Die Qual der Wahl – Fluorchinolone oder Aminoglykoside für die empirische Kombinationstherapie?

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GUIDELINES

Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock, 2012

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	2008	2012	Grading
D. Antibiotikatherapie			
1.a. Administration of effective iv ABs within the 1. hour of recognition of septic shock	1B	1B	
1.b. Administration of effective iv ABs within the 1. hour of recognition of severe sepsis	1D	1C	↑
2.a. Initial empiric anti-infective therapy of one or more drugs that have activity against all likely pathogens and that penetrate in adequate concentrations into tissues presumed to be the source of sepsis	1B	1B	
2.b. Antimicrobial regimen should be reassessed daily for potential deescalation	1C	1B	↑
3. Use of biomarkers to assist the clinician in the discontinuation of empiric antibiotics in patients who initially appeared septic, but have no subsequent evidence of infection	nn	2C	↑
4.a. Combination empirical therapy for			
neutropenic patients with severe sepsis	2D	2B	↑
for pts with difficult to treat, MDR bacterial pathogens f.e. Acinetobacter/Pseudomonas	nn	2B	↑
For pts with severe infections associated with respiratory failure and septic shock, combination therapy with an extended spectrum beta-lactam and either an aminoglycoside or a fluoroquinolone is for P. aeruginosa bacteremia	2D	2B	↑
A combination of beta-lactam and macrolide for patients with septic shock from bacteremic Streptococcus pneumoniae infections	nn	2B	↑
4.B Empiric combination therapy not be for more than 3–5 days. De-escalation to the most appropriate single therapy as soon as the susceptibility profile is known	2D	2B	↑
5. Duration of therapy typically 7–10 days; longer courses may be appropriate in pts with a slow clinical response, undrainable foci of infection, bacteremia with S. aureus; some fungal and viral infections or immunologic deficiencies, including neutropenia	1D	2C	↓
6. Antiviral therapy initiated as early as possible in patients with severe sepsis or septic shock of viral origin	nn	2C	↑
7. Antimicrobial agents should not be used in patients with severe inflammatory states determined to be of noninfectious cause	1D	UG	↑

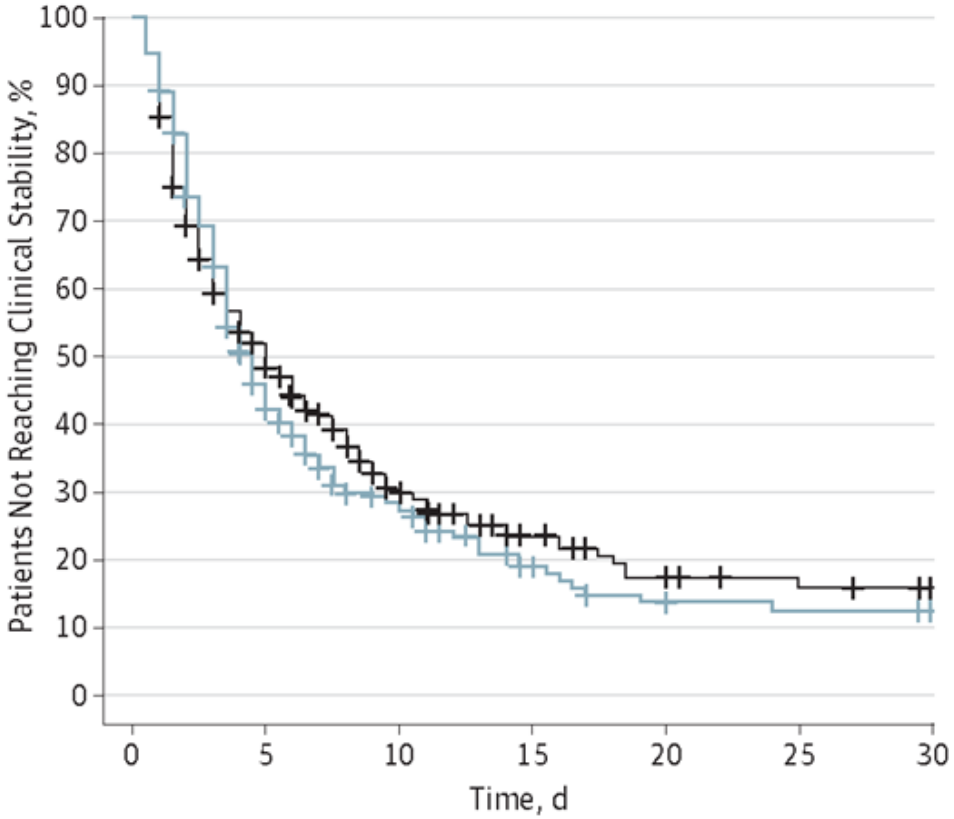
Why combination therapy?

- **Synergistic antibiotic effects**
  - **In vitro – yes**
  - **In vivo – only in specific circumstances**
  - **Increase of bactericidal effect?**
- **Gap Closing**
  - **For susceptible pathogens – no**
  - **For multidrug resistant pathogens – may be**

Schweregradklasse	Primärtherapie		Alternativtherapie
Leichte Pneumonie ohne Komorbidität (orale Therapie)	Amoxicillin		Moxifloxacin, Levofloxacin Clarithromycin, Azithromycin Doxycyclin
Leichte Pneumonie mit Komorbidität (orale Therapie) - chronische Herzinsuffizienz - ZNS-Erkrankungen mit Schluckstörungen - Schwere COPD, Bronchiektasen - Bettlägerigkeit, PEG	Amoxicillin/Clavulansäure		Moxifloxacin, Levofloxacin
Mittelschwere Pneumonie (in der Regel Sequenztherapie)	Amoxicillin/ Clavulansäure Ampicillin /Sulbactam Cefuroxim Ceftriaxon Cefotaxim	+/-Makrolid für 3 Tage +/-Makrolid für 3 Tage +/-Makrolid für 3 Tage +/-Makrolid für 3 Tage +/-Makrolid für 3 Tage	Moxifloxacin, Levofloxacin
Schwere Pneumonie (Beginn immer i.v., Sequenztherapie prinzipiell möglich)	Piperacillin/ Tazobactam Ceftriaxon Cefotaxim	jeweils + Makrolid für 3 Tage	Moxifloxacin, Levofloxacin (Monotherapie nicht bei septischem Schock)

β-Lactam Monotherapy vs β-Lactam-Macrolide Combination Treatment

Garin et al. JAMA Intern Med. 2014;174(12):1894-1901



- Open-label, multicenter, noninferiorit, randomized trial form Jan 2009- 2013
- Moderately severe CAP
- Beta- lactam mono vs. Beta-lactam combination
- 580 patients
- Endpoint: Clinical stability (heart rate <100/min, blood pressure > 90mmHg, temperature < 38°C, respiratory rate < 24/min and oxygen saturation > 90%) at day seven
- Noninferiority of Beta- lactam expect in patients with atypical pathogens and in PSI category IV

β-Lactam Monotherapy vs β-Lactam-Macrolide Combination Treatment

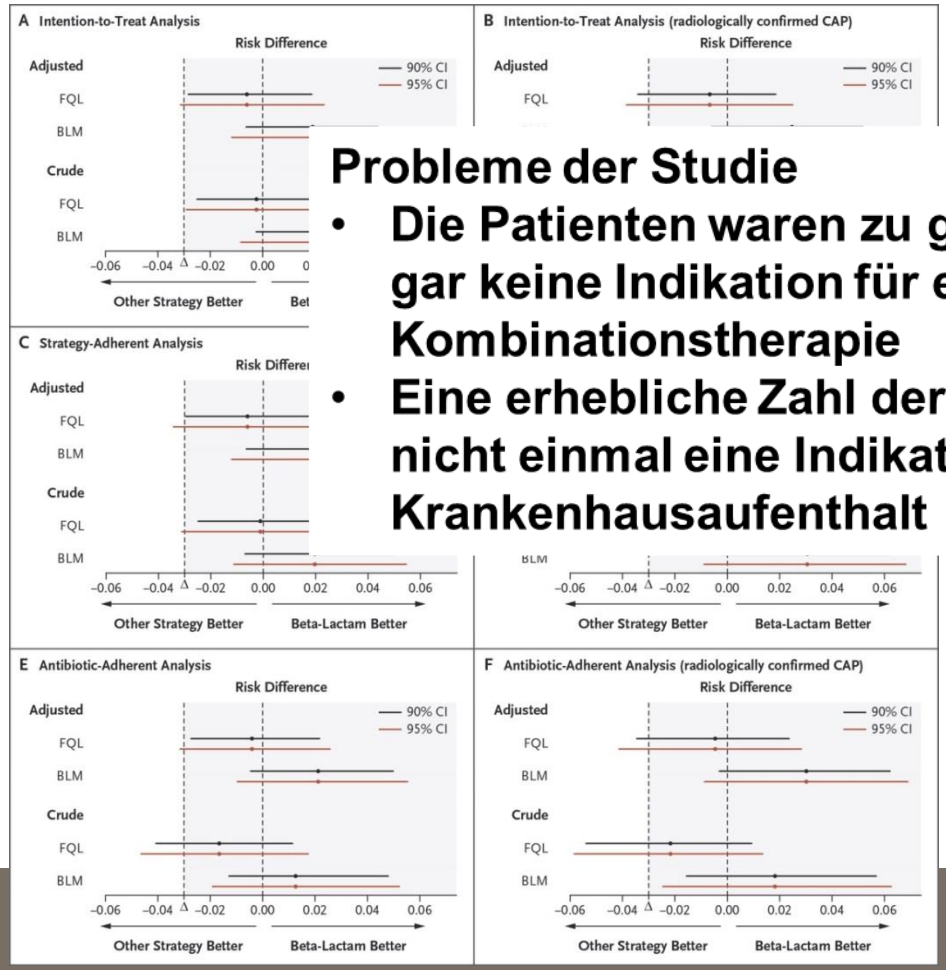
Garin et al. JAMA Intern Med. 2014;174(12):1894-1901

Adjusted and stratified analysis for the primary outcome

Reference category: combination therapy	Hazard ratio (95% CI)	P value
Unadjusted	0·93 (0·76-1·13)	0·46
Adjusted for age and PSI category	0·92 (0·76-1·12)	0·41
Stratified		
Atypical	0·33 (0·13-0·83)	0·02
Non-atypical	0·99 (0·80-1·22)	0·93
	0·03 for interaction	
PSI category IV	0·81 (0·59-1·10)	0·18
PSI category I-III	1·06 (0·82-1·36)	0·66
	0·18 for interaction	

Antibiotic Treatment Strategies for Community-Acquired Pneumonia in Adults

Postma DF et al. N Engl J Med 2015;372:1312-1323



Probleme der Studie

- **Die Patienten waren zu gesund und hatten gar keine Indikation für eine Kombinationstherapie**
- **Eine erhebliche Zahl der Patienten hatte nicht einmal eine Indikation für einen Krankenhausaufenthalt**

- Cluster- randomized crossover trial

f beta-lactam macrolide vs es

lly suspected to non-ICU ctam monotherapy was noninferior with betalactam-macrolide or fluorochinolone monotherapy with regard to 90-day mortality

Table 2. Baseline Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Antibiotic Treatment Strategy		
	Beta-Lactam (N=656)	Beta-Lactam–Macrolide (N=739)	Fluoroquinolone (N=888)
Median age (interquartile range) — yr	70 (60–79)	70 (59–80)	71 (59–79)
Male sex — no. (%)	381 (58.1)	431 (58.3)	505 (56.9)
Median duration of symptoms (interquartile range) — days	3 (1–7)	3 (1–7)	3 (1–7)
Received antibiotics before admission — no./total no. (%)	219/637 (34.4)	227/721 (31.5)	303/873 (34.7)
Current smoker — no./total no. (%)	109/627 (17.4)	154/723 (21.3)	196/872 (22.5)
Past smoker — no./total no. (%)	379/627 (60.4)	398/723 (55.0)	490/872 (56.2)
Received influenza vaccination — no./total no. (%)	453/624 (72.6)	466/700 (66.6)	572/847 (67.5)
Received pneumococcal vaccination — no./total no. (%)			
PPSV23	16/594 (2.7)	18/671 (2.7)	13/822 (1.6)
PCV13	19/656 (2.9)	7/739 (0.9)	10/888 (1.1)
Dependency in ADL — no./total no. (%)†	199/637 (31.2)	200/714 (28.0)	257/870 (29.5)
Had one or more hospital stays in the previous year — no./total no. (%)	271/653 (41.5)	298/722 (41.3)	351/881 (39.8)
Had coexisting condition — no. (%)			
Cardiovascular disease	153 (23.3)	154 (20.8)	172 (19.4)
COPD or asthma	260 (39.6)	281 (38.0)	377 (42.5)
Other chronic pulmonary disease	64 (9.8)	97 (13.1)	61 (6.9)
Diabetes mellitus	118 (18.0)	101 (13.7)	161 (18.1)
Cancer‡	106 (16.2)	124 (16.8)	151 (17.0)
HIV/AIDS — no. (%)	3 (0.5)	6 (0.8)	6 (0.7)
Chronic renal failure or nephrotic syndrome	10 (1.5)	14 (1.9)	7 (0.8)
Receiving immunosuppressive therapy — no. (%)	59 (9.0)	57 (7.7)	93 (10.5)
PSI score§¶		84.6±29.0	84.8±27.8	85.4±28.5
Median CURB-65 score (interquartile range)§		1 (1–2)	1 (1–2)	1 (1–2)
Had radiologically confirmed CAP — no. (%)	506 (77.1)	566 (76.6)	665 (74.9)
Blood culture obtained — no. (%)	508 (77.4)	559 (75.6)	670 (75.5)
Sputum culture obtained — no. (%)	306 (46.6)	347 (47.0)	390 (43.9)
PUAT performed — no. (%)	504 (76.8)	582 (78.8)	711 (80.1)
LUAT performed — no. (%)	492 (75.0)	574 (77.7)	668 (75.2)

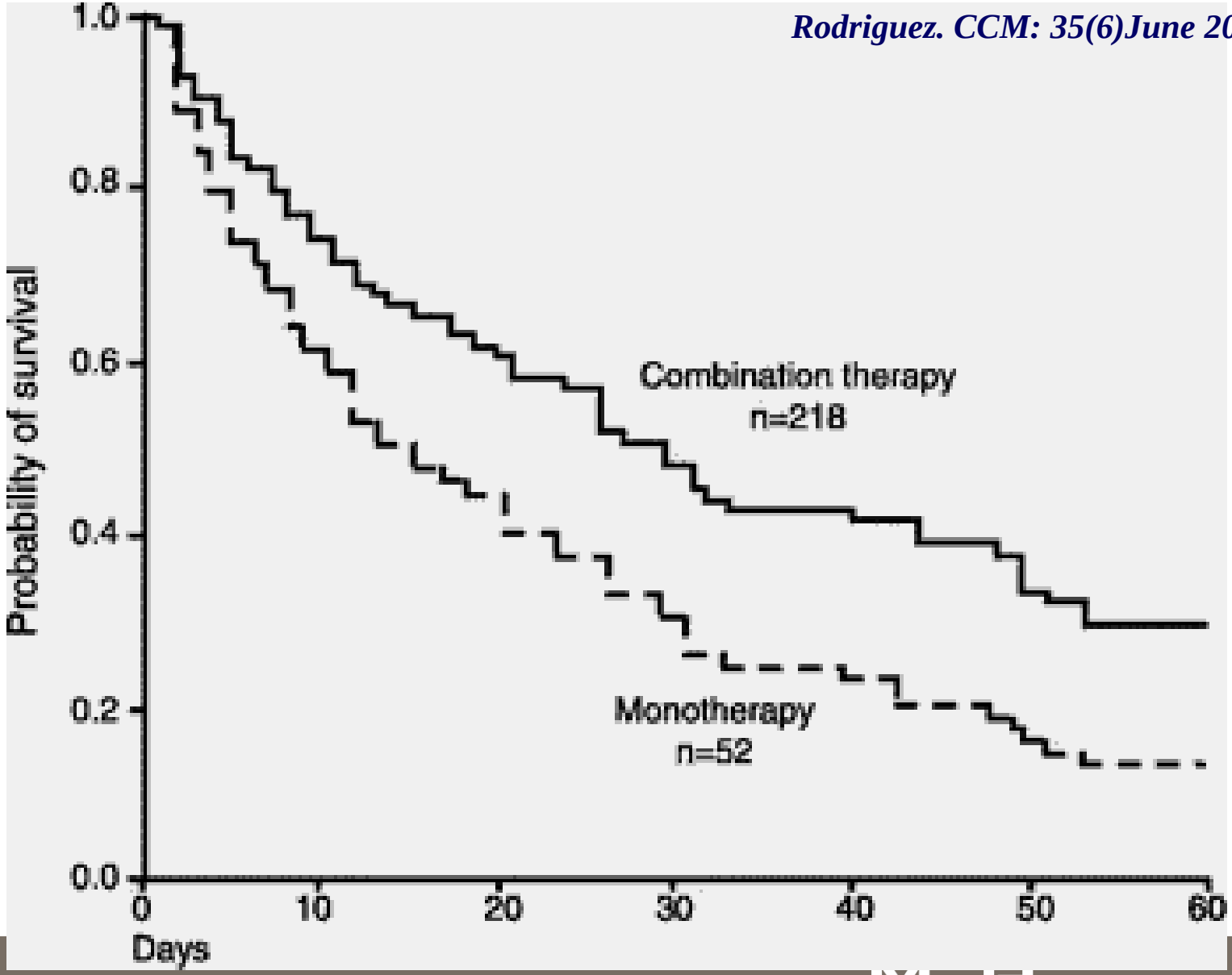
Postma DF et al.
N Engl J Med 2015;372:1312-1323

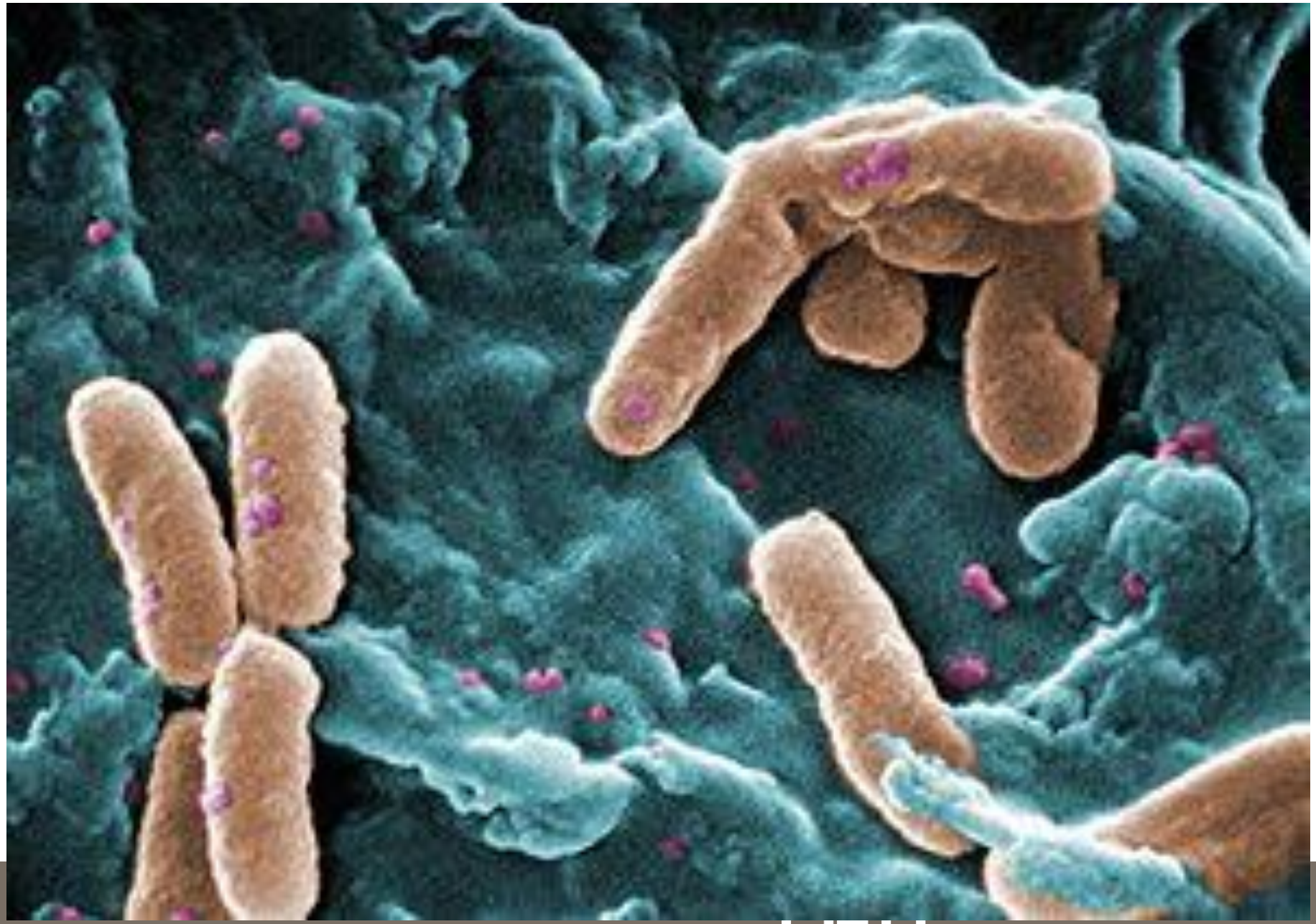
CAP – Septic Shock

- Secondary analysis of a prospective observational study (Bodi et al. CID 2005; 41)
- Antibiotics for minimally two days
- Monotherapy: ß-Lactams (Amoxy/Clav, FQ)
- Combination Therapy: ß-Lac/Macrolid or ß-Lac/FQ
- Inadaequate Therapy significantly increase with Monotherapy (31% vs 13%)
- Higher mortality in patients with septic shock with Monotherapy vs. Combination Therapy (HR 1.73)
- Higher mortality in patients with septic shock with adaequate Monotherapy vs adaequate Combination Therapy (HR 1,64)

Rodriguez et al. CCM 2007; 35

Rodriguez. CCM: 35(6)June 2007: 1493-1498





ß-Lactam Monotherapy vs. ß-Lactam-Aminoglycosid Combination Therapy in Sepsis: A Metaanalysis

Paul M.BMJ 2004; 328: 668

	N Studies	N Patients	ß-Mono vs. ß-AG Combi
Total Mortality	**43**	**5527**	**0,90 (0,77 - 1,06)**
Treatment Failure	**63**	**6616**	**0,87 (0,78 - 0,97)**
Bakterial Superinfection	**27**	**3085**	**0,79 (0,59 - 1,06)**
Adverse Events	**39**	**4945**	**0,91 (0,80 - 1,04)**
Nephrotoxicity	**45**	**5213**	**0,36 (0,28 - 0,47)**

Mono- vs. Combination Therapy for VAP

- **Randomised controlled trial in 740 pts**
  - **Mechanical ventilated**
  - **VAP suspected after 4 days in the ICU**
  - **Pts. with known Pseudomonas or MRSA excluded**
- **Meropenem 1g tid + Ciprofloxacin 400 mg bid**
- **vs. Meropenem alone**
- **Outcome Parameters:**
  - **No difference in 28-day mortality (RR 1.05, p=0.74)**

	Combination Therapy (n = 369)	Monotherapy (n = 370)	All (n = 739)
Age, yrs	59.1 ± 17.9	58.9 ± 17.7	59.0 ± 17.8
Female sex, no. of patients (%)	108 (29.3)	119 (32.2)	227 (30.7)
APACHE II score	19.9 ± 6.4	20.0 ± 6.2	20.0 ± 6.3
APACHE II score >24 (%)	86 (23.3)	84 (22.7)	170 (23.0)
Admission category, no. of patients (%)			
Medical	231 (62.6)	219 (59.2)	450 (60.9)
Surgical	138 (37.4)	151 (40.8)	289 (39.1)
Primary diagnosis at Admission, no. of patients (%)			
Cardiovascular disorder	86 (23.3)	95 (25.7)	181 (24.5)
Trauma	95 (25.7)	92 (24.9)	187 (25.3)
Respiratory disorder	67 (18.2)	61 (16.5)	128 (17.3)
Neurologic disorder	46 (12.5)	52 (14.1)	98 (13.3)
Gastrointestinal disorder	29 (7.9)	31 (8.4)	60 (8.1)
Other condition	26 (7.0)	22 (5.9)	48 (6.5)
Sepsis	16 (4.3)	13 (3.5)	29 (3.9)
Renal disorder	4 (1.1)	4 (1.1)	8 (1.1)
No. of comorbidities, no. of patients (%)			
0	105 (28.5)	114 (30.8)	219 (29.6)
1	100 (27.1)	86 (23.2)	186 (25.2)
2	73 (19.8)	72 (19.5)	145 (19.6)
3	91 (24.7)	98 (26.5)	189 (25.6)
Baseline Pao_2/Fio_2 at enrollment	223 ± 87.5	210 ± 77.1	217 ± 82.7
Multiorgan dysfunction score at day 1	5.4 ± 2.9	5.8 ± 3.0	5.6 ± 3.0
Pretest likelihood of ventilator associated pneumonia, no. of patients (%)			
High	180 (48.8)	159 (43.0)	339 (45.9)
Moderate	139 (37.7)	154 (41.6)	293 (39.6)
Low	50 (13.6)	57 (15.4)	107 (14.5)
No. of days in ICU before enrollment	8.0 ± 4.9	7.8 ± 5.5	7.9 ± 5.2
Time from start of mechanical ventilation to enrollment	7.8 ± 4.9	7.7 ± 5.7	7.7 ± 5.3
Use of antibiotics within 3 days before randomization			
None	131 (35.5)	140 (37.8)	271 (36.7)
Antibiotics in use but initiated beforehand	136 (36.9)	116 (31.4)	252 (34.1)
New antibiotics initiated	102 (27.6)	114 (30.8)	216 (29.2)

Heyland D. CCM 2008; 36: 737-44

ORIGINAL CONTRIBUTION

ONLINE FIRST

Effect of Empirical Treatment With Moxifloxacin and Meropenem vs Meropenem on Sepsis-Related Organ Dysfunction in Patients With Severe Sepsis

A Randomized Trial

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Context Early appropriate antimicrobial therapy leads to lower mortality rates associated with severe sepsis. The role of empirical combination therapy comprising at least 2 antibiotics of different mechanisms remains controversial.

Objective To compare the effect of moxifloxacin and meropenem with the effect of meropenem alone on sepsis-related organ dysfunction.

Design, Setting, and Patients A randomized, open-label, parallel-group trial of 600 patients who fulfilled criteria for severe sepsis or septic shock (n=298 for monotherapy and n=302 for combination therapy). The trial was performed at 44 intensive care units in Germany from October 16, 2007, to March 23, 2010. The number of evaluable patients was 273 in the monotherapy group and 278 in the combination therapy group.

Interventions Intravenous meropenem (1 g every 8 hours) and moxifloxacin (400 mg every 24 hours) or meropenem alone. The intervention was recommended for 7 days and up to a maximum of 14 days after randomization or until discharge from the intensive care unit or death, whichever occurred first.

Main Outcome Measure Degree of organ failure (mean of daily total Sequential Organ Failure Assessment [SOFA] scores over 14 days; score range: 0-24 points with higher scores indicating worse organ failure); secondary outcome: 28-day and 90-day all-cause mortality. Survivors were followed up for 90 days.

Results Among 551 evaluable patients, there was no statistically significant difference in mean SOFA score between the meropenem and moxifloxacin group (8.3 points; 95% CI, 7.8-8.8 points) and the meropenem alone group (7.9 points; 95% CI, 7.5-8.4 points) ($P=.36$). The rates for 28-day and 90-day mortality also were not statistically significantly different. By day 28, there were 66 deaths (23.9%; 95% CI, 19.0%-29.4%) in the combination therapy group compared with 59 deaths (21.9%; 95% CI, 17.1%-27.4%) in the monotherapy group ($P=.58$). By day 90, there were 96 deaths (35.3%; 95% CI, 29.6%-41.3%) in the combination therapy group compared with 84 deaths (32.1%; 95% CI, 26.5%-38.1%) in the monotherapy group ($P=.43$).

Conclusion Among adult patients with severe sepsis, treatment with combined meropenem and moxifloxacin compared with meropenem alone did not result in less organ failure.

Trial Registration clinicaltrials.gov Identifier: NCT00534287

JAMA. 2012;307(22):doi:10.1001/jama.2012.5833 www.jama.com

INAPPROPRIATE INITIAL ANTIMICROBIAL therapy (defined as an antimicrobial regimen that lacks in vitro activity against the isolated organisms responsible for the infection) is associated with increased mortality

Author Affiliations and a list of the German Study Group Competence Network Sepsis Investigators appear at the end of this article.
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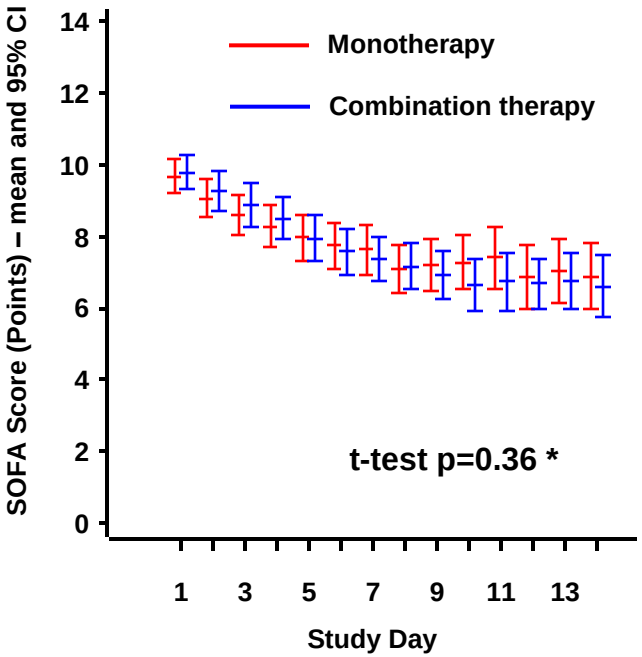
FM Brunkhorst, M Oppert, G Marx and coauthors

Effect of Empirical Treatment With Moxifloxacin and Meropenem vs Meropenem on Sepsis-Related Organ Dysfunction in Patients With Severe Sepsis: A Randomized Controlled Trial

Published online May 21, 2012

Organ Dysfunction (SOFA Score)

Intention-to-treat population



Patients evaluable:

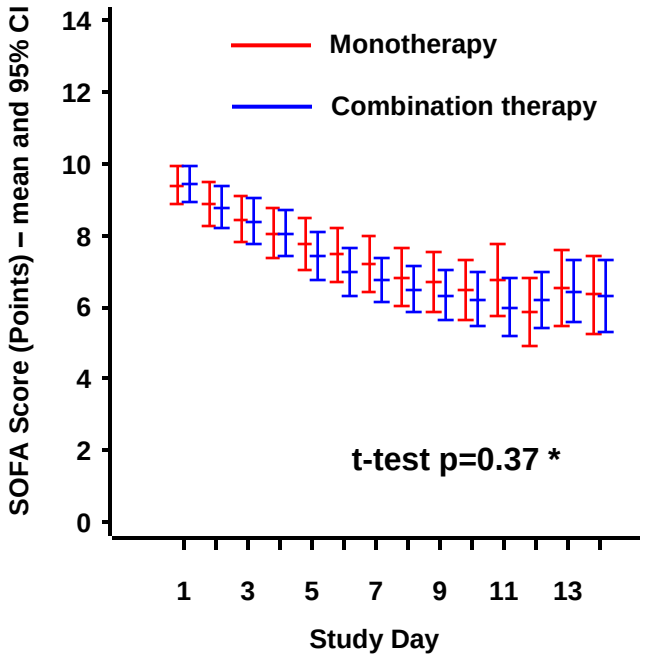
Monotherapy

249 212 167 137 124 103 89

Combination therapy

255 209 179 153 125 95 81

Per-protocol population



Patients evaluable

Monotherapy

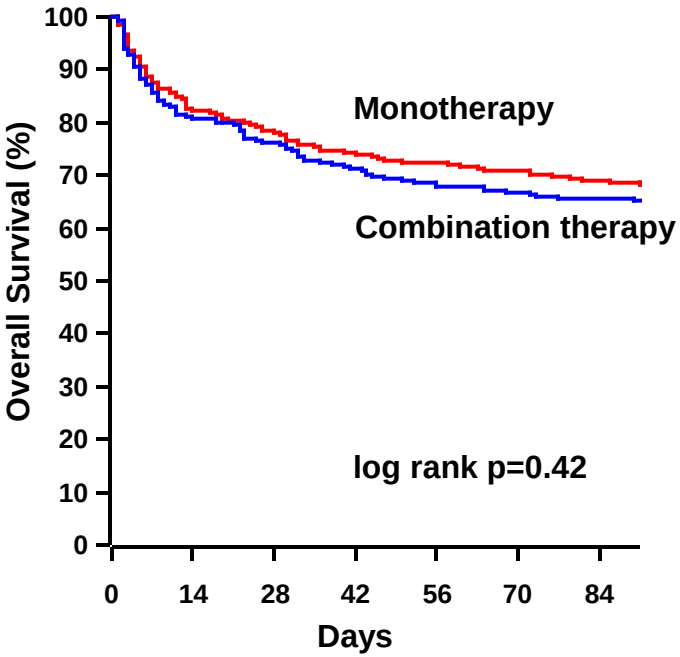
181 156 122 96 88 71 63

Combination therapy

198 165 141 119 96 71 57

Overall Survival

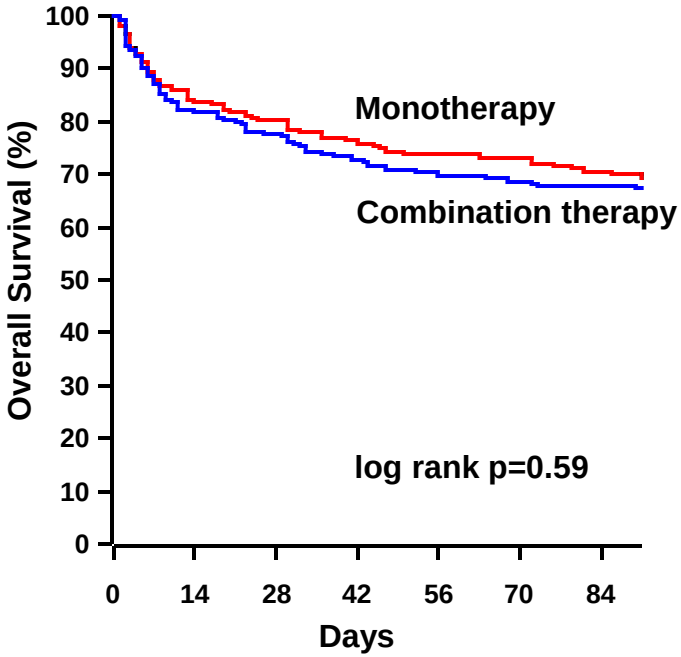
Intention-to-treat population



Patients at risk:

Monotherapy	273	222	211	193	188	184	179
Combination therapy	276	224	210	193	186	180	177

Per-protocol population

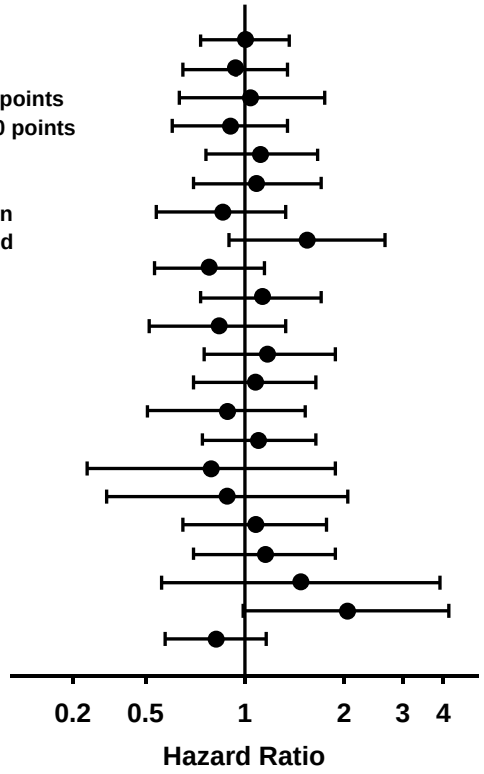


Patients at risk:

Monotherapy	199	164	156	143	138	137	132
Combination therapy	214	176	166	155	150	146	144

Subgroup Analyses - Mortality

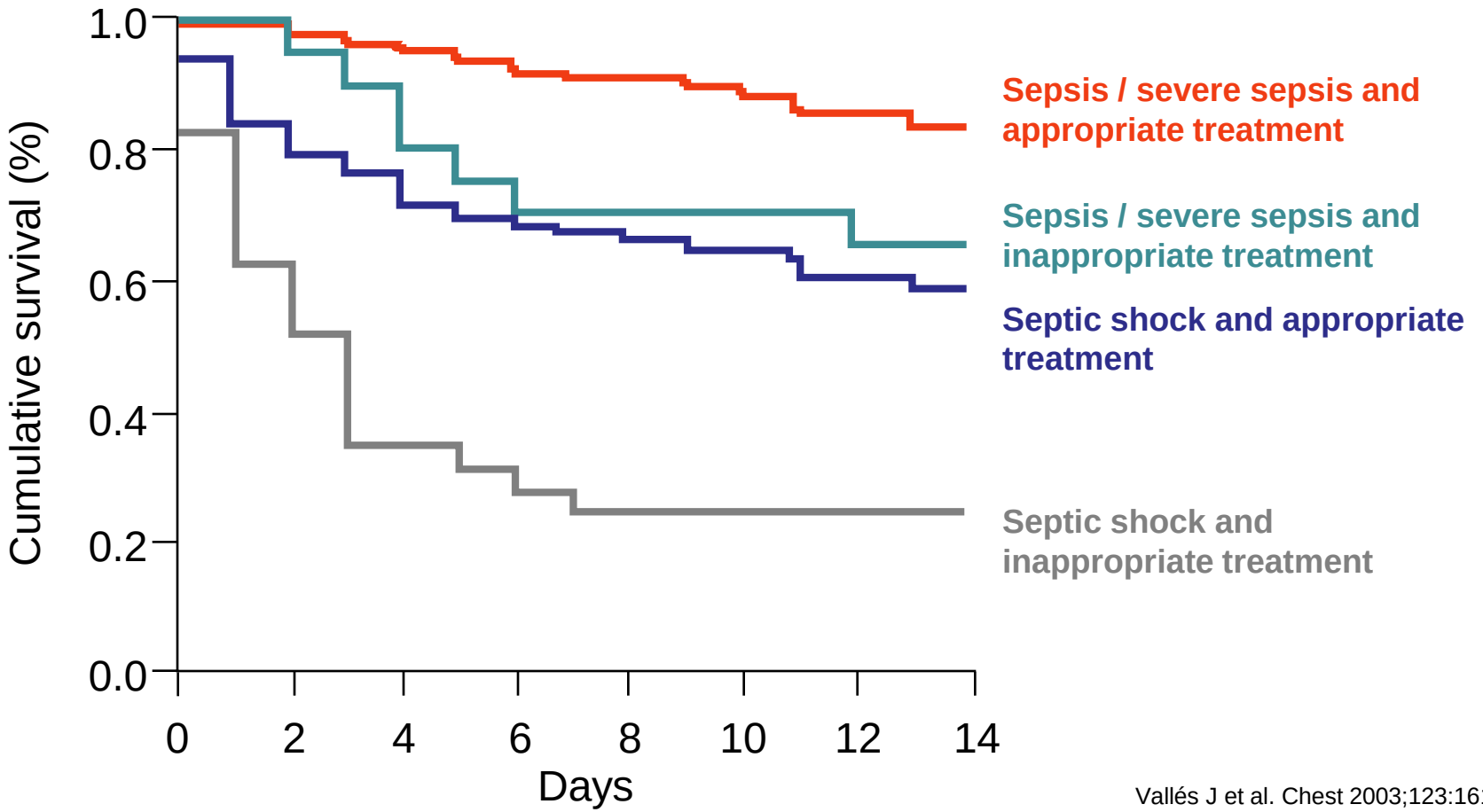
Adjusted proportional hazard models for the effect of addition of moxifloxacin on overall survival



	Monotherapy		Combination Therapy			
	No.	Death Cases	No.	Death Cases	adjusted HR (95% CI)	p-value
Intention to treat	273	85	276	96	1.00 (0.73; 1.36)	0.986
Per protocol set	199	59	214	70	0.94 (0.65; 1.35)	0.720
SOFA score at baseline <= 9 points	141	37	153	43	1.05 (0.63; 1.74)	0.864
SOFA score at baseline >= 10 points	132	48	123	53	0.90 (0.60; 1.34)	0.604
Study treatment >= 4 days	206	57	209	61	1.12 (0.76; 1.66)	0.572
Nosocomial infection	137	43	135	46	1.09 (0.70; 1.69)	0.710
Community acquired infection	136	42	141	50	0.84 (0.54; 1.32)	0.456
Microbiologically documented	97	32	98	28	1.54 (0.89; 2.66)	0.125
Clinically suspected	176	53	178	68	0.78 (0.53; 1.15)	0.209
Surgical patients	146	47	162	50	1.11 (0.73; 1.71)	0.618
Medical patients	127	38	114	46	0.82 (0.51; 1.32)	0.425
Gram-negative infection	149	47	120	46	1.19 (0.75; 1.88)	0.464
Gram-positive infection	140	43	155	53	1.07 (0.69; 1.64)	0.767
Bacteremic infection	90	30	93	37	0.88 (0.51; 1.52)	0.639
Non-bacteremic infection	183	55	183	59	1.10 (0.74; 1.63)	0.652
Gram-negative bacteremia	40	12	33	19	0.79 (0.33; 1.89)	0.597
Gram-positive bacteremia	49	14	58	15	0.88 (0.38; 2.06)	0.774
Pneumonia	105	32	119	38	1.07 (0.64; 1.77)	0.799
Intraabdominal	99	37	110	40	1.15 (0.70; 1.88)	0.591
Urogenital	39	14	25	8	1.48 (0.56; 3.92)	0.434
Severe Sepsis	74	18	84	20	2.01 (0.98; 4.12)	0.055
Septic Shock	199	67	192	76	0.81 (0.57; 1.16)	0.245

Less is more
Robert Browning.
Men and
Women.1855

Inadequate therapy as a risk factor for sepsis mortality



Vallés J et al. Chest 2003;123:1615-24

Combination versus montherapy for gram negative bacteremia

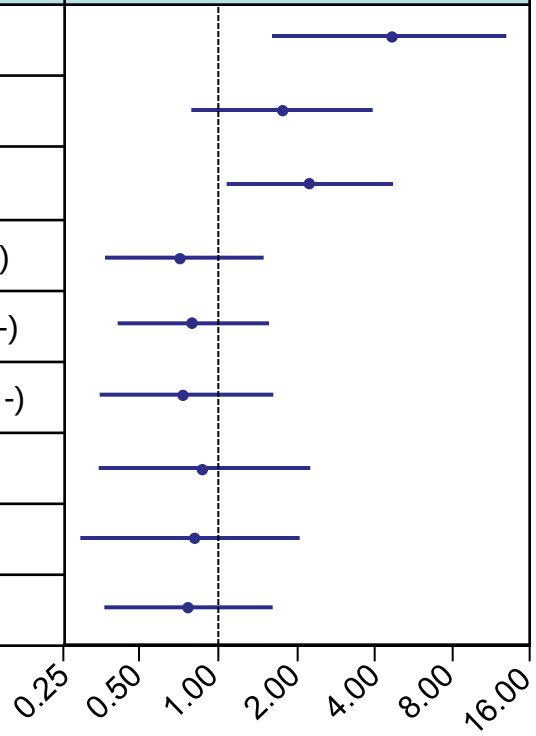
Micek ST et al. Antimicrob Agents Chemother. 2010 May;54(5):1742-8.

- **Retrospective analysis of 760 patients with severe sepsis/septic shock associated with Gram-negative bacteremia**
- **238 (31.3%) patients received inappropriate initial antimicrobial**
- **therapy (IIAT)**
- **Hospital mortality rate was statistically greater among patients receiving IIAT compared to those initially treated with an appropriate antibiotic regimen (51.7% versus 36.4%; *P* < 0.001).**

Antibiotic	% Susceptible to at least one antibiotic plus:		
	None	Ciprofloxacin	Gentamicin
Cefepime	83.4	86.4	89.9
Imipenem or meropenem	89.7	92.4	94.2
Piperacillin-tazobactam	79.6	87.0	91.4

Mono- vs combination therapy for VAP

	Combination therapy (n=39)	Monotherapy (n=17)	Combination / monotherapy RR (95% CI)
Adequacy of empirical therapy, n (%)[a]	32 (84.2)	3 (18.8)	
Clinical resolution at 28 days, n (%)	20 (51.3)	5 (29.4)	
Microbiological resolution at 28 days, n (%)[b]	25 (64.1)	5 (29.4)	
Duration of mechanical ventilation, days (IQR)[c]	10.7 (3.3, -)	15.0 (9.3, -)	
Duration of ICU stay, days (IQR)[c]	14.2 (8.1, -)	21.2 (14.1, -)	
Duration of hospital stay, days (IQR)[c]	55.0 (33.0, -)	111.4 (27.8, -)	
28-day mortality, n (%)	10 (25.6)	5 (29.4)	
ICU mortality, n (%)	9 (23.1)	5 (29.4)	
Hospital mortality, n (%)	13 (33.3)	7 (41.2)	



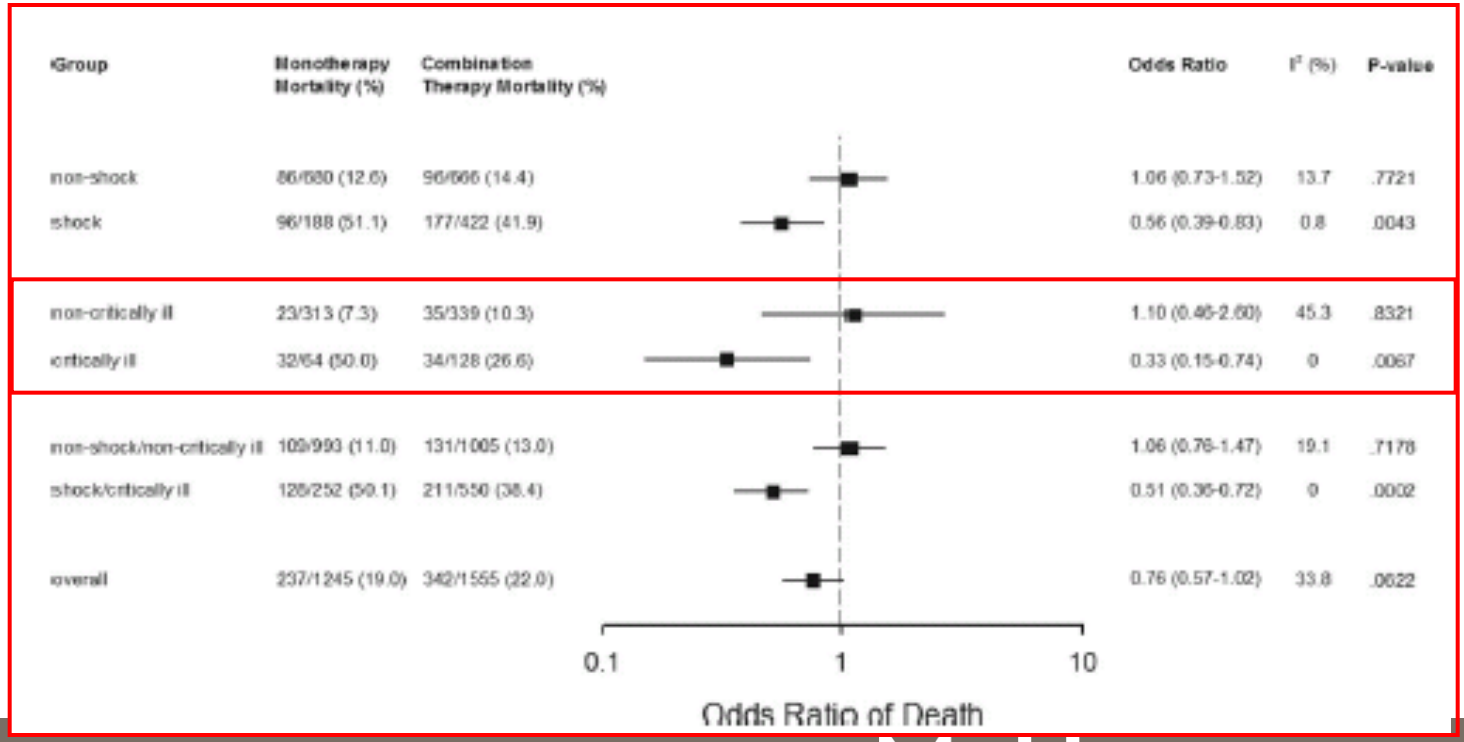
[a]n=38 for combination group, n=16 for monotherapy group (p<0.001); [b]p=0.014;
[c]median (IQR): the upper quartile range of the time to discharge is undefined for both groups because >25% of patients did not achieve the particular event
RR, risk ratio

Heyland DK et al. Crit Care Med 2008;36:737-44

Mono- versus Combination Therapy

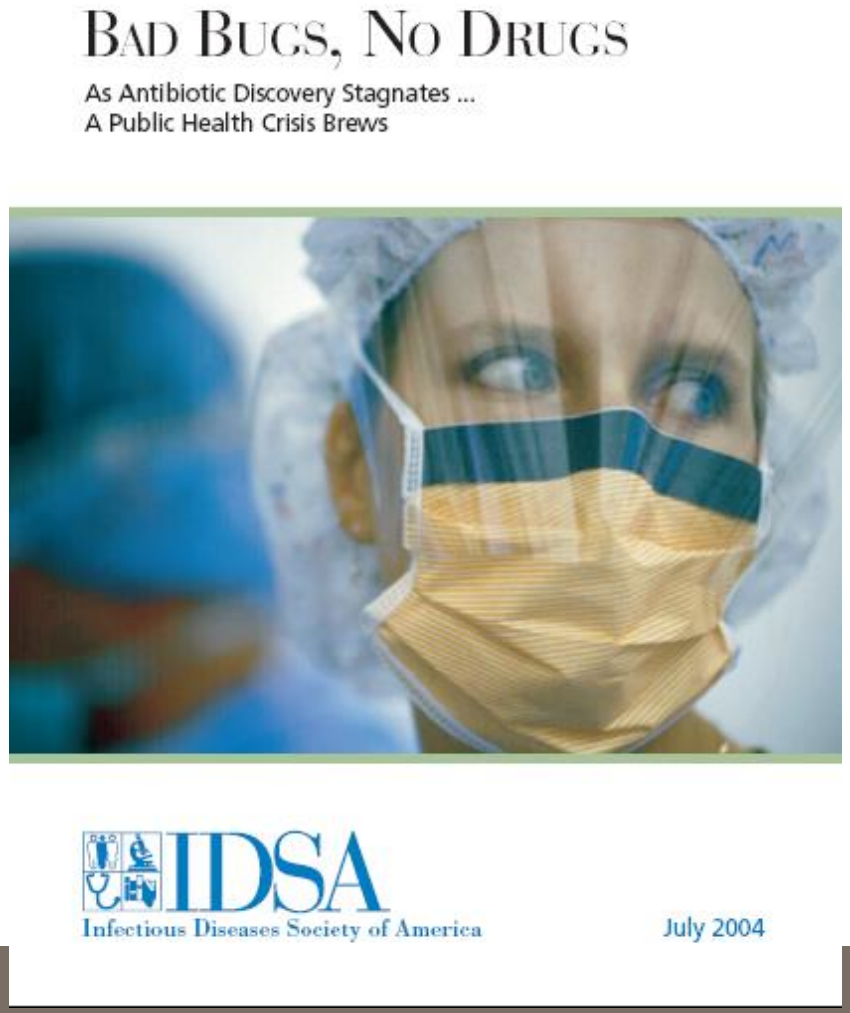
Kumar A. Crit Care Med 2010; 38:1651–1664

- Metaanalysis of RCTs or observational studies comparing mono- and combination therapy in patients with sepsis
- no overall mortality/clinical response benefit with combination therapy (odds ratio, 0.856)
- substantial benefit in the most severely ill subset (monotherapy risk of death >25%; odds ratio of death, 0.51)
- Meta-regression indicated that efficacy of combination therapy was dependent only on the risk of death in the monotherapy group.



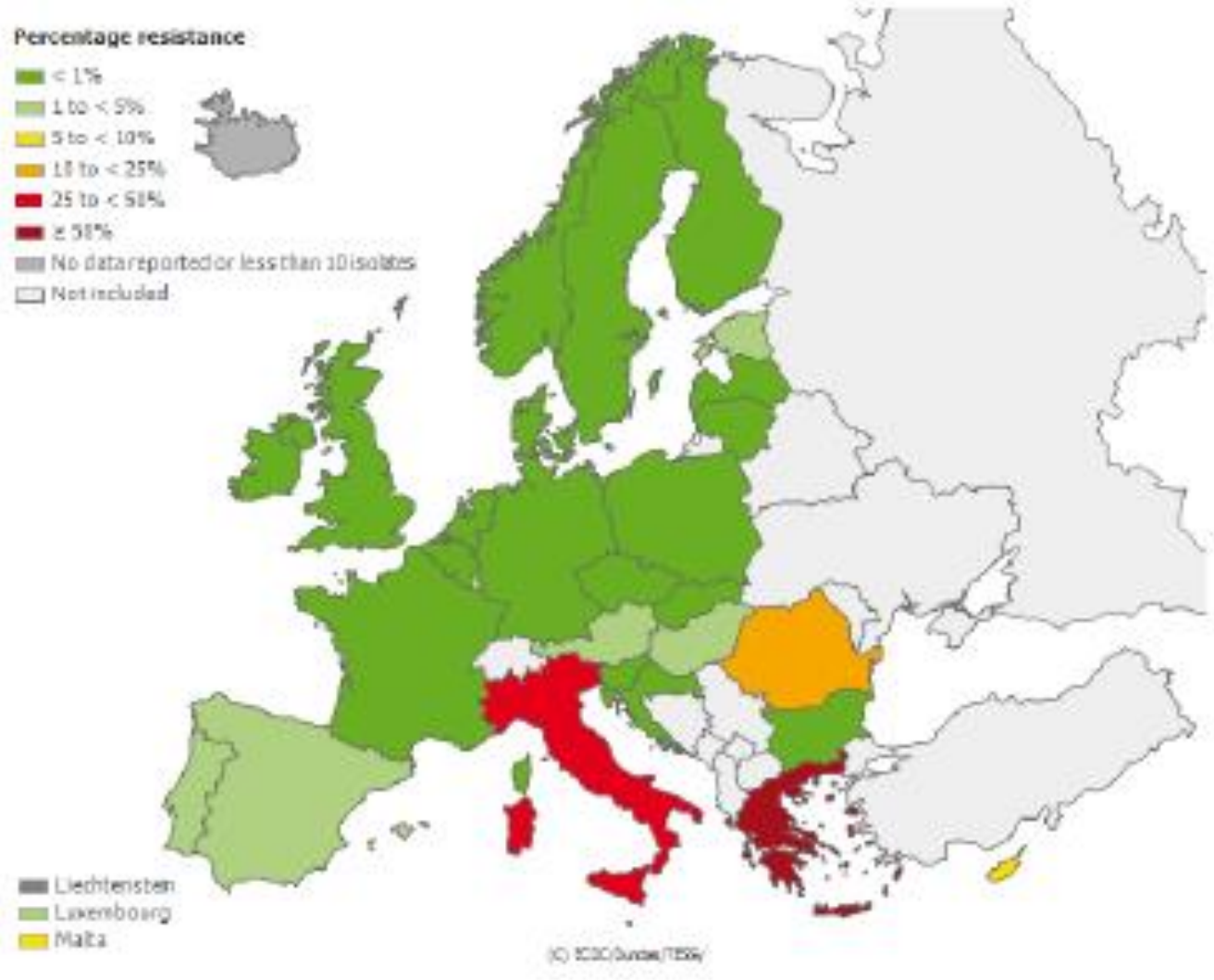
Die wirklich bösen Erreger

Infectious Disease Society of America.
Available at http://www.idsociety.org/badbugsnodrugs.html. Last accessed April 4, 2009.



- **Carbapenemase produzierende Enterobacteriacae**
- **Acinetobacter**
- **Pseudomonas aeruginosa**

European Antimicrobial Resistance Surveillance (EARS) – Net 2013
Carbapemem resistente K. pneumoniae



http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/map_reports.aspx

- **Multicenter retrospective cohort study, in 3 large Italian teaching hospitalsbetween 1 January 2010 and 30 June 2011**
- **125 patients with bloodstream infections (BSIs) caused by KPC-producing Kp isolates (KPC-Kp) diagnosed**
- **30-day mortality rate was 41.6%**
  - **monotherapy (54.3%**
  - **combined drug therapy 34.1%; P = .02).**
- **30-day mortality was independently associated with**
  - **Postantibiogram therapy with a combination of tigecycline, colistin, and meropenem was associated with lower mortality (OR: 0.11; P = .01)**

		No. (%)	
Meropenem MIC (mg/L)	Total	Nonsurvivors	Survivors
1	1	0	1 (100)
2	4	0	4 (100)
4	10	2 (20)	8 (80)
8	4	1 (25)	3 (75)
≥16	17	6 (35.2)	11 (64.7)
Total	36	9 (25)	27 (75)

Abbreviation: MIC, minimum inhibitory concentration.

Multivariate analysis of factors associated with death among patients with bloodstream infection due to KPC producing Klebsiella Pneumoniae.

Shock	-	-	**0.008**	**7.17 (1.65-31.03)**
Inadequate initial treatment	-	-	**0.003**	**4.17 (1.61-10.76)**
APACHE III score (mean ± SD)	-	-	**<0.001**	**1.04 (1.02-1.07)**
Tigecycline & Colistin & Meropenem	-	-	**0.01**	**0.11 (0.02-0.69)**

Tumbarello M, Viale PL, Viscoli C, Bassetti M et al. *Clin Infect Dis*, 2012; Oct;55(7):943-50

AAC
Journals.ASM.org

Effectiveness of a Double-Carbapenem Regimen for Infections in Humans Due to Carbapenemase-Producing Pandrug-Resistant *Klebsiella pneumoniae*

Helen Giamarellou, Lambrini Galani, Fotini Baziaka, Ilias Karaiskos
6th Department of Internal Medicine, Hygeia General Hospital, Athens, Greece

Antimicrob Agents Chemother 2013; May;57(5):2388-90

- **Ertapenem plus doripenem or meropenem were given in three patients suffering from pandrug-resistant, KPC-2-positive *Klebsiella pneumoniae* bacteremia (2 patients) and urinary tract infection (1 patient), respectively.**
- **All responded successfully, without relapse at follow-up.**
- **The results obtained should probably be attributed to ertapenem's increased affinity for the carbapenemases hindering doripenem/meropenem degradation in the environment of the microorganism.**

I-Zahl: 030443 1510

Befundet: 20.02.2016/Sedlacek

Material: Trachealsekret

Abnahme: 15.02.2016

Labornr.: v3333182

Befunddatum: 20.02.2016

[1] Acinetobacter baumannii

Prüfe: ICD B96.5!

4-fach multiresistenter gram-negativer Erreger (4MRGN nach KRINKO-Empfehlung). Isolationsmaßnahmen (ICD Z29.0) dringend empfohlen! Merkblatt: www.mh-hannover.de/16360.html. Prüfe: ICD U81!, U80.4!, U80.5! oder U80.6!

	[1]
Ampicillin-Sulbactam	R <=2.0
Piperacillin / Sulbactam	R
Gentamicin	R >=16.0
Tobramycin	S <=1.0
Levofloxacin	R >=8.0
Ciprofloxacin	R >=4.0
Moxifloxacin	R
Imipenem	R >=16.0
Meropenem	R >=16.0
Cotrimoxazol	R >=320.0

Material: Abstrich von Leiste

Abnahme: 15.02.2016

Labornr.: v3333183

Befunddatum: 20.02.2016

[1] Acinetobacter baumannii

Prüfe: ICD B96.5!

4-fach multiresistenter gram-negativer Erreger (4MRGN nach KRINKO-Empfehlung). Isolationsmaßnahmen (ICD Z29.0) dringend empfohlen! Merkblatt: www.mh-hannover.de/16360.html. Prüfe: ICD U81!, U80.4!, U80.5! oder U80.6!

	[1]
Ampicillin	R >32.0
Ampicillin-Sulbactam	S <=1.0
Piperacillin-Tazobactam	R >32.0
Cefuroxim	R >16.0
Cefotaxim	R >8.0
Ceftazidim	R >32.0
Gentamicin	R >8.0
Tobramycin	S <=1.0
Tigecyclin	R 4.0
Tetracyclin	R >16.0
Ciprofloxacin	R >4.0
Moxifloxacin	R >2.0
Aztreonam	R >16.0
Meropenem	R >16.0
Ertapenem	R >4.0
Cotrimoxazol	R >16.0
Colistin	S <=0.5

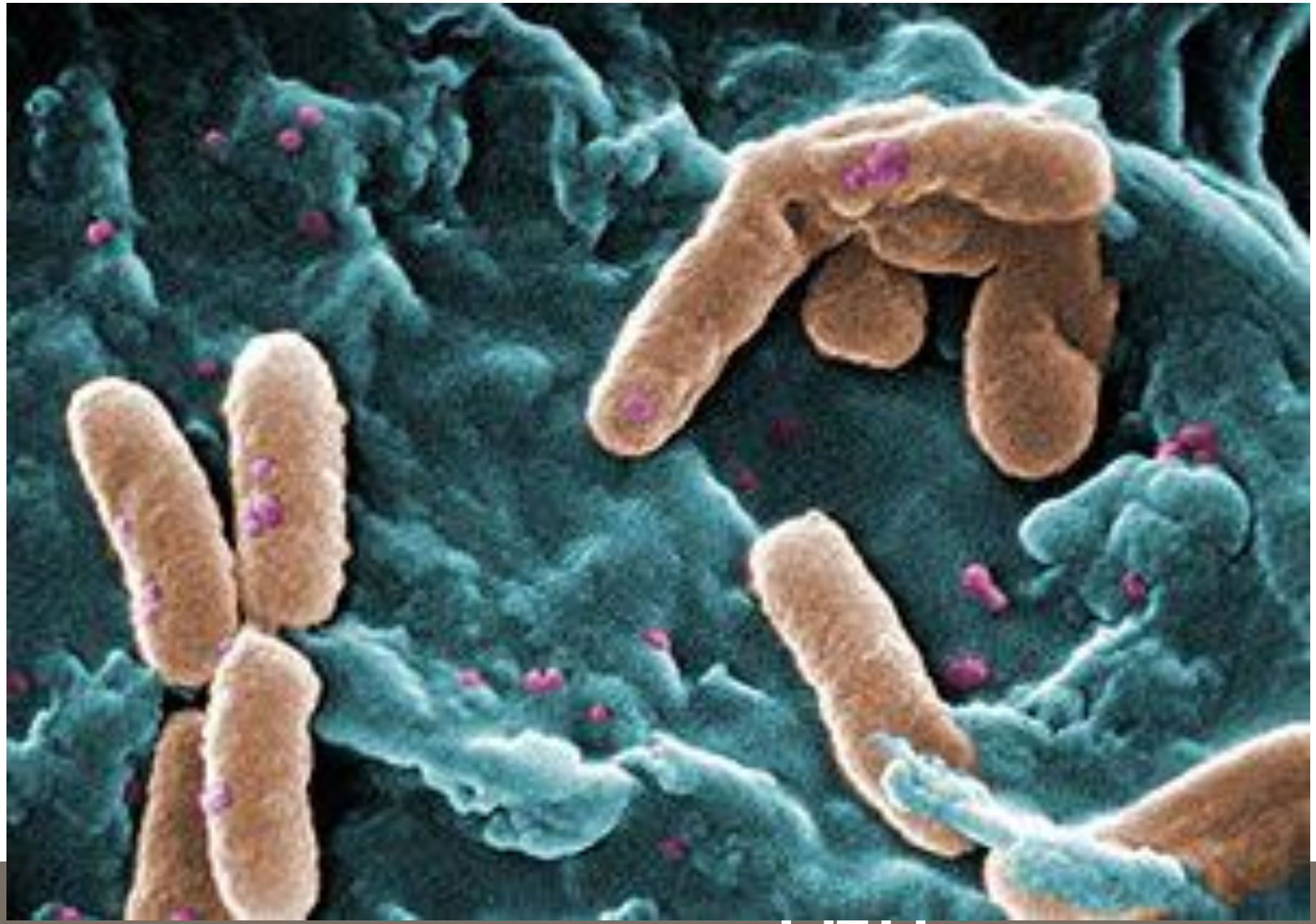
Why Colistin plus Rifampin ?

- **Two-steps, sequential mechanism of action**
- **Colistin disrupt the outer bacterial cytoplasmic membrane**
- **Rifampin inhibit DNA-dependent RNA-polymerase at the ribosomal β-subunit**
- **Some preliminary experience on *A. baumannii***

	Colistin + Rifampicin arm N = 104	Colistin arm N = 105	p
Primary outcome			
30-day mortality			
Yes	45 (43.3%)	45 (42.9%)	0.95 §
No	59 (56.7%)	60 (57.1%)	
Secondary outcomes			
Infection-related death at 30 days			
Yes	22 (21.15%)	28 (26.6.2%)	0.29 §
No	23 (22.1%)	17 (16.2%)	
Acinetobacter baumannii eradication			
Yes	63 (60.6%)	47 (44.8%)	0.034 §
No	38 (36.5%)	54 (51.4%)	
Median hospitalization length (IQR), days	41 (26-61)	44 (27-59)	0.96 *
Development of colistin resistance, %	0	0	-

§exact chi-square test; *log-rank test
IQR: interquartile range

Durante-Mangoni E. et al. Clinical Infectious Diseases 2013; 57(3):349–58



Substanz	Dosierung (pro Tag)
Pseudomonaswirksames Betalaktam	
Piperacillin/Tazobactam	3 – 4 x 4,5 g
oder	
Cefepim	3 x 2 g
Ceftazidim	3 x 2 g
oder	
Imipenem/Cilastatin	3 x 1 g
Meropenem	3 x 1 g
Doripenem	3 x 0.5 – 1 g
plus	
Fluorchinolon	
Ciprofloxacin	3 x 400 mg
Levofloxacin	2 x 500 mg
oder	
Aminoglykosid	
Gentamicin	1 x 3 – 7 mg/kg (Talspiegel < 1 µg/ml)
Tobramycin	1 x 3 – 7 mg/kg (Talspiegel < 1 µg/ml)
Amikacin	1 x 15 – 20 mg/kg (Talspiegel < 4 µg/ml)
bei MRSA-Verdacht	
plus Glykopeptid od. Oxazolidinon	
Vancomycin	2 x 15 mg/kg (Talspiegel: 15 – 20 µg/ml)
Linezolid	2 x 600 mg

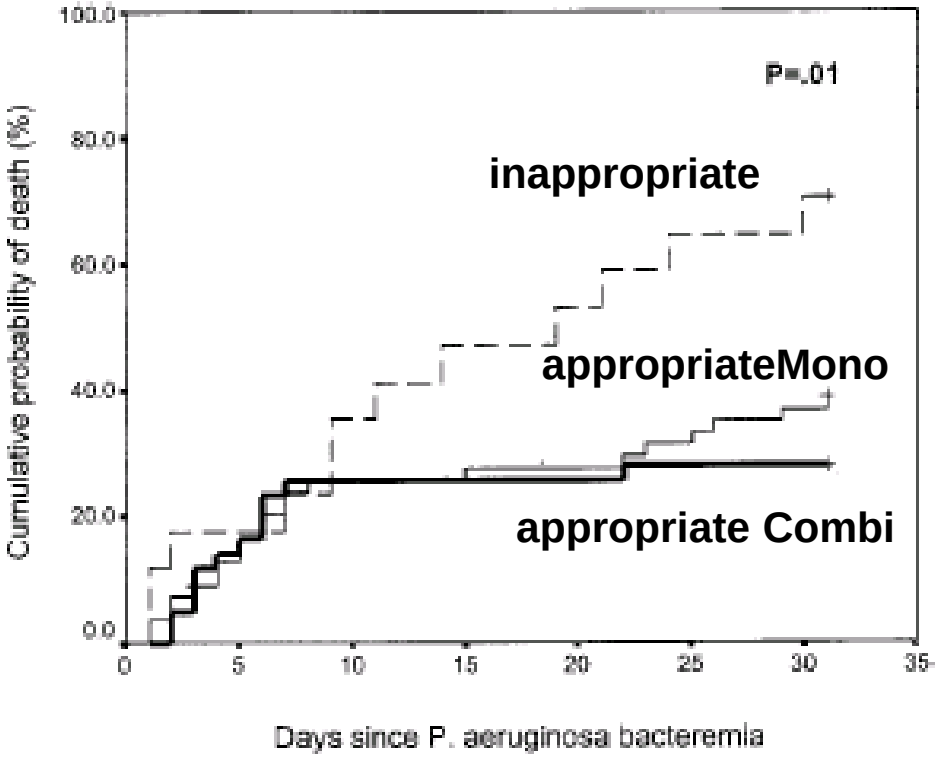
Dalhoff K et al.
Pneumologie 2012; 66:707-65.

Combination Therapy in Pseudomonas Sepsis

Retrospective Study of 115 Episodes of Pseudomonas Sepsis in Geneva

Mortality risk (compared to appropriate Combination Therapy)
- **for inappropriate Therapy 5.0**
- **for appropriate Monotherapy 3.7**

Mortality risk for definitive therapy (vs. appropriate combination therapy)
- **for inappropriate Therapy 2.7**
- **for appropriate Monotherapy 0.6**



Chamot E. AAC 2003; 47: 2756-64

Seltene Erreger

Abbott IJ. Semin Respir Crit Care Med 2015;36:99–110

Organism	First line	Second line	Combination	Alternative combination
S. maltophilia	Trimethoprim–sulfamethoxazole	Moxifloxacin/levofloxacin Ticarcillin–clavulanate Minocycline/tigecycline[a] Colistin (± rifampicin)	Trimethoprim–sulfamethoxazole PLUS Any 2nd line agent, or ceftazidime	Ticarcillin–clavulanate *PLUS* Aztreonam *PLUS* Moxifloxacin/levofloxacin
B. cepacia complex	Trimethoprim–sulfamethoxazole Ceftazidime Meropenem	Minocycline Chloramphenicol Ciprofloxacin[b] Piperacillin–tazobactam Ticarcillin–clavulanate	Combination of any 1st line or 2nd lines agents	Meropenem *PLUS* Ceftazidime PLUS Ciprofloxacin PLUS Minocycline, or amikacin PLUS Tobramycin (inhaled[c])
A. xylosoxidans	Piperacillin–tazobactam Meropenem Trimethoprim–sulfamethoxazole	Ceftazidime Minocycline Colistin Chloramphenicol	Meropenem PLUS Ciprofloxacin/levofloxacin[d]	Meropenem PLUS Minocycline, or levofloxacin[d] PLUS Chloramphenicol PLUS Colistin (inhaled[c])

Kombinationstherapie mit Fluorchinolonen
Pros und Cons

- **Pros**
  - **bakterizides Breitbandantibiotikum**
  - **Gute Penetrabilität in viele Gewebe**
  - **Überschaubares Nebenwirkungsspektrum**

- **Con**
  - **Ciprofloxacinresistenz der „bösen“ Erreger**
  - **Fehlende Evidenz in allen Anwendungsbereichen**

Austrian HAP guideline: high-dosage strategy

Initial adult doses for empirical therapy of HAP, including VAP and HCAP in patients with late-onset disease or risk factors for MDR

Antibiotic	Dosage
Antipseudomonal cephalosporin	
Cefepime	1–2 g every 8–12 h
Ceftazidime	2 g every 8 h
Carbapenems	
Imipenem	500 mg every 6 h or 1 g every 8 h
Meropenem	1 g every 8 h
Beta-lactam / beta-lactamase inhibitor	
Piperacillin / tazobactam	4.5 g every 6 h
Aminoglycosides	
Gentamycin	7 mg/kg/day
Tobramycin	7 mg/kg/day
Amikacin	20 mg/kg/day
Antipseudomonal quinolones	
Levofloxacin	750 mg every 24 h
Ciprofloxacin	400 mg every 8 h
Vancomycin	15 mg/kg every 12 h
Linezolid	600 mg every 12 h

1. ATS, IDSA. Am J Respir Crit Care Med 2005;171:388-416;
2. Thalhammer F et al. Austrian Society for Infectious Diseases and Tropical Medicine, Physicians' Supplement: HAP/VAP Anti-infective Therapies, 2009

Patients with normal renal function and normal body weight[2]

Antibiotikum	Maximale Tagesdosis
Betalaktame	
Ampicillin/Sulbactam	9–12g
Piperacillin/ Tazobactam	13,5–27g
Cefotaxim	6–12g
Cefepim, Cefpirom	6–12g
Ceftazidim	6–12g
Doripenem	1,5–3g
Imipenem/Cilastatin	2–6g
Meropenem	3–6g
Chinolone	
Ciprofloxacin	0,8–1,2g
Levofloxacin	1g
Moxifloxacin	0,4g

MHH Medizinische Hochschule Hannover

Kombinationstherapie mit Fluorchinolonen Pros und Cons

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  - bakterizides Breitbandantibiotikum
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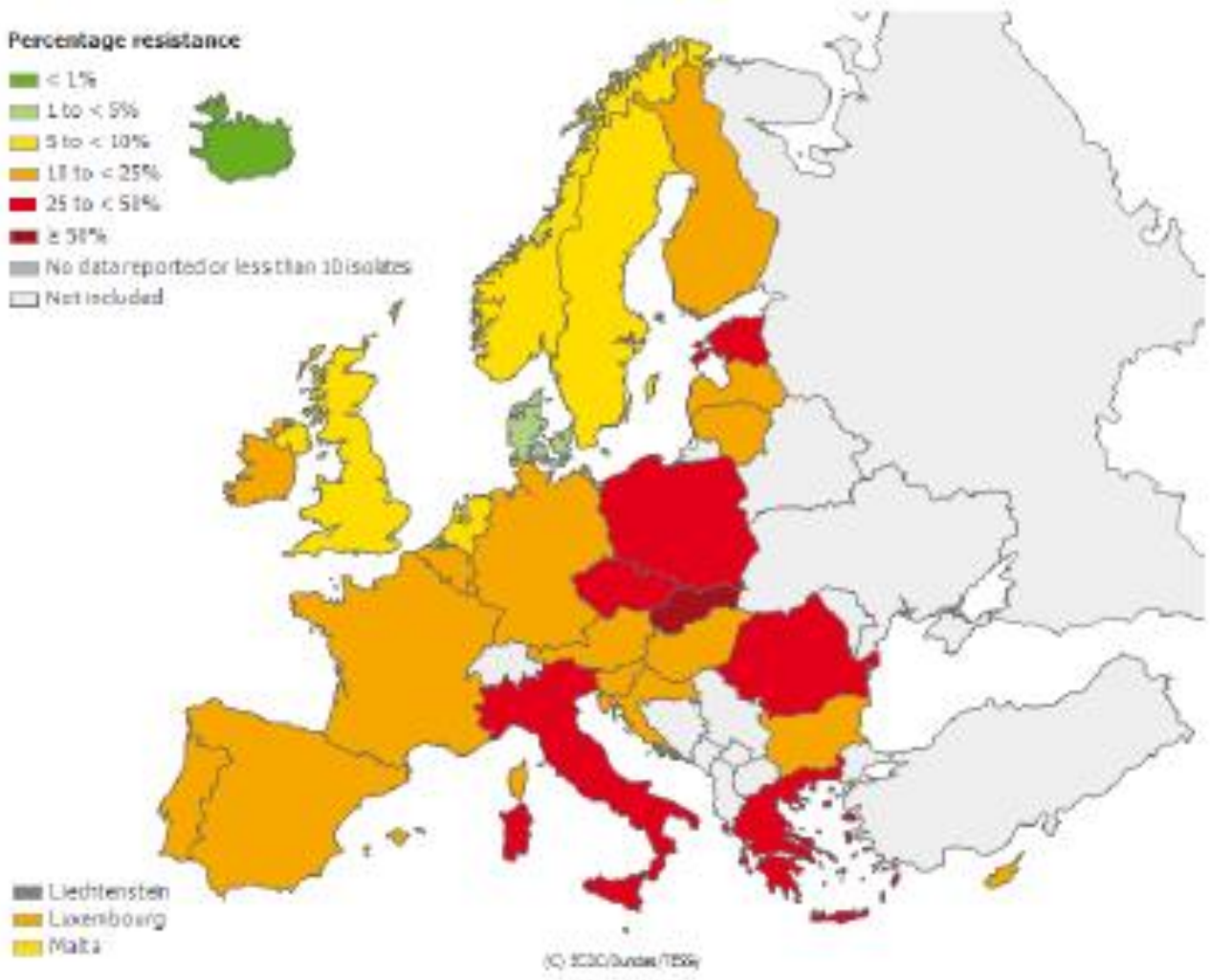
  - **Ciprofloxacinresistenz der „bösen“ Erreger**
  - **Fehlende Evidenz in allen Anwendungsbereichen**

European Antimicrobial Resistance Surveillance (EARS) – Net 2013
Fluorchinolon resistente Ps. aeruginosa



http://ecdc.europa.eu/en/healthtopics/antimicrobial_resistance/database/Pages/map_reports.aspx

Kombinationstherapie mit Aminoglykosiden Pros und Cons

- **Pros**
  - **bakterizides Breitbandantibiotikum**
  - **Resistenzsituation hervorragend**
  - **Gute Penetrabilität in viele Gewebe**
    - **Lunge?**
- **Con**
  - **Negative Evidenz für die dreimal tägliche Anwendung, keine Studien zu einmal täglich**
  - **Nebenwirkungen**
    - **Nephrotoxizität**

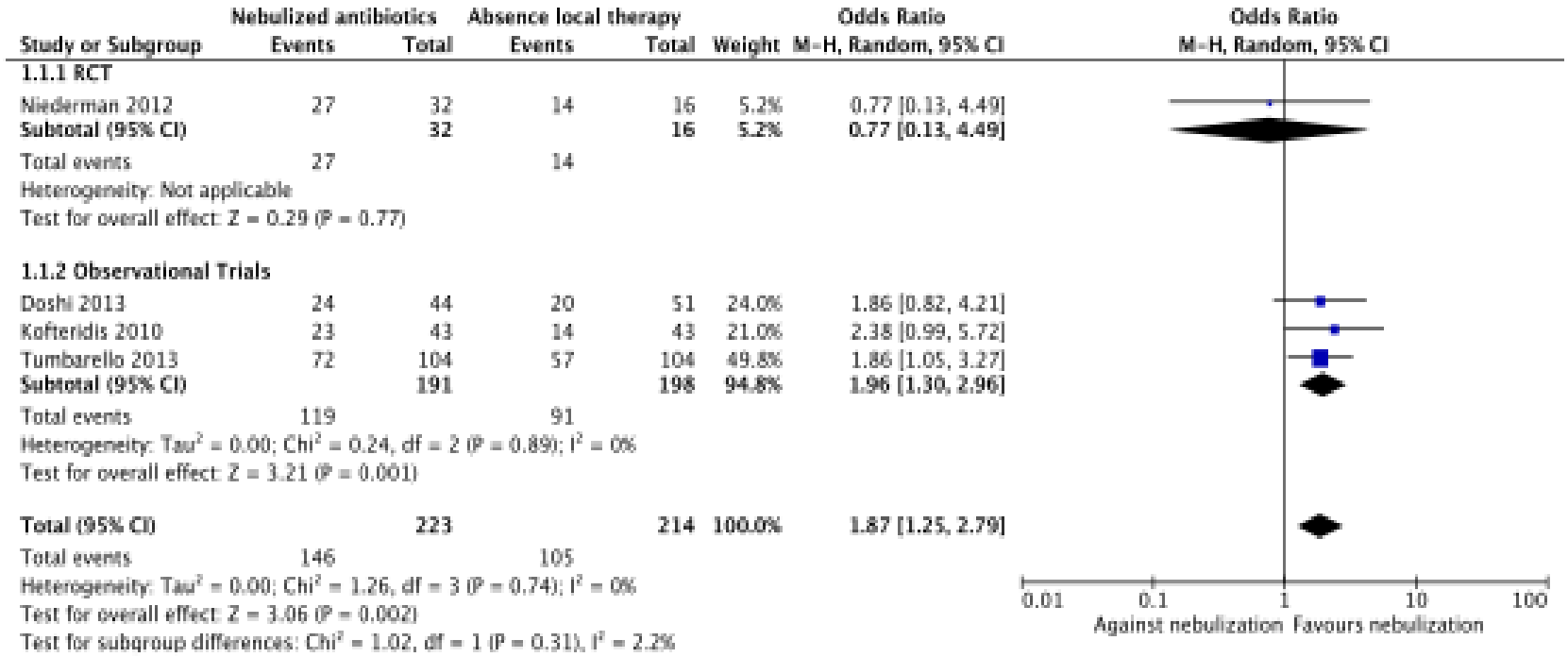
Intracheal Administration of Antimicrobial Agents

- **The most common prescribed nebulized agents were**
  - **colistin methanesulfonate and sulfate (36/87, 41.3% and 24/87, 27.5%), tobramycin (32/87, 36.7%) and amikacin (23/87, 26.4%).**
  - **Colistin methanesulfonate, amikacin and tobramycin daily doses for VAP were significantly higher than for VAT ($p < 0.05$).**
  - **Combination of parenteral and nebulized antibiotics occurred in 50 (86%) of 58 prescriptions for VAP and 36 (64.2%) of 56 of prescriptions for VAT.**
  - **The use of nebulized antimicrobial agents in MV patients is common. There is marked heterogeneity in clinical practice, with significantly different in use between patients with VAP and VAT.**

Candela Solé-Lleonart et al. Clin Microbiol Infect. 2015 Dec 23. pii: S1198-743X(15)01042-3. doi: 10.1016/j.cmi.2015.12.016. [Epub ahead of print]

Clinical resolution of patients treated with nebulized antibiotics for VAP caused by resistant pathogens

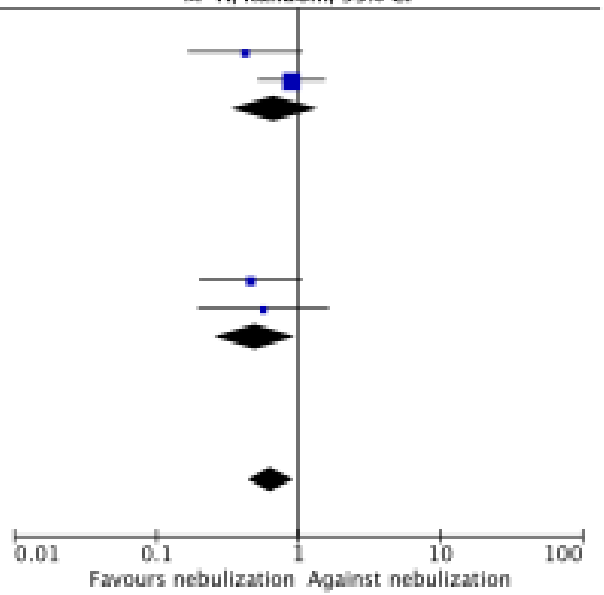
Candela Solé-Lleonart et al. Chest 2016 (in revision)



Mortality of patients treated with nebulized antibiotics for VAP caused by resistant pathogens

Candela Solé-Lleonart et al. Chest 2016 (in revision)

Study or Subgroup	Nebulized antibiotics Events	Total	Absence local therapy Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.3.1 All-cause						
Kofteridis 2010	10	43	18	43	16.9%	0.42 [0.17, 1.07]
Tumbarello 2013	45	104	48	104	48.9%	0.89 [0.51, 1.54]
Subtotal (95% CI)		**147**		**147**	**65.8%**	**0.68 [0.33, 1.37]**
Total events	55		66			
Heterogeneity: $Tau^2 = 0.13$; $Chi^2 = 1.85$, df = 1 (P = 0.17); $I^2 = 46\%$						
Test for overall effect: Z = 1.09 (P = 0.28)						
1.3.2 VAP-related						
Doshi 2013	15	44	27	51	21.2%	0.46 [0.20, 1.06]
Kofteridis 2010	7	43	11	43	13.0%	0.57 [0.20, 1.63]
Subtotal (95% CI)		**87**		**94**	**34.2%**	**0.50 [0.26, 0.96]**
Total events	22		38			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0\%$						
Test for overall effect: Z = 2.09 (P = 0.04)						
Total (95% CI)		**234**		**241**	**100.0%**	**0.64 [0.44, 0.94]**
Total events	77		104			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.83$, df = 3 (P = 0.42); $I^2 = 0\%$						
Test for overall effect: Z = 2.26 (P = 0.02)						
Test for subgroup differences: $Chi^2 = 0.39$, df = 1 (P = 0.53), $I^2 = 0\%$						



Medizinische Hochschule Hannover

Kombinationstherapie mit Aminoglykosiden Pros und Cons

- Pros
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    - Lunge?
- **Con**
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  - **Nebenwirkungen**
    - **Nephrotoxizität**

A high-dose aminoglycoside regimen combined with renal replacement therapy for the treatment of MDR pathogens

- All adult patients who had MDR GN sepsis
- HDA and high-flow (>45 mL/kg/h) CVVHDF when
  - an isolated pathogen was susceptible or had intermediate susceptibility to aminoglycosides
  - patient's condition was not improving with conventional therapy
  - Optimal antibacterial activity was defined as a peak concentration of at least eight times the MIC.
- Fifteen patients infected with MDR GN pathogens were treated with amikacin (n=11), gentamicin (n=3) or tobramycin (n=1) and high-flow CVVHDF
- Clinical response was observed in eight (53%) patients, including three in whom microbial eradication was obtained
- Six patients were discharged alive from the ICU, and five from the hospital. No renal toxicity was observed among survivors

Brasseur A et al. J Antimicrob Chemother. 2016 Jan 31


NO.
YES.
MAYBE.
MAYBE YES.
MAYBE NO.