**
  M.R. Mulvey et al.
  (358 KB, 10 pages)
- **Emergence of New Delhi Metallo-β-Lactamase, Austria**
  G. Zarfel et al.
  (88 KB, 4 pages)

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Infektionen durch CPE & Co therapieren

- Keim identifiziert
- Antibiogramm vorhanden
- Ort der Infektion bekannt
  - Bakteriämie, Lunge, Knochen, etc.

- Grunderkrankung des Patienten (Niere, etc.)

Carbapenem resistente Enterobakterien

- Wirksamkeit verschiedener ABs gegen 81 CPE aus UK
  - Temocillin gegen 4.9% der Isolate
  - Chloramphenicol, Ciprofloxacin und Nitrofurantoin <25%

Livermore. Internat Journal of Antimicrobial Agents 37 (2011) 415–419

Carbapenem resistente Enterobakterien

- Wirksamkeit verschiedener ABs gegen 81 CPE aus UK
  - Temocillin gegen 4.9% der Isolate
  - Chloramphenicol, Ciprofloxacin und Nitrofurantoin <25%
  - Tigecycline 46.9% (38/81) der Isolate
    - Zusätzl. intermediär bei 33.3%
  - Fosfomycin 60.5% (49/81) der Isolate
    - 25/52 Klebsiella spp empfindlich
  - Colistin 92.6% (75/81) der Isolate
  - Aktivität von Colistin, Fosfomycin und Tigecycline unabhängig vom Carbapenem Resistenzmechanismus

Livermore. Internat Journal of Antimicrobial Agents 37 (2011) 415–419

Therapie bei Carbapenem Resistenz

Drug	Potential	Limitations
Polymyxin B and E (colistin) (i.v.)	Active vs. >90% of producers. Case reports of successful use in a range of infections due to carbapenemase producers.	Significant nephro- and neuro-toxicity and poor lung penetration. Use high dose, with possible addition of nebulised colistin in pneumonia.
Tigecycline (i.v.)	Active in vitro vs. most carbapenem-resistant *E. coli*. Licensed for skin and soft tissue and complicated intra-abdominal infections. Case reports of success in various infections with carbapenemase producers.	Low blood concentrations; off-label use should be cautious; unsuitable in urinary infections as only 22% excreted in urine. Excess deaths in some trials, esp. ventilator pneumonia (not a licensed indication). Many *Klebsiella* only intermediately susceptible (MIC, 2 mg/L); some resistant.
Fosfomycin (oral and i.v.)	Active against most *E. coli* with carbapenemases, including NDM-1. Effective in urinary infections.	Borderline susceptibility common in *Klebsiella* spp. Risk of mutational resistance. Not marketed in the UK, but pharmacists can import.

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http://www.hpa.org.uk/webc/HPAwebFile/HPA

Carbapenem Resistenz

- Wirksame ABs
  - Colistin
  - Tigecyclin
    - Nicht bei Pseudomonas
    - auch bei Harnwegsinfekten?
  - Ev. Fosfomycin
  - Ev. Aztreonam
  - Ev. Aminoglycoside
  - Ev. Chinolone
  - Ev. Temocillin
  - Ev. Chloramphenicol
  - Ev. Azithromycin
  - Ev. Sulbactam
  - Ev. Kombi mit Rifampicin

Kanj. Mayo Clin Proc. 2011;86(3):250-259
Nix. J. Antimicrob. Chemother. (2010) 65 (6): 1311-1312
Livermore.
http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1294740725984

Colistin

Colistin (Grünenthal, Forest)

- Polymyxin E
- Unwirksam gegen Proteus spp., Gram pos. Kokken...
- Zellwandhemmung
- Dosis
  - 75.000 IE/kg KG (aufgeteilt auf 2-3 Applikationen)
  - Kurzfristig 150.000 IE/kg KG
  - ??

- NW
  - Nephrotoxizität
  - Neurotoxizität
  - Neuromuskuläre Blockade
  - Krampfanfälle bei intrathekaler Anwendung

Colistin

- Colistin ≠ Colistinmethansulfonat

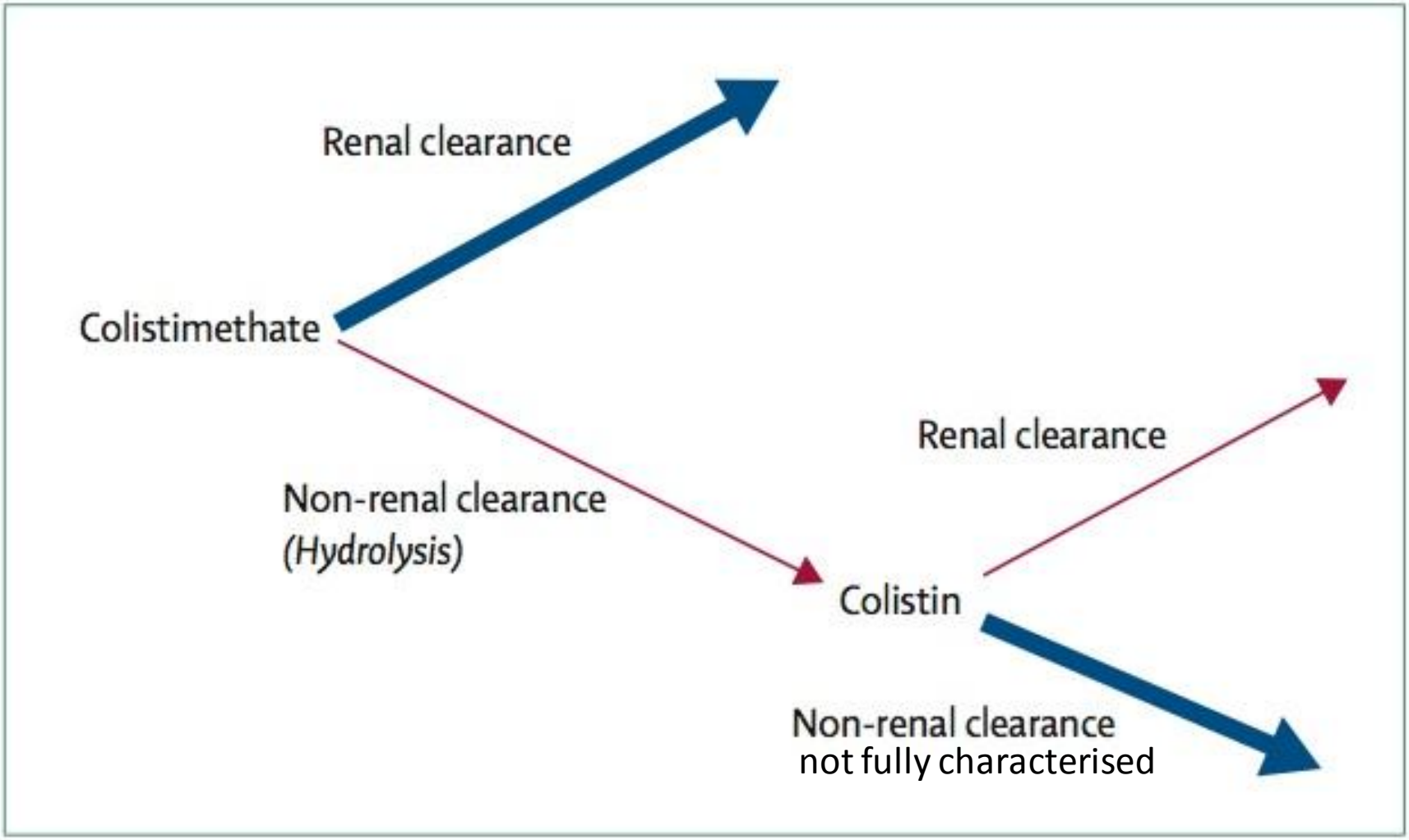
- Terminologie
  - Colistin
    - =Colistin sulfate
  - Colistimethate sodium
    - =Colistin methanesulfonate sodium
    - =Colistin sulfomethate sodium

Colistin

- Colistinmethansulfonat (Prodrug, inaktiv)
  - Tubulär sezerniert
  - Renal eliminiert
  - Wenig/nicht nephrotoxisch

- Colistin (aktiv)
  - Tubulär reabsorbiert
  - Nicht renal eliminert
  - nephrotoxisch

Colistin und Colistin Methan Sulfonate



Li. Lancet Infect Dis 2006; 6: 589–601

Colistin

- Nephrotoxizität?
  - Bei 3x2Mio Einheiten keine Nephrotoxizität
  - Jedoch N-acetyl-β-D- glucosaminidase erhöht
    - Subklinischer tubulärer Nierenschaden
  - Bei 10 Mio Einheiten ca 50% Nephrotoxizität
    - 63% davon persistierende Kreatininerhöhung

Li. Lancet Infect Dis 2006; 6: 589–601
Garonzik AAC 2011;50:3284–3294

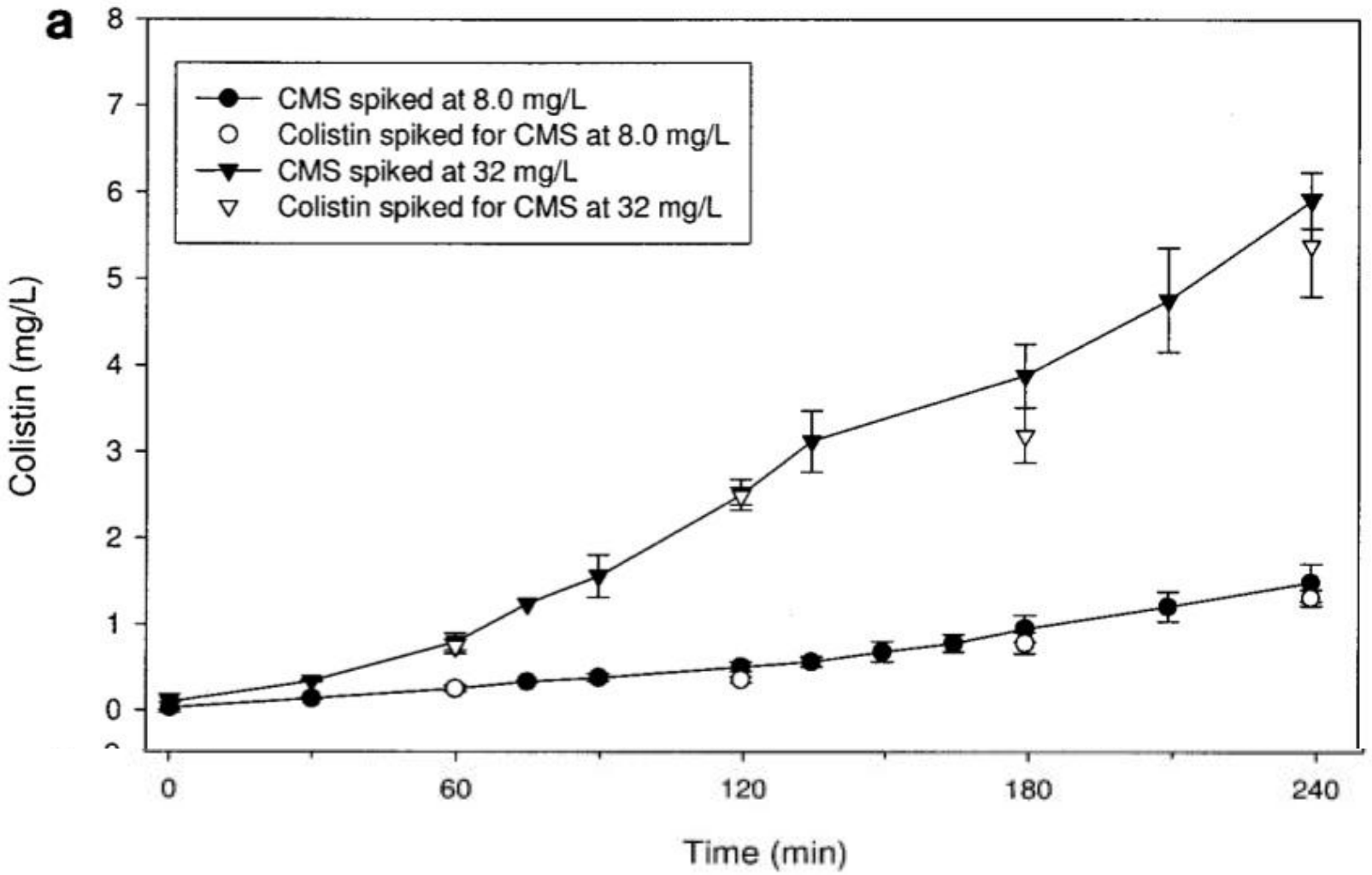
Colistin

- Europa
  - Colistinmethansulfat
    - 1Mio Einheiten = 80mg =„30mg Colistin base activity“
    - Dosis 6Mio Einheiten = 480mg
    - 75000IE/kg KG iv geteilt auf 2-3 Dosen
- USA
  - Colistinmethansulfat
    - 5Mio Einheiten = 400mg = „150mg Colistin base activity“
    - Dosis 10Mio Einheiten = 800mg

- „...the pharmacokinetic and pharmacodynamic information required to underpin prescribing recommendations in the product information is lacking.“

Li. Lancet Infect Dis 2006; 6: 589–601
Falagas. Crit Care 2006; 10:R27

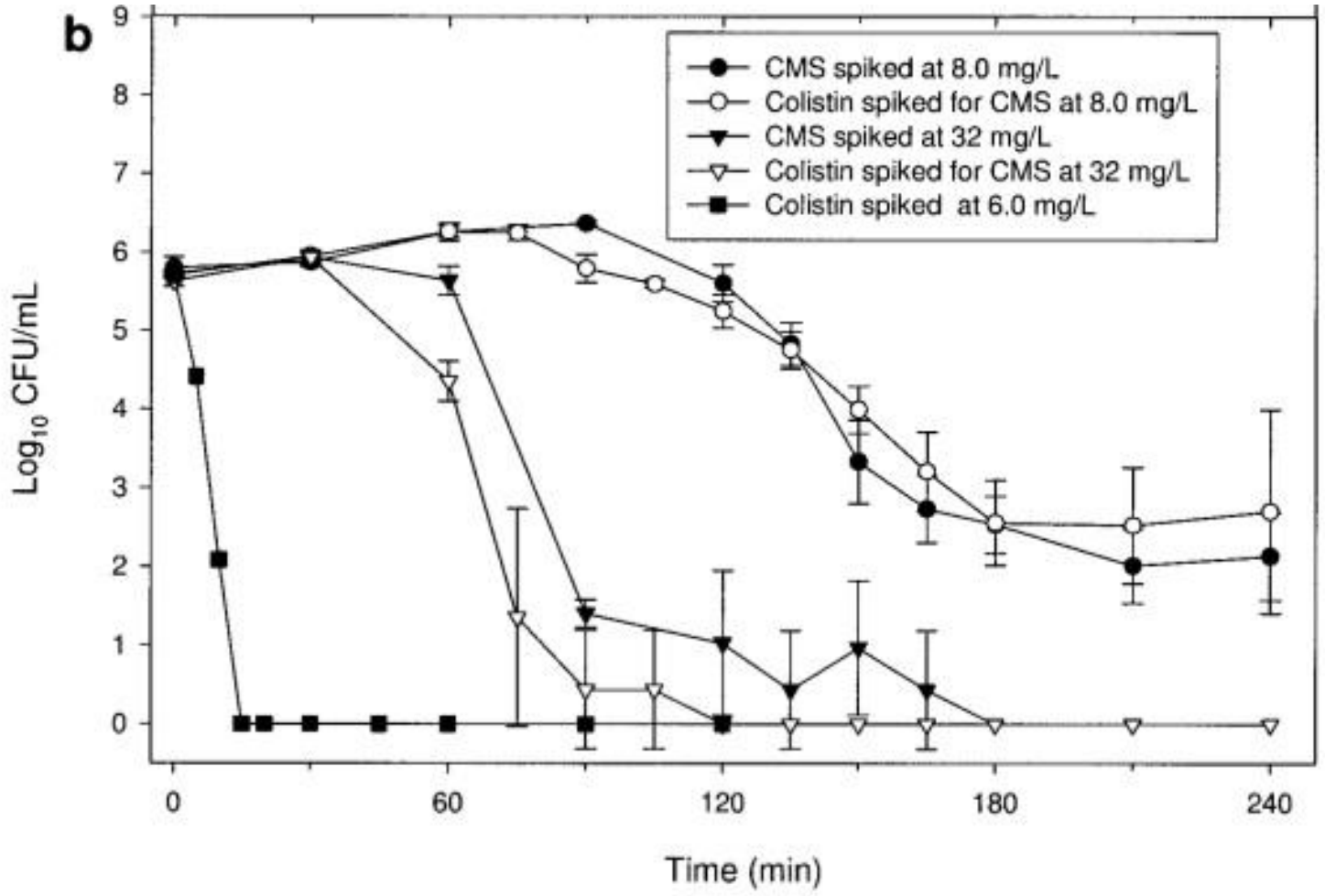
Colistin und Colistin methan Sulfonate



C entsteht langsam aus CMS
Offene Symbole: C nachgespielt

Bergen. AAC 2006;50:1953

Colistin und Colistin methan Sulfonate u. Ps. aeruginosa



Beginn des killings abhängig von Colistinpräsenz

Bergen. AAC 2006;50:1953

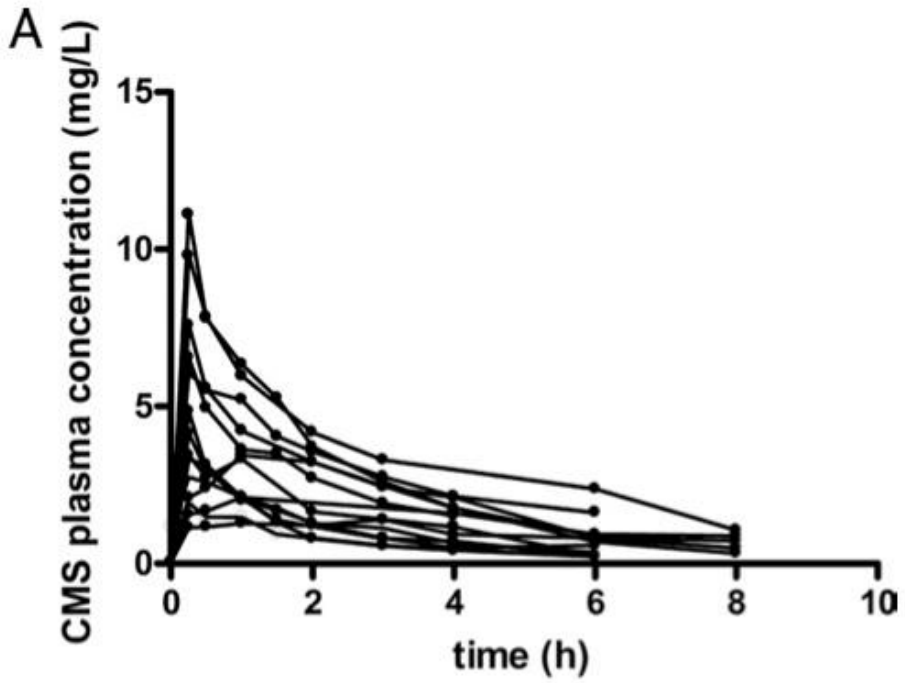
Colistin und Colistinmethansulfonat

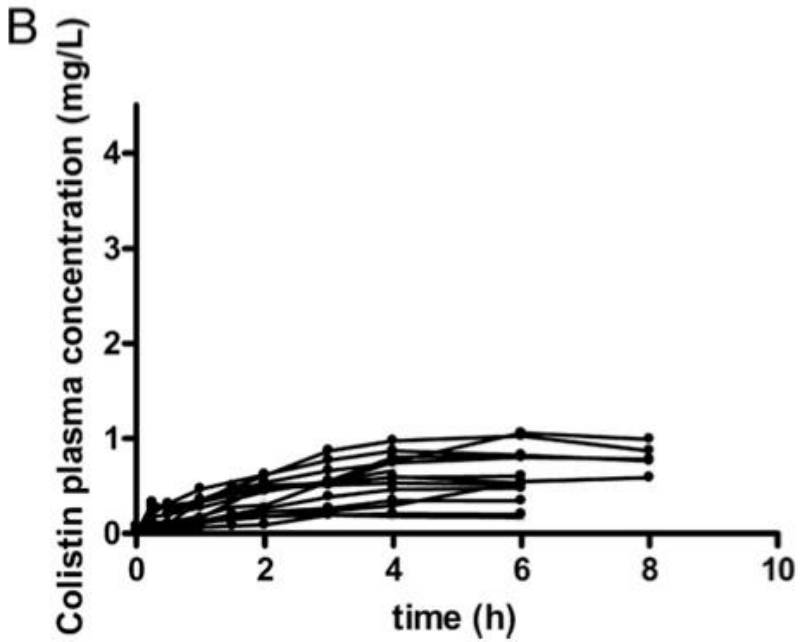
- 18 ICU Patienten
- 3x3Mio Einheiten (=3x240mg)
- Messung von Colistin und Colistinmethansulfonat nach 1. und 4. Infusion

- Modell für Dosis

Placouras AAC 2009;53:3430

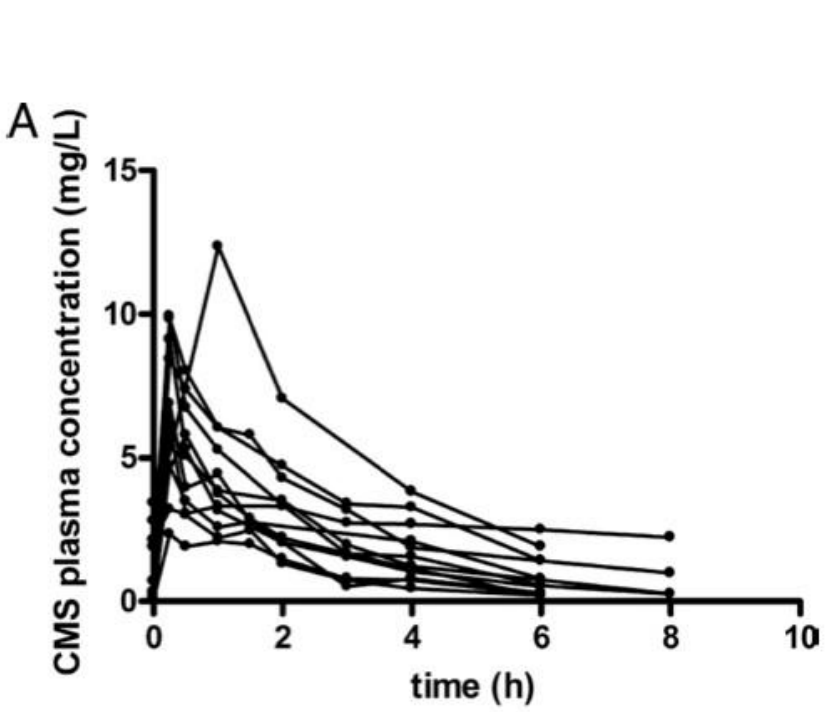
Colistin und Colistinmethansulfonat nach 1. Infusion

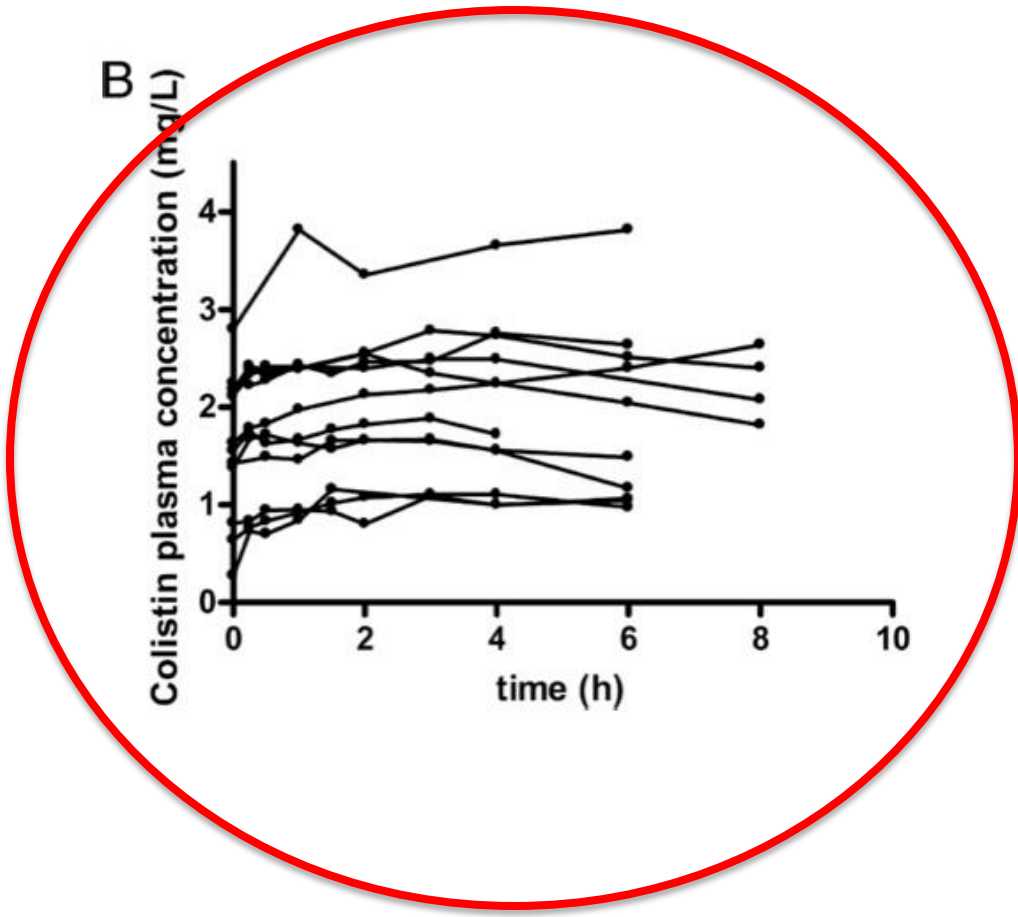




Placouras AAC 2009;53:3430

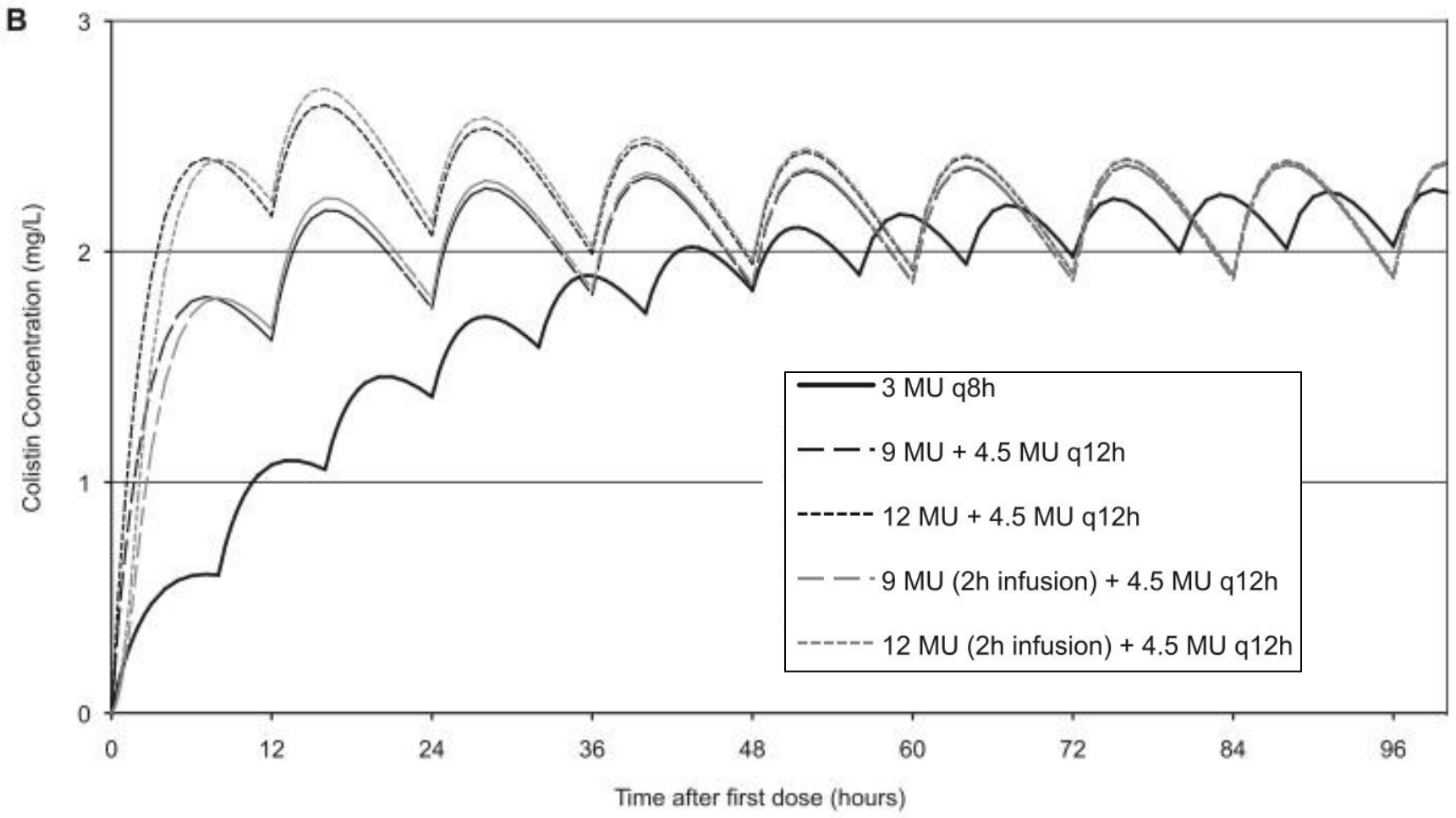
Colistin und Colistinmethansulfonat nach 4. Infusion





Placouras AAC 2009;53:3430

Colistin und Colistinmethansulfonat Modell



Placouras AAC 2009;53:3430

Colistin und Colistin Methan Sulfonate

- Loading dose
  - je mehr CMS gegeben wird, desto schneller entsteht Colistin mit bakterizider Wirkung
  - Zeitvorteil 4h (in vitro Daten) LIT 1
  - Zeitvorteil 2 Tage LIT 2

  - Loading dose 10-12 Mio Einheiten?? LIT 2

- Dosierintervall
  - Colistinmethansulfonate Halbwertszeit 2h
  - Colistin Halbwertszeit 14h, Kumulation

- Breakpoint ≤2mg/l passend?? LIT 2

Bergen. AAC 2006;50:1953
Placouras AAC 2009;53:3430

Colistin und Colistin Methan Sulfonate

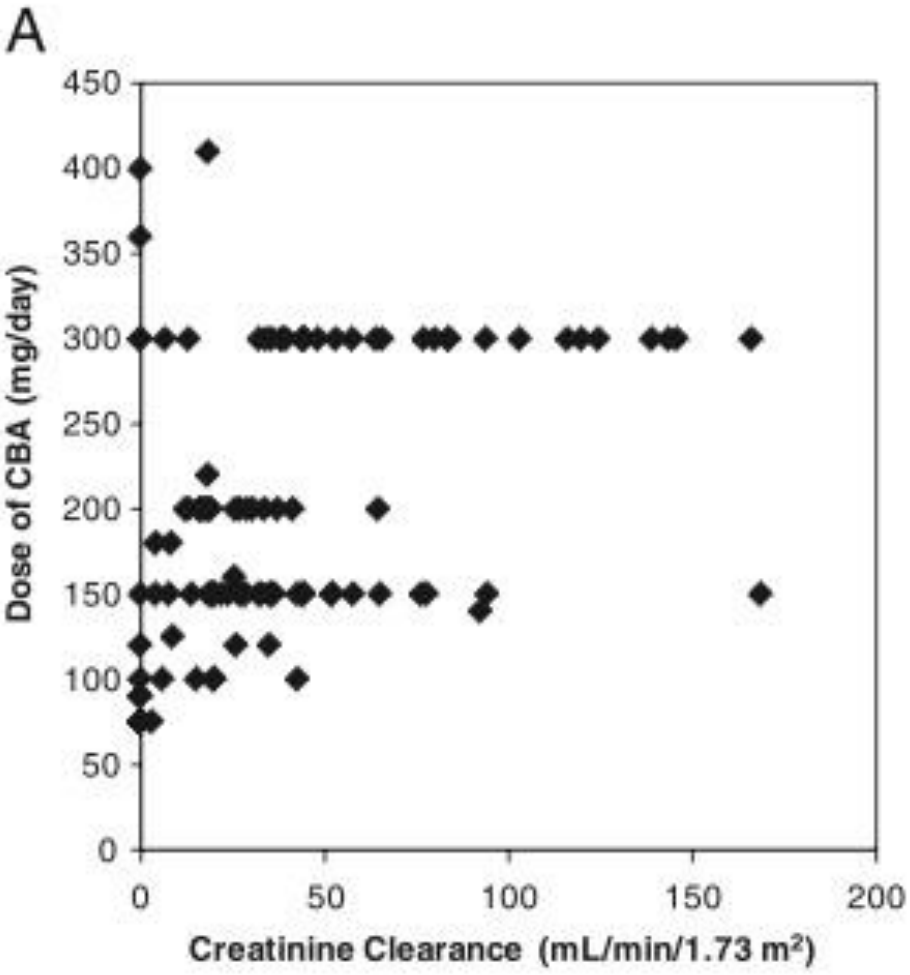
- 105 Patients with pneumonia and or bloodstream infection
- 12 on intermittant hemodialysis
- 4 on continuous renal replacement therapy

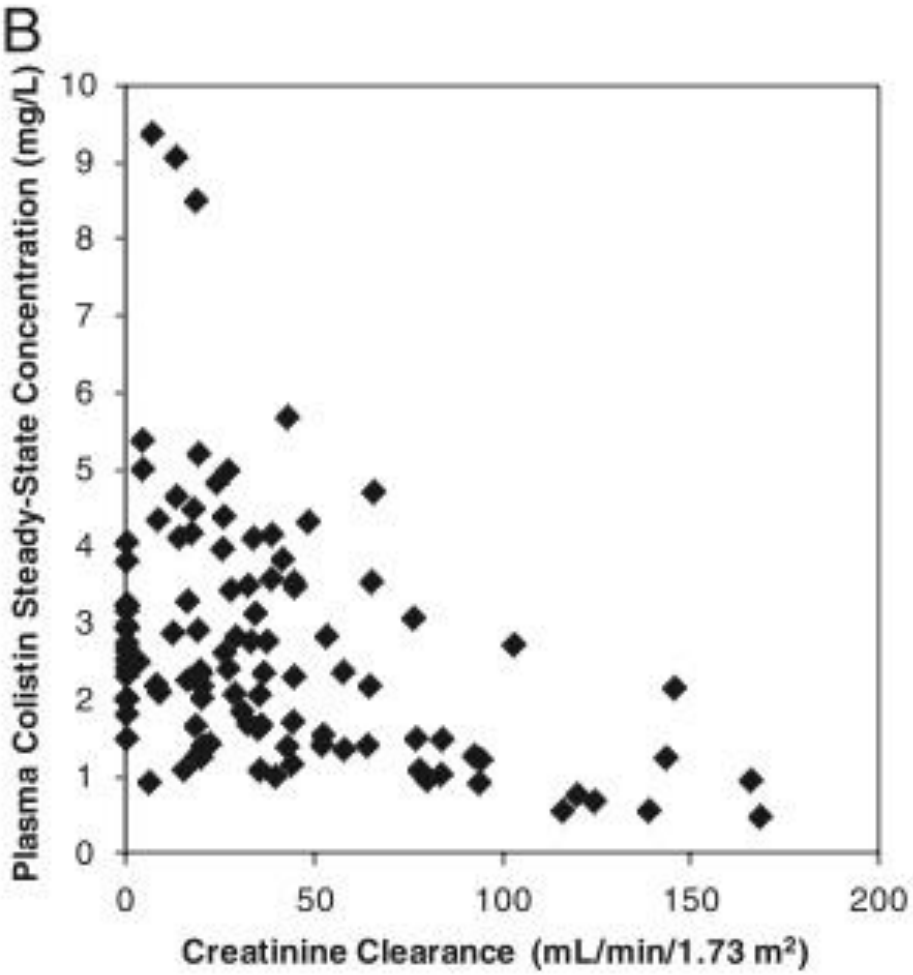
- Pharmakokinetics of Colistin and Colistin Methan Sulfonate

- Development of algorithm for dosage

Garonzik AAC 2011;50:3284–3294

Colistin und Colistin Methan Sulfonate





Garonzik AAC 2011;50:3284–3294

Colistin und Colistin Methan Sulfonate

Loading dose	All patient categories	Equation 9: Loading dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × 2.0 × body wt (kg).[c] See caveat in footnote *c*. First maintenance dose should be given 24 h later.
Maintenance dose	Not on renal replacement	Equation 10: Daily dose of CBA (mg) = colistin $C_{ss,avg}$ target[b] × (1.50 × CrCL + 30).[d] Recommended dosage intervals based on CrCL: <10 ml/min/1.73 m^2, every 12 h, 10-70 ml/min/1.73 m^2 every 12 (or 8) h, and >70 ml/min/1.73 m^2 every 12 (or 8) h. See important caveat in footnote *d*.

- Colistin Zielspiegel 2,5mg/l

Garonzik AAC 2011;50:3284–3294

Colistin und Colistin Methan Sulfonate

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- 55kg Patient mit CrCl 40ml/min/1,7m2
- Loading dose
  - 275mg Colistin base activity (=9Mio Einheiten)
- Ab Tag 2 (7 Mio Einheiten)
  - 2/3/2 Mio Einheiten

Garonzik AAC 2011;50:3284–3294

Colistin und Colistin Methan Sulfonate

- 89 patients not on renal replacement[LIT1]
  - 87/89 patients ≤ CMS maintenance dose of 300 mg CBA per day or less
  - 43/89 (48%) had a rise in serum creatinine of >50%
  - 27/43 (63%), levels remained elevated at the end of the study
  - these findings are similar to those reported for other studies[LIT2,3]

  - At this time, we do not recommend use of the algorithm for patients with CrCL of >70 ml/min/1.73 m2

LIT 1 Garonzik AAC 2011;50:3284–3294
LIT 2 Deryke. AAC 2010;54:4503–4505
LIT 3 Hartzell. CID 2009;48:1724–1728

Colistin und Colistin Methan Sulfonate

- In vitro Acinetobacter und Pseudomonas Infektionsmodell

Study (reference)	Strain	MIC (mg/liter)	>2 log kill
P. aeruginosa murine thigh infection (12)	19056	0.5	22.9
	PAO1	1	2.9
	ATCC 27853	1	2.9
P. aeruginosa murine lung infection (12)	19056	0.5	28.6
	PAO1	1	2.9
	ATCC 27853	1	2.9
A. baumannii murine thigh infection (13)	248-01-C.248	1	2.9
	N-16870.213	0.5	58.1
	ATCC 19606	1	2.9
A. baumannii murine lung infection (13)	248-01-C.248	1	2.9
	N-16870.213	0.5	0.0
	ATCC 19606	1	2.9

% killing

Garonzik AAC 2011;50:3284–3294

Colistin und Colistin Methan Sulfonate

- In vitro Acinetobacter und Pseudomonas Infektionsmodell

- „300mg Colistin base activity...

  ... would not be reliably effective against isolates with MICs greater than 0.5 mg/liter“

- Breakpoint ≤2mg/l ??

Garonzik AAC 2011;50:3284–3294
Deryke. AAC 2010;54:4503–4505
Hartzell. CID 2009;48:1724–1728

Colistin und Colistin Methan Sulfonate

- ...it appears that colistin might best be used as part of a highly active combination
- ...this is especially likely to be the case for patients with moderate to good renal function

Garonzik AAC 2011;50:3284–3294

Colistin und Colistin Methan Sulfonate

- Für die Praxis
  - Hohe Dosen (ca 10 Mio IE Tagesdosis)
  - Nephrotoxizität prüfen
  - Adaption an Nierenfunktion und Nierenersatztherapie
  - Colistin nur als Kombinationspartner

Carbapenem Resistenz

- Wirksame ABs
  - Tigecyclin
    - Carbapenem resistente E. coli meist empfindlich
    - Carbapenem resistente Klebsiellen oft intermediär od. resistent
    - Nicht bei Harnwegsinfektionen oder Bakteriämie

Livermore.
http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/12
40725984

Carbapenem Resistenz

- Wirksame ABs
  - Ev. Fosfomycin
    - Wirksam bei E. coli mit Carbapenemasen
    - Harnwegsinfektionen
    - „Borderline susceptibility“ bei Klebsiella spp.[LIT1]
      - Jedoch gute in vitro Wirksamkeit bei blaKPC [LIT 2]

Livermore.
http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1240725984
Endimiani AAC2009

Carbapenem Resistenz

- Wirksame ABs
  - Ev. Aztreonam
    - Stabil gegenüber IMP, VIM, NDM (Metallo BL)
    - Jedoch oft unwirksam wg. Co-Produktion von ESBL oder AmpC
    - Nicht stabil gegenüber OXA 48 und KPC

Livermore.
http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/12
40725984

Carbapenem Resistenz

- Ev. wirksame ABs
  - Temocillin in Ö nicht verfügbar, hohe MICs
  - Ceftazidim, Cefotaxim aktiv gegen CPE mit OXA-48, meist jedoch zusätzl. ESBL oder AmpC vorliegend
  - Carbapeneme bei low level Resistenz ev. wirksam
  - Aminoglycoside variabel, oft jedoch unwirksam
  - Chloramphenicol, Cipro, SXT meist unwirksam

Livermore. Internat Journal of Antimicrobial Agents 37 (2011) 415–419
Livermore.
http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/12947

Carbapenem resist. Acinetobacter

- In the kill-curve studies
  - azithromycin and rifampin were rapidly bactericidal
  - sulbactam was more slowly bactericidal
  - Trovafloxacin and doxycycline were bacteriostatic
  - none of the antimicrobials tested were bactericidal against all strains tested

- The synergy studies demonstrated that the combinations of sulbactam with azithromycin, rifampin, doxycycline, or trovafloxacin were generally additive or indifferent.

- Supported by a grant from Pfizer Inc.

Applemann. 2000;44:1035-1040

Carbapenem resist. Acinetobacter 2 Jahres-Zeiträume (A-D) in Chile

Table. *In vitro* activities of ampicillin, sulbactam and the ampicillin/sulbactam combination against 280 Acb clinical isolates

Antibiotic	Time period	MIC (mg/L)			Resistant isolates (%)[a]
		MIC_{50}	MIC_{90}	range	
Ampicillin	A	>512	>512	32–>512	100
	B	>512	>512	32–>512	97.4
	C	>512	>512	32–>512	95.6
	D	>512	>512	32–>512	98.4
Sulbactam	A	8	16	1–128	30.8
	B	16	32	2–128	40.1
	C	16	32	2–128	51.5
	D	16	64	2–128	54.7
Ampicillin/ sulbactam	A	8/4	16/8	1/0.5–16/8	0
	B	16/8	16/8	4/2–32/16	10.3
	C	16/8	32/16	4/2–128/64	36.8
	D	32/16	128/64	4/2–256/128	56.3

[a]According to the following MIC breakpoints for resistance recommended by the NCCLS:[6] ampicillin ≥32 mg/L; ampicillin/sulbactam ≥32/≥16 mg/L. As a breakpoint for sulbactam alone has not been recommended, the concentration recommended for the sulbactam in the combination, i.e. ≥16 mg/L, has been adopted.

Bello. JAC. 2000;45:712-13

Summary

Infektionen durch CPE und Co therapieren

- Wirksame ABs
  - Colistin
  - Tigecyclin
    - Nicht bei Pseudomonas
    - auch bei Harnwegsinfekten?
  - Ev. Fosfomycin
  - Ev. Aztreonam
  - Ev. Aminoglycoside
  - Ev. Chinolone
  - Ev. Temocillin
  - Ev. Chloramphenicol
  - Ev. Azithromycin
  - Ev. Sulbactam
  - Ev. Kombi mit Rifampicin

Kanj. Mayo Clin Proc. 2011;86(3):250-259
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http://www.hpa.org.uk/webc/HPAwebFile/HPA