Does empiric antibiotic therapy improves outcome for infections due to MDR bacteria?

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- Cirrhosis or renal insufficiency and having lived in a nursing home before hospitalization or having been admitted to an intensive care unit were each independently associated with death (after adjusting for covariates in the model); **each increased the risk of dying by 7%–15%.**
- **A consultation with an infectious diseases specialist decreased the risk for death by 11%.**
- Neither a VISA nor hVISA strain was independently associated with all-cause death after covariates in the models were controlled for.

Outcome of MRSA bacteremia (n = 630)

Pastagia, PlosOne 2012

Table 1
Cohort study: appropriate antibiotic treatment

	Patients	Physician[a]	TREAT[a]	*P* value[b]
Israel	164	87 (53.0)	121 (73.8)	<0.001
Germany	105	62 (59.0)	71 (67.6)	0.108
Italy	81	50 (61.7)	53 (65.4)	0.690
Overall	350	199 (56.9)	245 (70.0)	<0.001

Paul, JAC 2006

Empiric therapy and outcome

- Appropriate treatment, **that is matching the *in vitro* susceptibilities of subsequently isolated pathogens**, reduces the overall fatality rate of severe infections with adjusted odds ratios varying between 1.6 and 6.9.
- However, **20–50%** of patients are given inappropriate empirical antibiotic treatment
- Increasing interest in the impact of empiric therapy with the increased spread of antibiotic resistance
- Many confounding factors
- Most considered outcome is 30-day mortality

Table 4 Hospital mortality relative to initial antimicrobial adequacy

Adequacy	No. of deaths/episodes (%)	*P*
Overall (n = 54)		0.304
Inadequate	6/20 (30%)	
Adequate	15/34 (44.1%)	
Gram-positive organism (n = 35)		0.476
Inadequate	4/12 (33.3%)	
Adequate	12/23 (52.2%)	
Gram-negative bacilli (n = 28)		0.639
Inadequate	1/7 (14.3%)	
Adequate	6/21 (28.6%)	
Excluding culture-negative patients		

Antimicrobial effectiveness and mortality: always clear?

Kim, Critical Care 2012

TABLE 3. Meta-regression analysis to assess the effect of confounders on the association between appropriate empirical antibiotic treatment and all-cause mortality[a]

Variable	Unadjusted			Adjusted		
	ROR (95% CI)	No. of studies	*P* value	ROR (95% CI)	No. of studies	*P* value
Univariate analysis						
Septic shock (% of patients)	0.98 (0.35–2.73)	44				0.033
				3.60 (1.11–11.65)	29	
Neutropenia (% of patients)	0.49 (0.02–10.07)	16		0.20 (0.01–0.31)	15	
Study year (1-yr increment)						0.092
	1.01 (0.99–1.04)	62		1.03 (0.99–1.07)	41	
Age (yr [mean for study])	1.02 (0.99–1.05)	53		1.00 (0.96–1.03)	35	
Multivariable analysis						
Joint test, with septic shock[b]	Not relevant				34	0.047
Joint test, without septic shock[b]	Not relevant				48	0.015

Bacteremia, empiric therapy, and mortality

Paul M, AAC 2010

- Short-term mortality
- Attributable mortality
- Adverse effects
- Cost
- Length of hospitalisation
- Long term complications
- Clinical efficacy
- Microbiological effectiveness
- Relapse
- Hospital readmission

Indicators of therapy effectiveness

- Evidence of the impact of empiric therapy of infections due to MDR bacteria and mortality
- Confounding
- Evidence on other outcomes
- Gray areas where further research is needed

Road map

- 30 studies
- **Mortality**
  - Infection severity and underlying diseases +++
  - multidrugresistance, inappropriate treatment, and increasing age ++
- Including **only MDR-GN infections**
  - Cancer
  - Prior or current ICU stay
- Comparing **MDR-Gn with not-MDR-GN infections (RR)**
  - septic shock (1.5)
  - ICU stay (3.3)
  - pneumonia (1.65)
  - MDR-GN bacteria (1.49)
  - **inappropriate definitive (2.05) and empirical treatment (1.37)**
  - male gender (1.13)

The study, the patient, the bug or the drug?

Verdakas, J infection 2013

MDR-Gram negative

UNIVERSITÄTS KLINIKUM TÜBINGEN

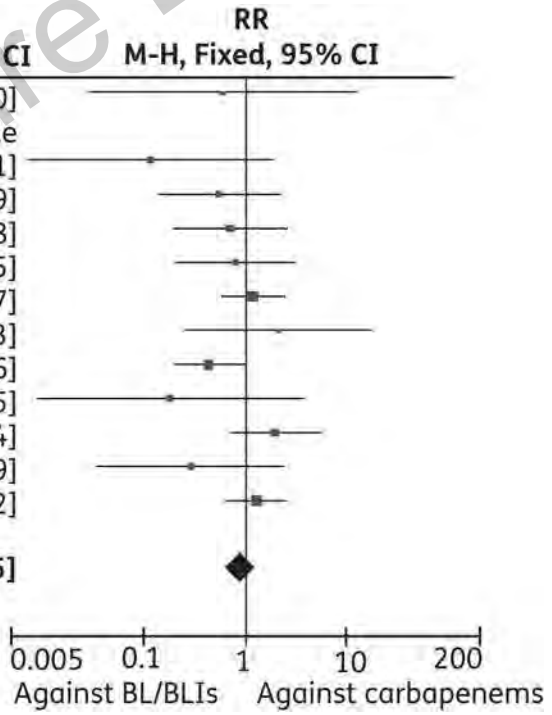
Forest plot depicting the RRs of all-cause mortality of patients with ESBL-positive bacteraemia treated empirically with carbapenems versus BL/BLIs.

21 studies

Study or subgroup	Carbapenems Events	Carbapenems Total	BL/BLIs Events	BL/BLIs Total	Weight	RR M-H, Fixed, 95% CI
Apisarnthanarak *et al.* (2008)[19]	0	5	1	10	1.9%	0.61 [0.03, 12.80]
Bin *et al.* (2006)[21]	0	3	0	7		Not estimable
Chaubey *et al.* (2010)[22]	0	10	6	16	9.0%	0.12 [0.01, 1.91]
De Rosa *et al.* (2011)[23]	8	57	2	8	6.2%	0.56 [0.14, 2.19]
Ferrandez *et al.* (2011)[26]	2	6	6	13	6.7%	0.72 [0.20, 2.58]
Gudiol *et al.* (2010)[27]	2	5	3	6	4.8%	0.80 [0.21, 3.05]
Kang *et al.* (2012)[29]	21	78	8	36	19.3%	1.21 [0.59, 2.47]
Lee *et al.* (2010)[30]	4	24	1	13	2.3%	2.17 [0.27, 17.43]
Metan *et al.* (2009)[32]	7	22	5	7	13.4%	0.45 [0.21, 0.96]
Qureshi *et al.* (2011)[34]	0	8	1	4	3.4%	0.19 [0.01, 3.75]
Rodriguez-Bano *et al.* (2012)[14]	6	31	7	72	7.4%	1.99 [0.73, 5.44]
Tumbarello *et al.* (2007)[35]	1	28	4	33	6.5%	0.29 [0.03, 2.49]
Velaphi *et al.* (2009)[20]	13	40	12	48	19.2%	1.30 [0.67, 2.52]
Total (95% CI)		**317**		**273**	**100.0%**	**0.91 [0.66, 1.25]**
Total events	64		56			

Heterogeneity: $\chi^2 = 12.95$; df = 11 ($P = 0.30$); $I^2 = 15\%$

Test for overall effect: $Z = 0.58$ ($P = 0.56$)



Bacteremia due to ESBL+Enterobacteriaceae

Vardakas, JAC 2012

- Retrospective study: 232 patients
- 140 episodes (60%) were nosocomial
- **Empiric therapy: 24 hrs**
- Comorb: malignancy (34%) and recurrent urinary tract infection(UTI) (15%)
- Inappropiate empiric therapy 63%
- Inappropiate empiric therapy in known ESBL carriers 46%
- 30-day mortality: 20%.
  - Charlson comorbidity index of ≥ 3
  - age of ≥ 75 years
  - intensive care unit (ICU) stay
  - a non-UTIbacteremia source,
  - severe sepsis,

Bacteremia due to ESBL+Enterobacteriaceae

Frakking, AAC 2013

- Retrospective cohort: 92 patents
- Community-acquired cases
- Independent risk factors for mortality:
  - underlying liver disease
  - severity of illness
- Mortality in patients receiving inappropriate initial antimicrobial therapy was not significantly higher than mortality in those receiving appropriate empirical antimicrobial therapy, **if antimicrobial therapy was adjusted appropriately according to susceptibility results.**

Bacteremia due to CA- ESBL+Enterobacteriaceae

Kang, Scand J Infect Dis 2013

Retrospective study

125 patients

30-day mortality septic shock at BSI onset (7.17, 1.65–31.03)
inadequate initial antimicrobial therapy (4.17; 1.61–10.76);
high APACHE III scores (1.04; 1.02–1.07)

Table 3. Multivariate Analysis of Risk Factors for Mortality in Patients With Bloodstream Infection Caused by *Klebsiella pneumoniae* Carbapenemase–Producing *K. pneumoniae*

Variable	*P* Value	OR (95% CI)
Presentation with septic shock	.008	7.17 (1.65–31.03)
Inadequate initial antimicrobial treatment	.003	4.17 (1.61–10.76)
High APACHE III score	<.001	1.04 (1.02–1.07)
Postantibiogram therapy with tigecycline + colistin + meropenem	.01	0.11 (.02–.69)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; CI, confidence interval; OR, odds ratio.

Bacteremia due to CR-K. pneumoniae

Tumbarello, Clin Infect Dis 2013

Bacteremia due to P. aeruginosa

202 patients
40% inappropriate

High risk site:
pneumonia or
non-hepatobiliary tract IA

Inappropriate initial therapy is risk factor for mortality in patients with **high-risk sites** of infection (8.69), along with renal disease, corticosteroid use, polymicrobial infection and higher Pitt bacteraemia score.

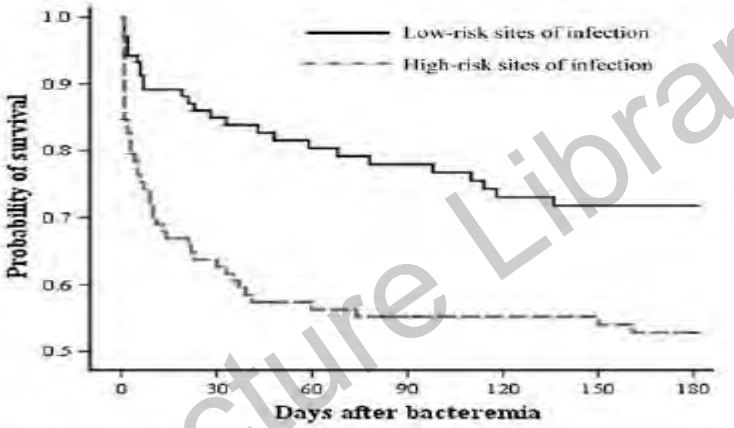


Fig. 1 Long-term outcome of patients with *Pseudomonas aeruginosa* bacteraemia. The survival probability of patients with high-risk sites of infection was significantly lower than that of patients with low-risk sites of infection ($P < 0.05$, log-rank test)

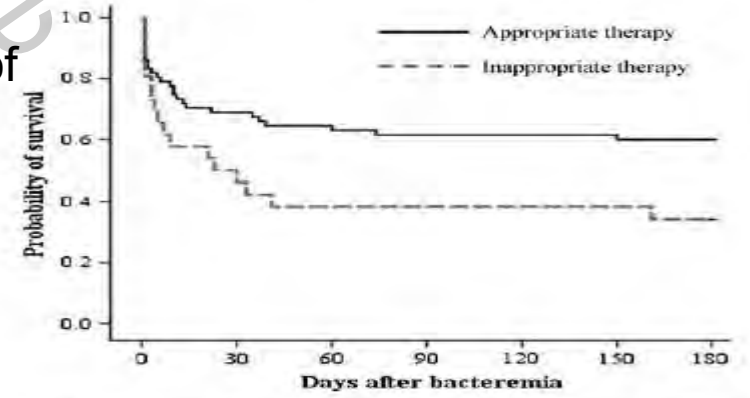


Fig. 2 Long-term outcomes of patients with high-risk sites of infection. The survival probability of patients who received inappropriate initial therapy was significantly lower than that of patients who received appropriate therapy ($P < 0.05$, log-rank test)

Joo infection 2011

Table 1 Baseline characteristics of patients who received adequate antibiotic monotherapy and combination therapy, and inadequate therapy

	Total (n = 100)	Adequate therapy (n = 65)		Inadequate therapy (n = 35)	*P* value
		Monotherapy (n = 32)	Combination therapy (n = 33)		
Age (median years, range)	59 (53–67)	60	56	61	0.24
Male gender	74 (74.0)	27 (84.4)	24 (72.7)	23 (65.7)	0.22
Overall mortality					
7-day mortality	21 (21.0)	5 (15.6)	6 (18.2)	10 (28.6)	0.382
14-day mortality	30 (30.0)	8 (25.0)	6 (18.2)	16 (45.7)	0.035
28-day mortality	51 (51.0)	17 (53.1)	10 (30.3)	24 (68.6)	0.01

Retrospective study
100 patients with P.aeruginosa pneumonia
Inappropriate initial therapy: 35%

Pneumonia due to P. aeruginosa

Yoon-Park, BMC Infect Diis 2012

- 116 patients (60% MDR)
- The overall in-hospital and pneumonia-related mortality rates were 47.4%
  - MDR, PDR, high APACHE II score, inappropriate empirical antimicrobial therapy, and inappropriate definitive antimicrobial treatment (All $p < 0.05$).
  - Among these, a high APACHE II score and **inappropriate definitive antimicrobial therapy** were found to be independent factors associated with a high mortality, **after adjustment for other variables**

HA-pneumonia due to A. baumannii

Jong, J infect 2010

MDR-Gram positive

- 267 patients
- Mortality rate: 11%

Table 2 Propensity score adjusted associations between receipt of nafcillin or cefazolin versus vancomycin and 30-day in-hospital mortality

Association	Adjusted hazard ratio and 95% confidence interval	Variables included in the propensity score
Receipt of nafcillin or cefazolin versus vancomycin and 30-day in-hospital mortality	0.21 (0.09, 0.47)	Severity of illness Aggregate comorbidity Admission to the ICU Age Hemodialysis Endocarditis Time to receipt of appropriate therapy Receipt of other anti-staphylococcal antibiotic
Switch from vancomycin to nafcillin or cefazolin versus remaining on vancomycin and 30-day in-hospital mortality	0.31 (0.10, 0.95)	Severity of illness Aggregate comorbidity Admission to the ICU Community-associated infection Hemodialysis Age Endocarditis Time to receipt of appropriate therapy

Those receiving nafcillin or cefazolin had 79% lower mortality hazards compared with those who received vancomycin alone

Bacteremia due MSSA

Schweizer BMC Infect Dis 2011

- Retrospective study: 627 patients

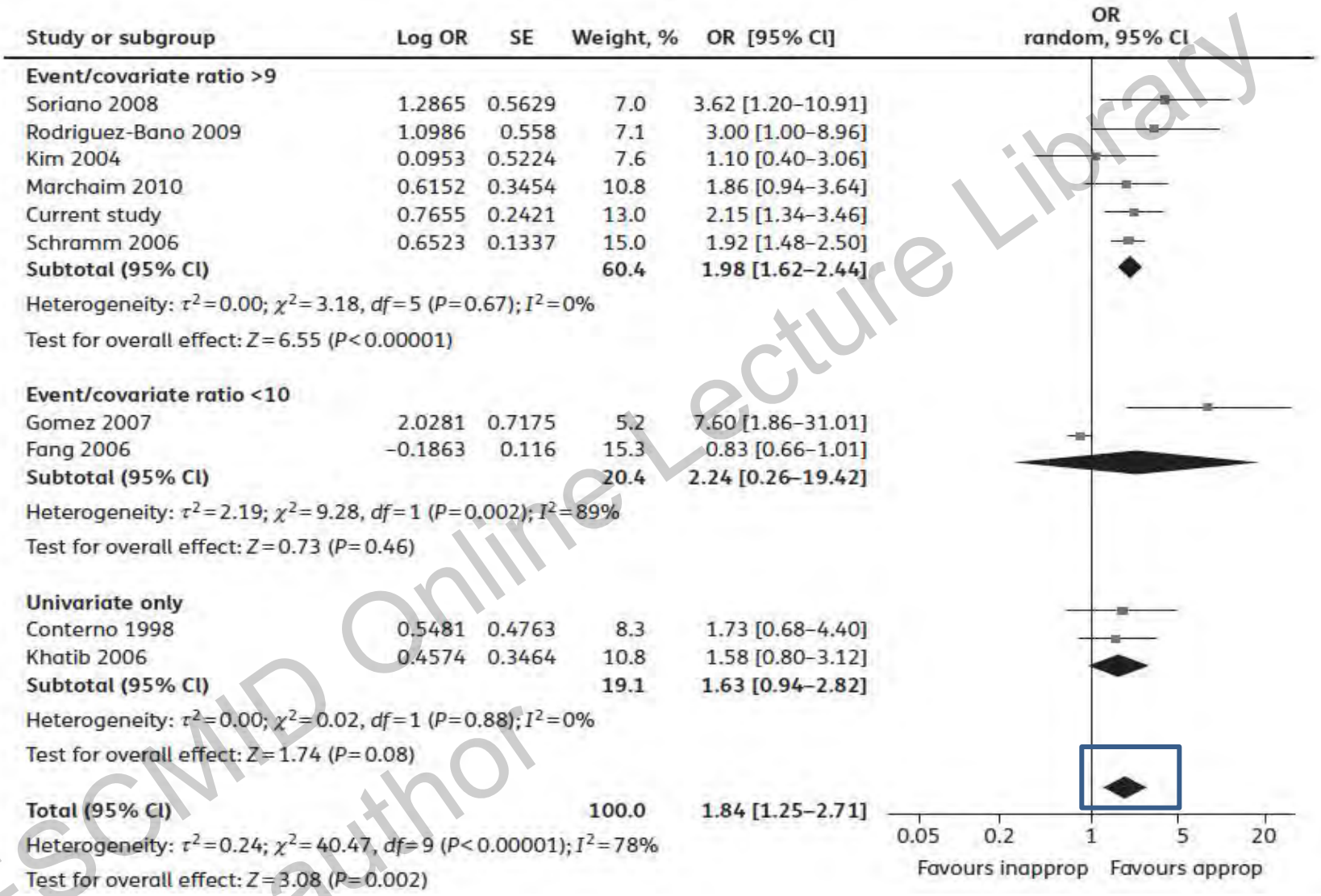
Table 4 Comparison of outcomes of cases of community-acquired pneumonia requiring admission to the intensive care unit based on initiation of empiric MRSA therapy versus standard therapy

Outcome	RR or HR; 95 % CI (unadjusted/adjusted)	*p* (unadjusted/adjusted)
In-hospital mortality	RR 1.69; 95 % CI 0.91–3.13/ RR 1.4; 95 % CI 0.80–2.32	0.16/0.25
28-day mortality	RR 0.89; 95 % CI 0.49–1.60/ RR 0.97; 95 % CI 0.65–1.44	0.81/0.87
Time to clinical stability	HR 0.51; 95 % CI 0.21–1.20/ HR 0.64; 95 % CI 0.38–1.08	0.14/0.10
Length of hospital stay	HR 0.52; 95 % CI 0.22–1.26/ HR 0.85; 95 % CI 0.53–1.37	0.15/0.50

RR relative risk, *HR* hazard ratio, *95 % CI* 95 % confidence interval

CAP due MRSA

Griffin, Infection 2013

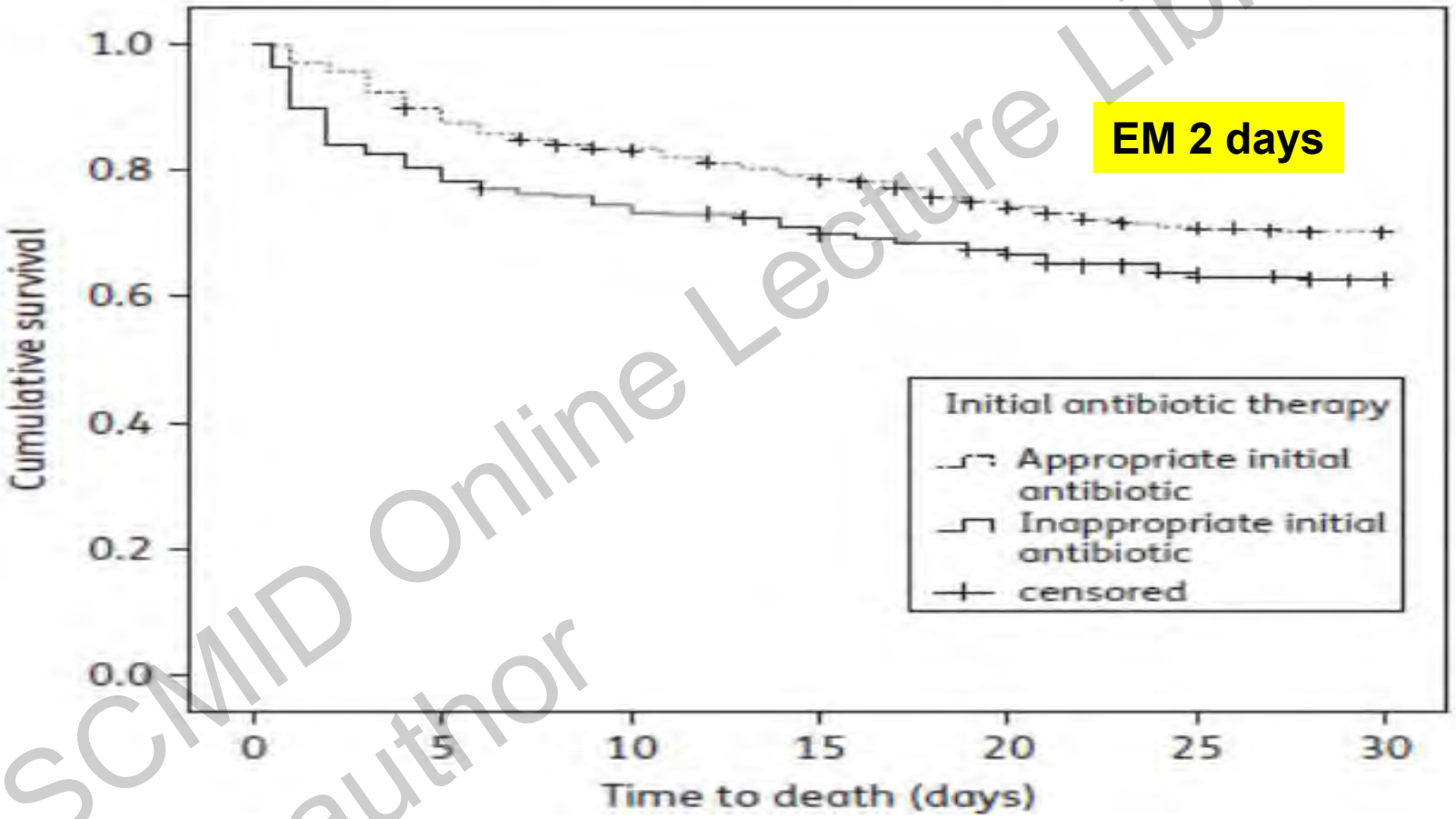


Study or subgroup	Log OR	SE	Weight, %	OR [95% CI]
Event/covariate ratio >9				
Soriano 2008	1.2865	0.5629	7.0	3.62 [1.20–10.91]
Rodriguez-Bano 2009	1.0986	0.558	7.1	3.00 [1.00–8.96]
Kim 2004	0.0953	0.5224	7.6	1.10 [0.40–3.06]
Marchaim 2010	0.6152	0.3454	10.8	1.86 [0.94–3.64]
Current study	0.7655	0.2421	13.0	2.15 [1.34–3.46]
Schramm 2006	0.6523	0.1337	15.0	1.92 [1.48–2.50]
Subtotal (95% CI)			**60.4**	**1.98 [1.62–2.44]**
Heterogeneity: $\tau^2=0.00$; $\chi^2=3.18$, $df=5$ ($P=0.67$); $I^2=0\%$				
Test for overall effect: $Z=6.55$ ($P<0.00001$)				
Event/covariate ratio <10				
Gomez 2007	2.0281	0.7175	5.2	7.60 [1.86–31.01]
Fang 2006	−0.1863	0.116	15.3	0.83 [0.66–1.01]
Subtotal (95% CI)			**20.4**	**2.24 [0.26–19.42]**
Heterogeneity: $\tau^2=2.19$; $\chi^2=9.28$, $df=1$ ($P=0.002$); $I^2=89\%$				
Test for overall effect: $Z=0.73$ ($P=0.46$)				
Univariate only				
Conterno 1998	0.5481	0.4763	8.3	1.73 [0.68–4.40]
Khatib 2006	0.4574	0.3464	10.8	1.58 [0.80–3.12]
Subtotal (95% CI)			**19.1**	**1.63 [0.94–2.82]**
Heterogeneity: $\tau^2=0.00$; $\chi^2=0.02$, $df=1$ ($P=0.88$); $I^2=0\%$				
Test for overall effect: $Z=1.74$ ($P=0.08$)				
Total (95% CI)			**100.0**	**1.84 [1.25–2.71]**
Heterogeneity: $\tau^2=0.24$; $\chi^2=40.47$, $df=9$ ($P<0.00001$); $I^2=78\%$				
Test for overall effect: $Z=3.08$ ($P=0.002$)				

Bacteremia due MRSA

Paul, JAC 2010

Prospective study, 579 patients



Bacteremia due MRSA

Gasch, JAC 2013

- Mortality: 179 patients (31%)
  - EM: 49 (8.5%)
  - LM: 130 (22.5%)
- Independent risk factors for EM:
  - initial Pitt score >3
  - previous rapid fatal disease
  - source of infection lower respiratory tract or unknown
  - non-nosocomial acquisition
  - Inappropriate initial antibiotic therapy
- **Inappropriate therapy was not a risk factors for mortality after 2 days**

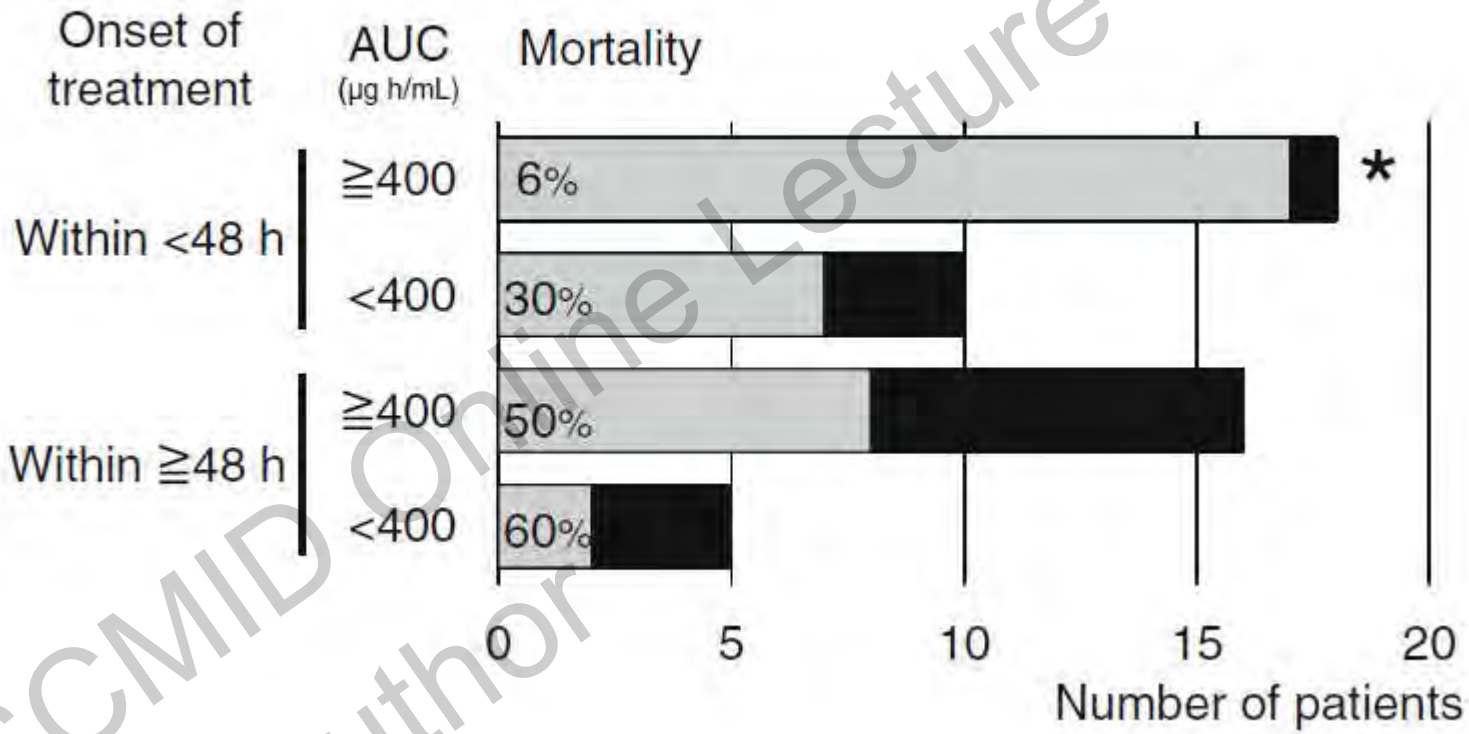
Bacteremia due MRSA

Gasch, JAC 2013

Confounding

- Definition of duration of empiric therapy (more or less 24 hrs) is a key issue
- Analysis of mortality including pathogens with different cross-resistance introduce significant bias
- Analysis of combination versus monotherapy should be always adjusted by other confounding factors
- The definition of inappropriate cannot be only microbiologically defined

Confounding: major considerations



Duration of empirical antibiotic therapy

- The impact of age in the evaluation of the impact of empiric therapy should be further explored:
  - bacteremia
  - inappropriate empirical antibiotic therapy similar (69% vs 64%)
  - 28-day mortality rate > in older patients (11.8% vs 6.1%, P = .02)
  - inappropriate empirical antibiotic therapy was independent risk factor of 28-day mortality only in the elderly population

Confounding: major considerations

Lee, Am J Med 2013

Other outcomes indicators

- Retrospective HA-SSI: 527 patients
- 405 (76.9%) received appropriate treatment.
  - decubitus ulcer (29.5%vs. 10.9%, P < 0.001)
  - device-associated infection (42.6% vs. 28.6%, P = 0.004)
  - bacteremia (68.9% vs. 57.8%, P = 0.028)
  - low overall unadjusted mortality rate did not vary based on initial treatment
  - inappropriate therapy had an attributable increase in **hospital LOS** of 1.8 days (95% CI, 1.4-2.3).

HA-complicated skin and skin structure infections

Zilberbegr, J hosp med 2010

- 494 hospitalsied patients
- **Composite economic outcome**:
  - Any subsequent hospital admissions
  - Emergency department visits
  - Unscheduled visits related to the study infection
- LOS was 7.4 days
- 23.1% received inappropriate intial therapy
  - longer LOS (marginal LOS = 2.43 days, P = 0.01)
  - more likely to have the composite economic outcome in all study cohorts (OR: overall = 1.79; HCA = 3.09; MRSA = 3.66; MRSA + HCA = 6.92; all P < 0.05).

HA-complicated skin and skin structure infections

Lipsky BA, Diagn Microbiol Infect Dis. 2014

How we do reduce the rate of inappropriate therapy? Practical daily life

- Reduce **duration of empiric antibiotic therapy**
- Improve algorithm for **rapid diagnosis**
- Improve **knowledge** of epidemiological and clinical variables associated with appropriate antibiotic therapy by MDR-bacteria

Hospital mortality increased as empiric antibiotic duration increased (P<0.001)

Table 3 Multivariable analysis of the effect of intervention group and empiric antibiotics on hospital mortality

	OR (95% CI)	*P* value
Intervention effect base model:		
Prompted group	0.41 (0.18-0.92)	0.032
APACHE IV predicted mortality	47.8 (10.3-222)	<0.001
Empiric antibiotics mediating effect model:[a]		
Prompted group	0.50 (0.21-1.2)	0.11
APACHE IV predicted mortality	37.0 (7.6-180)	<0.001
Empiric antibiotics 4–6days	2.1 (0.76-6.0)	0.15
Empiric antibiotics ≥7days	2.5 (0.92-6.6)	0.074
Independent empiric antibiotics model:[a]		
APACHE IV predicted mortality	30.5 (6.6-140)	<0.001
Empiric antibiotics 4–6days	2.3 (0.81-6.3)	0.12
Empiric antibiotics ≥7days	3.1 (1.2-8.0)	0.019

[a] Category 1 (empiric antibioticduration 1–3days) used as reference
OR: Odds ratio ofdeath. CI: confidence interval.

Weiss, BMC health series research 2012

TABLE 2. Multivariate Analysis of Predictors of Appropriate Empirical Therapy

Characteristic	OR (95% CI)
Previous knee or hip arthroplasty	3.04 (1.21–7.60)
McCabe score of 1 at admission	1.83 (1.16–2.83)
Hemodialysis	1.36 (1.00–1.85)
Central venous catheter present at admission	1.72 (1.01–2.93)
Primary bloodstream infection	0.41 (0.27–0.63)
Bowel incontinence	0.41 (0.19–0.92)

Previous MRSA infection was not predictive

Appropriate therapy of nosocomial MRSA [291/592= 52%]

Herzke, Infect Control Hosp Epidemiol 2009

Table 3.. Two logistic regression analyses of risk factors associated with healthcare-associated MRSA bacteraemia within 24 h of hospitalization, including (first model) and excluding (second model) a history of previous MRSA infection or

Variables	OR	95%CI	*P* value
First model			
previous MRSA infection or colonization	17.04	4.98–58.27	<0.001
cellulitis at hospital admission	4.27	1.52–11.94	0.006
presence of a central venous catheter	3.30	1.71–6.38	<0.001
skin ulcers at hospital admission	3.12	1.37–7.11	0.007
Second model			
presence of a central venous catheter	3.24	1.76–5.97	<0.001
hospitalization in the previous 6 months	2.01	1.11–3.65	0.02
quinolone therapy in the previous 30 days	1.99	1.07–3.69	0.02
diabetes mellitus	1.84	1.05–3.22	0.03

Tacconelli E, JAC, 2004

- Prospective study: 729 patients
- Higher rate of IAT was observed in PN (23%) and wound infections (WI) (19%)
- **COIs were more frequently associated to IAT than HAI (48% vs 31%**; OR = 1.7, 95% CI = 1.2-2.4)
- Overall mortality rate: 12%
  - higher in COI (20%) compared to HAI (10%)
- IAT significantly increased the risk of mortality in COI systemic infections (RR=8.3, 95%CI 1.01-13.3). Stratifying by type of infection, IAT increased the risk of mortality of BSI by 8-time (95%CI, 2 -46.3)

Knowledge of the site of acquisition makes a difference

Tacconelli, under submission

Conclusions (I)

- The rate of inappropriate empiric initial therapy is unacceptable high
- The impact is still to be defined in term of outcome indicators
- Knowledge of local situation and patients' risk factors are crucial to perform appropriate analysis and define most appropriate areas of interventions to increase adequate coverage of MDR-GN and improve patients' safety

Conclusions (II)

- Research are urgently need to define new outcome indicators as well as how to analyse the impact of **empiric therapy in non microbiologically proven** infections that still represents an importance rate in our hospitals. **New study design to evaluate the role of empiric therapy** are also needed.
- Until now, the major focus has been on the organism and its susceptibility to the drug. However, evaluation of the context, the host, and the environment cannot be ignored.

- **SIMPLIFIED MATHEMATICAL CALCULATION TO DETERMINE THE MOST APPROPRIATE ANTIBIOTIC COMBINATION IN A SCENARIO WHERE MONOTHERAPY IS DOOMED TO FAILURE.**

- The susceptibility pattern of 11 antibiotics from 216 positive blood cultures from January 2012 to January 2013 was analyzed based on local policy.
- Bacteremia in ward or intensive care unit

- A total of 55 possible mathematical associations were found combining 2 by 2, 165 associations with 3 by 3 and 330 combinations with 4 by 4.
- **Only three drugs combined reached a susceptibility rate higher than 90% anywhere in the hospital. Several regimens using four drugs combined reached 100% of susceptibility.**
- **CONCLUSIONS:**
- **Association of three drugs is necessary for adequate coverage of empirical treatment of bacteremia in both the intensive care unit and the ward.**