AZIENDA OSPEDALIERA CARLO POMA

Sistema Sanitario Regione Lombardia

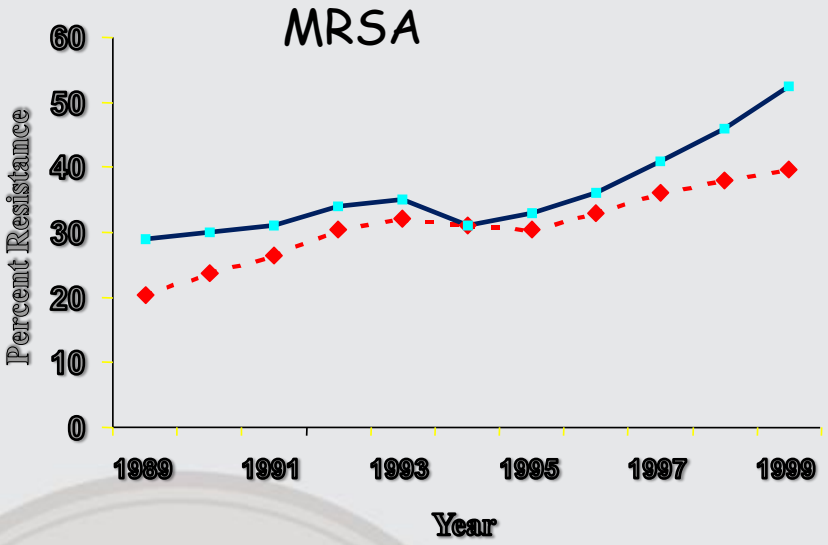
ECOCARDIOCHIRURGIA.it

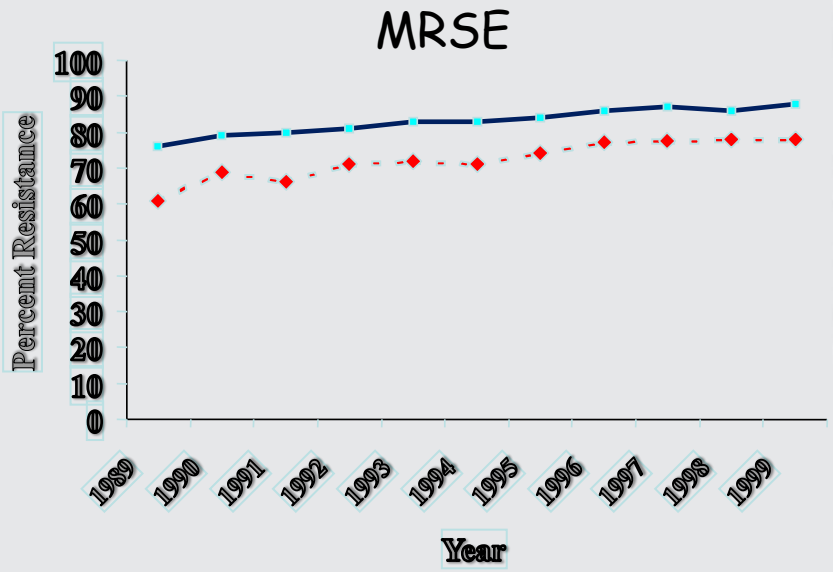
Milano,
20-21/5/2013

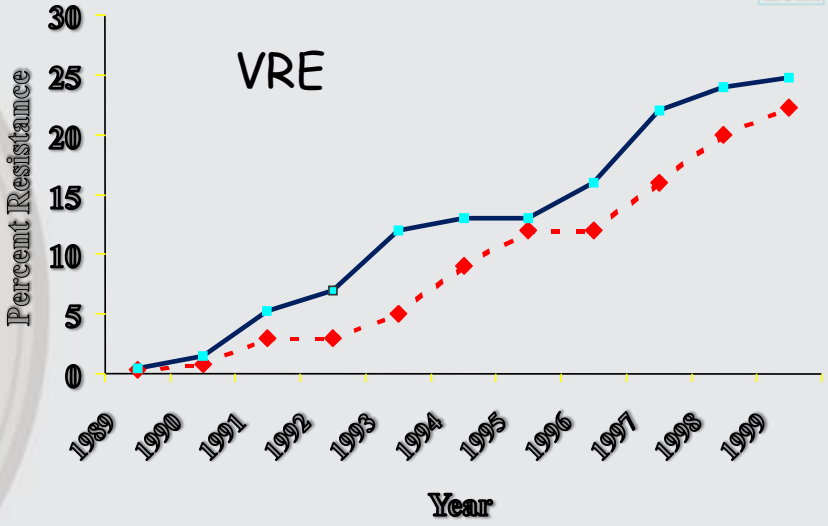
Regole essenziali per la terapia antibiotica in ICU

G. Gattuso
SC Malattie Infettive
Azienda Ospedaliera "Carlo Poma"
MANTOVA

USA 1989-99
trend dell'antibiotico resistenza nelle batteriemie da Gram +





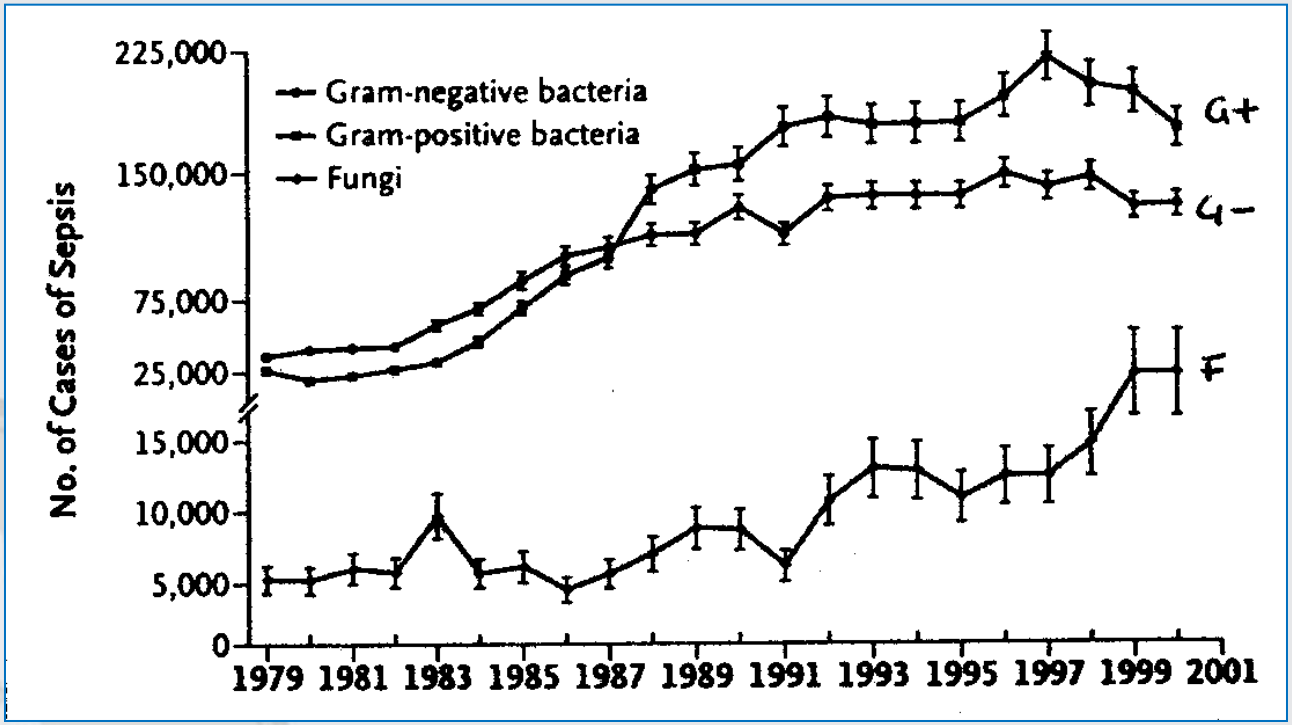


T. intensiva

Area medica/ chirurgica

Source: NNIS DATA

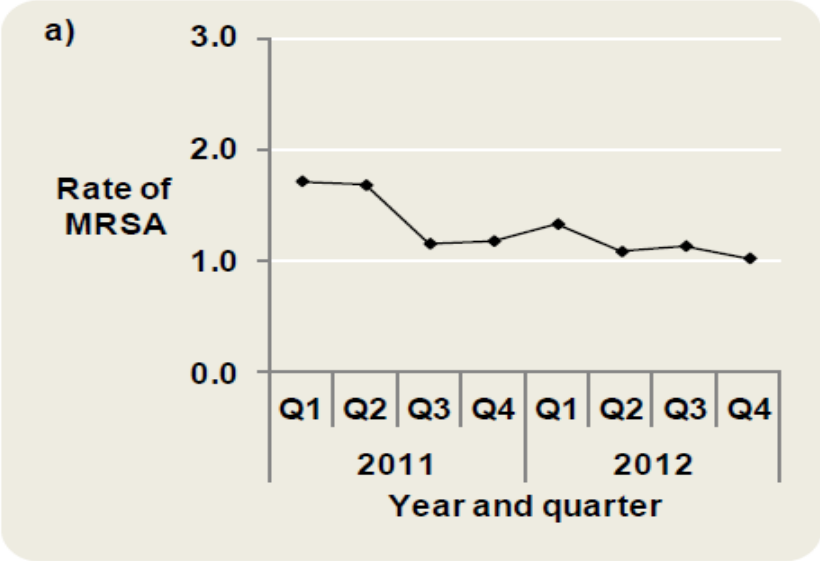
Casi di sepsi negli Stati Uniti, in relazione all'agente eziologico, dal 1979-2000

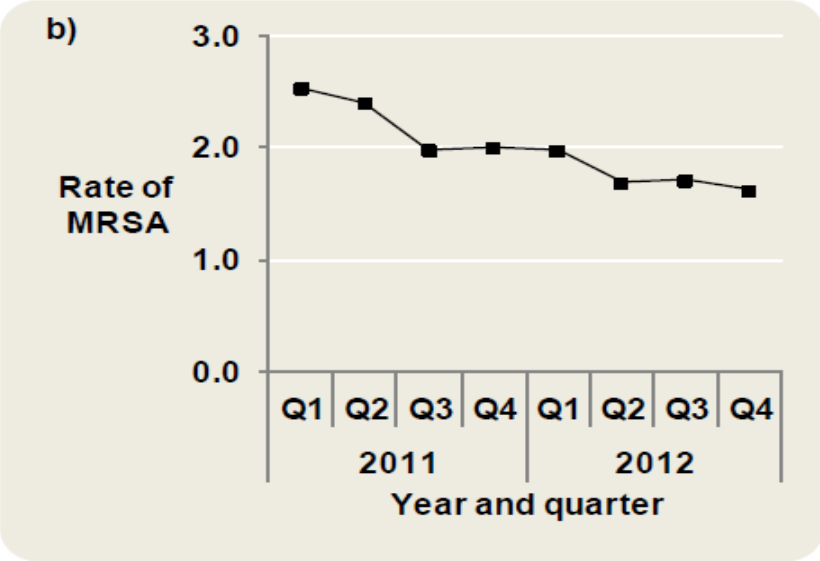


Martin GS et al. N Engl J Med 2003

UK *S.aureus* bacteremia surveillance 2011-2012

a) Trust apportioned rate (per 100,000 bed-days) b) All reports (per 100,000 population)





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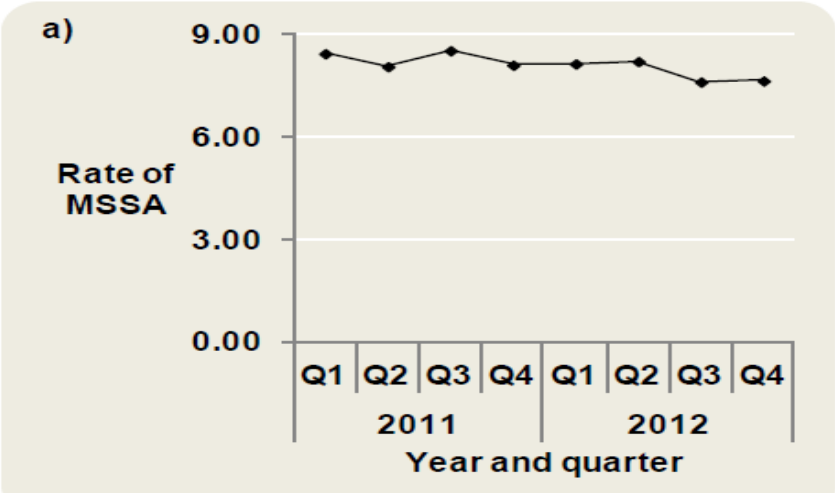
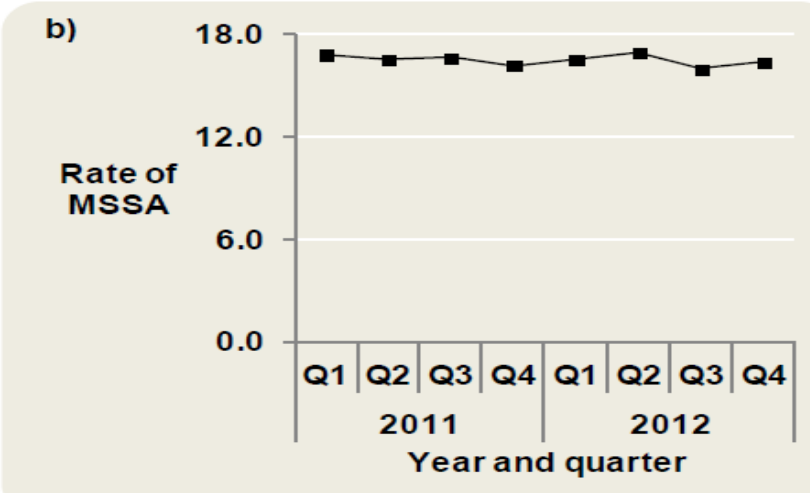




Antimicrobial-Resistant Pathogens Associated with Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010

CDC
ICHE 2013

TABLE 11. Changes in Percent Resistance among Pathogens Associated with VAPs Reported to the National Healthcare Safety Network, 2007–2010

Resistant pathogen, antimicrobial agents[a]	Resistance percentage, 2007–2008, % (95% CI)	Resistance percentage, 2009–2010, % (95% CI)	Overall change, %	*P* value
Staphylococcus aureus				
Oxacillins	51.9 (49.6, 54.1)	48.4 (46.2, 50.6)	−6.7	.03
Enterococcus species				
E. faecium, vancomycin	82.4 (64.2, 100.5)	82.6 (67.1, 98.1)	0.3	.98
E. faecalis, vancomycin	6.4 (−0.6, 13.4)	9.8 (0.7, 18.8)	52.8	.56
Klebsiella (*pneumoniae*/*oxytoca*)				
ES cephalosporins 4	21.5 (18.5, 24.5)	23.8 (20.8, 26.9)	10.9	.29
Carbapenems	9.9 (7.5, 12.4)	11.2 (8.7, 13.7)	12.6	.48
Multidrug resistant 1	11.8 (9.3, 14.4)	13.4 (10.8, 16.0)	13.0	.41
Escherichia coli				
ES cephalosporins 4	14.2 (10.6, 17.9)	16.3 (12.8, 19.8)	14.5	.43
Fluoroquinolones 3	33.3 (28.6, 38.1)	35.2 (30.9, 39.5)	5.6	.57
Carbapenems	3.0 (1.0, 5.1)	3.5 (1.5, 5.4)	15.1	.75
Multidrug resistant 1	1.7 (0.2, 3.1)	3.3 (1.5, 5.1)	95.9	.20
Enterobacter species				
ES cephalosporins 4	34.6 (30.9, 38.3)	30.1 (26.7, 33.6)	−13.0	.08
Carbapenems 2	4.6 (2.7, 6.6)	3.6 (2.0, 5.2)	−22.7	.41
Multidrug resistant 1	2.5 (1.1, 3.8)	1.4 (0.4, 2.3)	−43.8	.20
Pseudomonas aeruginosa				
Aminoglycosides	10.8 (8.9, 12.7)	11.3 (9.3, 13.4)	4.6	.73
ES cephalosporins 2	28.5 (26.1, 30.8)	28.4 (26.0, 30.8)	−0.2	.98
Fluoroquinolones 2	32.7 (30.3, 35.2)	32.7 (30.3, 35.2)	0.0	.99
Carbapenems 2	31.1 (28.4, 33.8)	30.2 (27.6, 32.8)	−2.8	.65
Piperacillin/tazobactam	19.2 (16.8, 21.6)	19.1 (16.7, 21.4)	−0.8	.93
Multidrug resistant 2	16.6 (14.7, 18.6)	17.7 (15.6, 19.7)	6.2	.48
Acinetobacter baumannii				
Carbapenems	56.7 (52.8, 60.6)	61.2 (56.7, 65.8)	8.1	.13
Multidrug resistant 3	67.4 (63.9, 71.0)	63.4 (59.4, 67.4)	−6.0	.14

NOTE. The 2007–2008 numbers may differ from those in the previous report,[1] which was limited to a slightly shorter time period. CI, confidence interval; VAP, ventilator-associated pneumonia.

Prevalence and epidemiology of microbial pathogens causing bloodstream infections: results of the OASIS multicenter study

Francesco Luzzaro[a,*,1], Giuseppe Ortisi[b,1], Monica Larosa[c,1], Monica Drago[b,1], Gioconda Brigante[a,1], Giovanni Gesu[b,1]

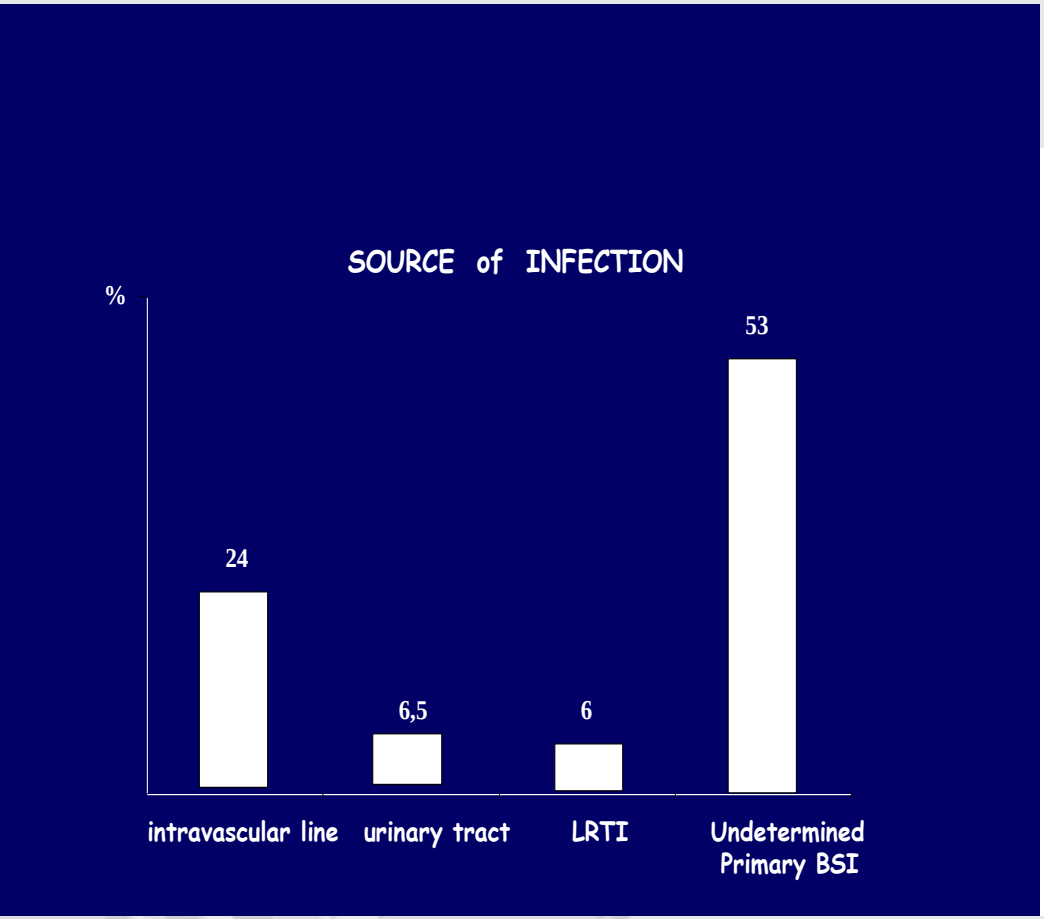
DMID 2011

Table 2
Prevalence of microbial pathogens causing BSIs in hospitalized patients: hospital- and community-acquired infections are shown according to the hospital setting

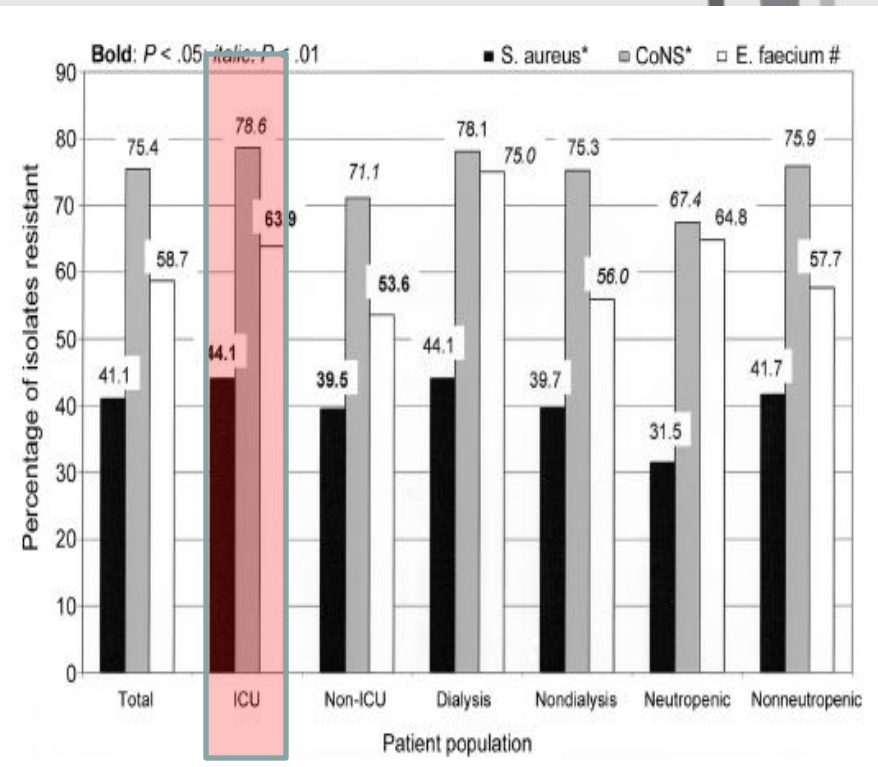
Microorganism	Medical wards (n = 8035)					Surgical wards (n = 2265)					ICUs (n = 2481)				
	No. (%)		HA	CA	Ratio	No. (%)		HA	CA	Ratio	No. (%)		HA	CA	Ratio
Gram-positives	3650	(45.4)	2274	1736	1.31	884	(39.0)	718	166	4.32	1074	(43.3)	792	282	2.81
Staphylococcus aureus	1332	(16.6)	785	547	1.44	284	(12.5)	227	57	3.98	293	(11.8)	198	95	2.08
Staphylococcus epidermidis	621	(7.7)	508	113	4.50	191	(8.4)	172	19	9.05	242	(9.8)	199	43	4.63
Enterococcus faecalis	449	(5.6)	282	167	1.69	148	(6.5)	115	33	3.48	201	(8.1)	160	41	3.90
Enterococcus faecium	321	(4.0)	265	56	4.73	110	(4.9)	88	22	4.00	108	(4.4)	92	16	5.75
Streptococcus pneumoniae	209	(2.6)	39	170	0.23	9	(0.4)	2	7	0.29	50	(2.0)	6	44	0.14
Gram-negatives	3834	(47.7)	2256	1578	1.43	1077	(47.6)	810	267	3.03	1147	(46.2)	839	308	2.72
Escherichia coli	2011	(25.0)	1067	944	1.13	470	(20.7)	297	173	1.72	297	(12.0)	164	133	1.23
Pseudomonas aeruginosa	501	(6.2)	346	155	2.23	130	(5.7)	111	19	5.84	260	(10.5)	210	50	4.20
Klebsiella pneumoniae	309	(3.8)	208	101	2.06	118	(5.2)	93	25	3.72	125	(5.0)	95	30	3.17
Enterobacter cloacae	160	(2.0)	105	55	1.91	64	(2.8)	53	11	4.82	79	(3.2)	68	11	6.18
Proteus mirabilis	135	(1.7)	81	54	1.50	28	(1.2)	19	9	2.11	41	(1.7)	28	13	2.15
Serratia marcescens	46	(0.6)	37	9	4.11	61	(2.7)	57	4	14.25	77	(3.1)	68	9	7.56
Klebsiella oxytoca	83	(1.0)	53	30	1.77	53	(2.3)	43	10	4.30	32	(1.3)	24	8	3.00
Stenotrophomonas maltophilia	73	(0.9)	59	14	4.21	25	(1.1)	24	1	24.00	43	(1.7)	38	5	7.60
Anaerobes	115	(1.5)	66	49	1.35	50	(2.2)	34	16	2.12	26	(1.1)	18	8	2.25
Fungi	436	(5.4)	358	78	4.59	254	(11.2)	232	22	10.54	234	(9.4)	196	38	5.16
C. albicans	215	(2.7)	181	34	5.32	153	(6.7)	141	12	11.75	127	(5.1)	115	12	9.58
C. parapsilosis	84	(1.0)	66	18	3.67	37	(1.6)	33	4	8.25	54	(2.2)	34	20	1.70

HA = hospital-acquired BSI (i.e., occurring at least 72 h after admission); CA = community-acquired BSI (i.e., occurring within 72 h after admission).

Nosocomial Bloodstream Infections in US Hospitals: Analysis of 24,179 Cases from a Prospective Nationwide Surveillance Study



Antimicrobial resistance (pts with bacteremia)



Wisplinghoff H et al. Clin Infect Dis 2004

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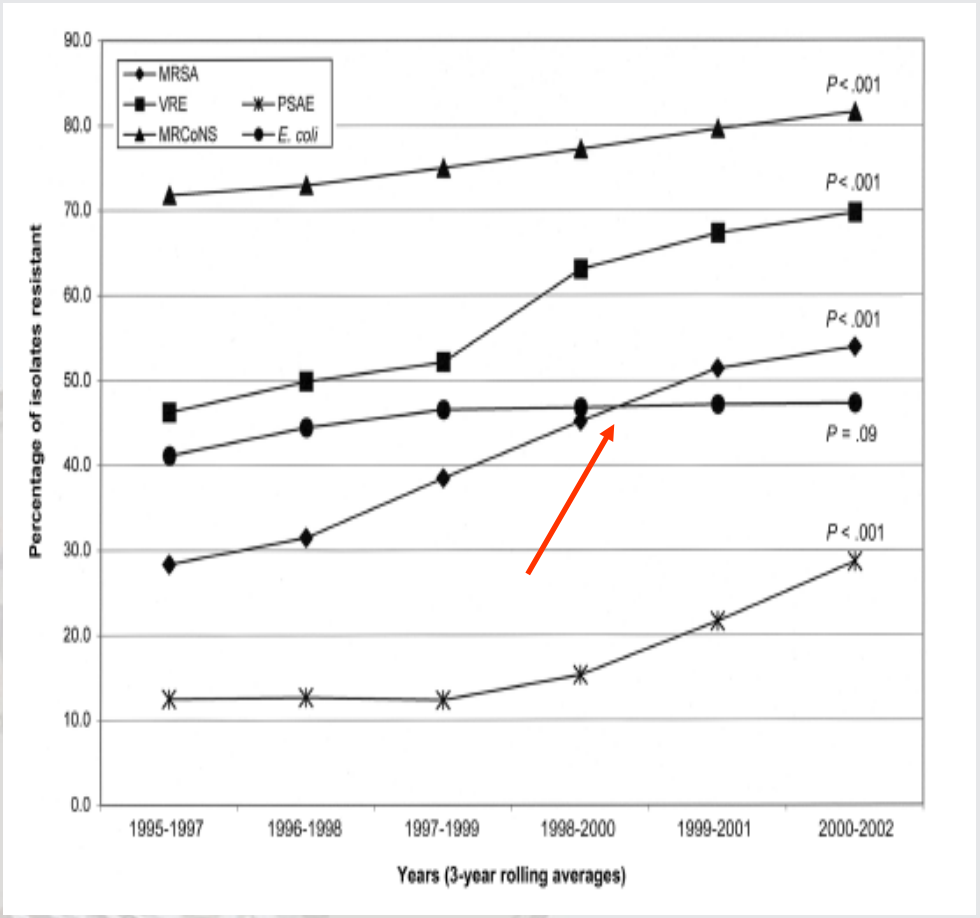

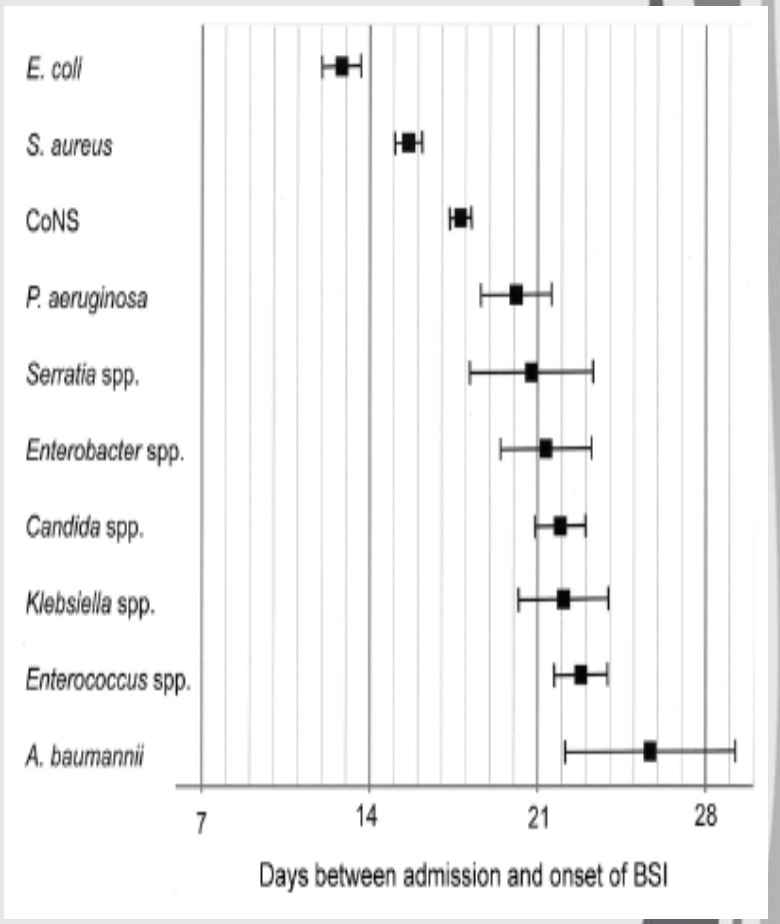

Wisplinghoff H et al. Clin Infect Dis 2004

Table 6. Variables associated with related and crude mortality, in terms of estimated adjusted odds ratios and 95% confidence intervals.

Variable	Related mortality, OR (95% CI)	Crude mortality, OR (95% CI)
Septic shock	11.7 (5.1–26.8)	3.1 (1.6–5.9)
ARDS	3.75 (1.6–8.3)	3.9 (1.9–8.3)
Acute renal failure	3.0 (1.3–6.8)	2.0 (1.0–3.8)
MOF	2.35 (1.0–5.4)	2.5 (1.0–5.9)
Gram-negative or candidal bacteremia	2.2 (1.1–4.3)	. . .
Noncatheter origin of bacteremia	2.3 (1.1–4.8)	. . .
Severe sepsis	2.05 (0.8–5.1)	. . .
Mechanical ventilation	. . .	2.4 (1.1–5.0)
Chronic hepatic failure	. . .	2.2 (1.0–4.9)
APACHE II score of ≥15 at the time of bacteremia	. . .	1.8 (1.1–2.8)

G+ infections in ICU

- Host factors impact outcomes: there has been a change in the type of patients developing Gram positive infection and

- "aggressive surgeries", debilitating chronic illness, immunosuppression, severe comorbidities and exposure to "advanced" resuscitative interventions are now common risk factors for infections

Why do we see more resistance?

- Sicker inpatient population
- Patients chronically ill
- Larger immunocompromised population
- More instrumentation/new procedures
- Presence of devices
- Increasing resistance in community
- Emerging pathogens
- Complacency regarding antibiotics
- Increased use of (empiric) broad-spectrum antibiotics
- Ineffective infection control and compliance
- Crowding of patients in confined areas
- Decreasing nurse/patient ratio

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Returning to the pre-antibiotic era in the critically ill: The XDR problem*

David L. Paterson, MBBS, FRACP, FRCPA, PhD
Jeffrey Lipman, MBBCh, DA, FFA, FJFICM, MD

Crit Care Med 2007 Vol. 35, No. 7

Risk factors for resistant pathogens[2,4,5]

MDR *P aeruginosa*	ESBL-producing *E coli*	MDR *Acinetobacter* spp
Immunocompromised state	Catheterization	Male sex
Protracted hospital stay	Diabetes	Mechanical ventilation
Prolonged antibiotic use	Previous antibiotic use	Ischemic heart disease
Advanced age	Underlying disease	Home antibiotic treatment
Mechanical ventilation		
Intravenous drug abuse		

Antibiotics

- "Deaths in the US declined by 220 per 100,000 with the introduction of sulfonamides and penicillin. This far outweighs any other medical advance in the past century."

Armstrong et al. JAMA 1999

- From 1983 to 2010, FDA approval of new antibiotics has continuously declined, from 4 per year in the early 1980s to less than 1 antibiotic per year now

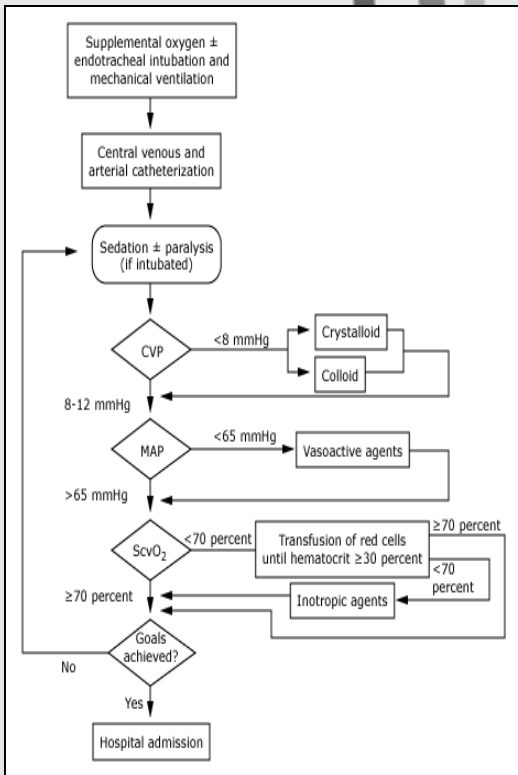
- The last class of drugs with a novel mechanism of action against GN bacteria goes back 40 years. A review of drugs currently in trials revealed no such new drugs.

- For the US, antibiotic resistance is responsible for nearly 100,000 deaths caused by hospital-acquired infections per year at an estimated annual cost of $23 billion.

Roberts et al CID 2009

Sepsis -Treatment

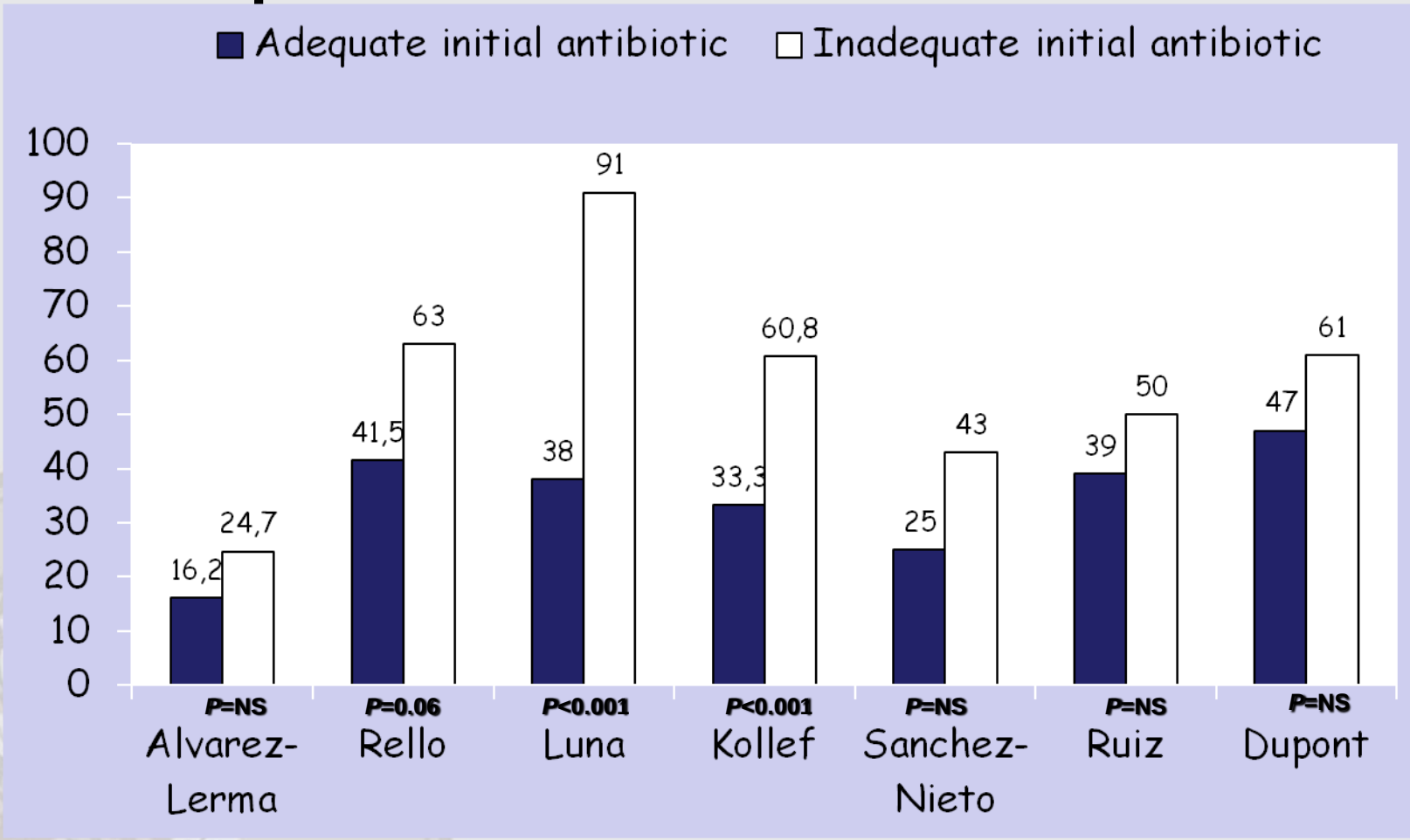
- Antibiotics
  - Targeted at known organisms or empiric treatment
  - Within 4-6 hours (*golden hours*)
- Early Goal Directed Therapy



Inadequate Antibiotic Therapy in Critically Ill Patients Leads to an Increase in:

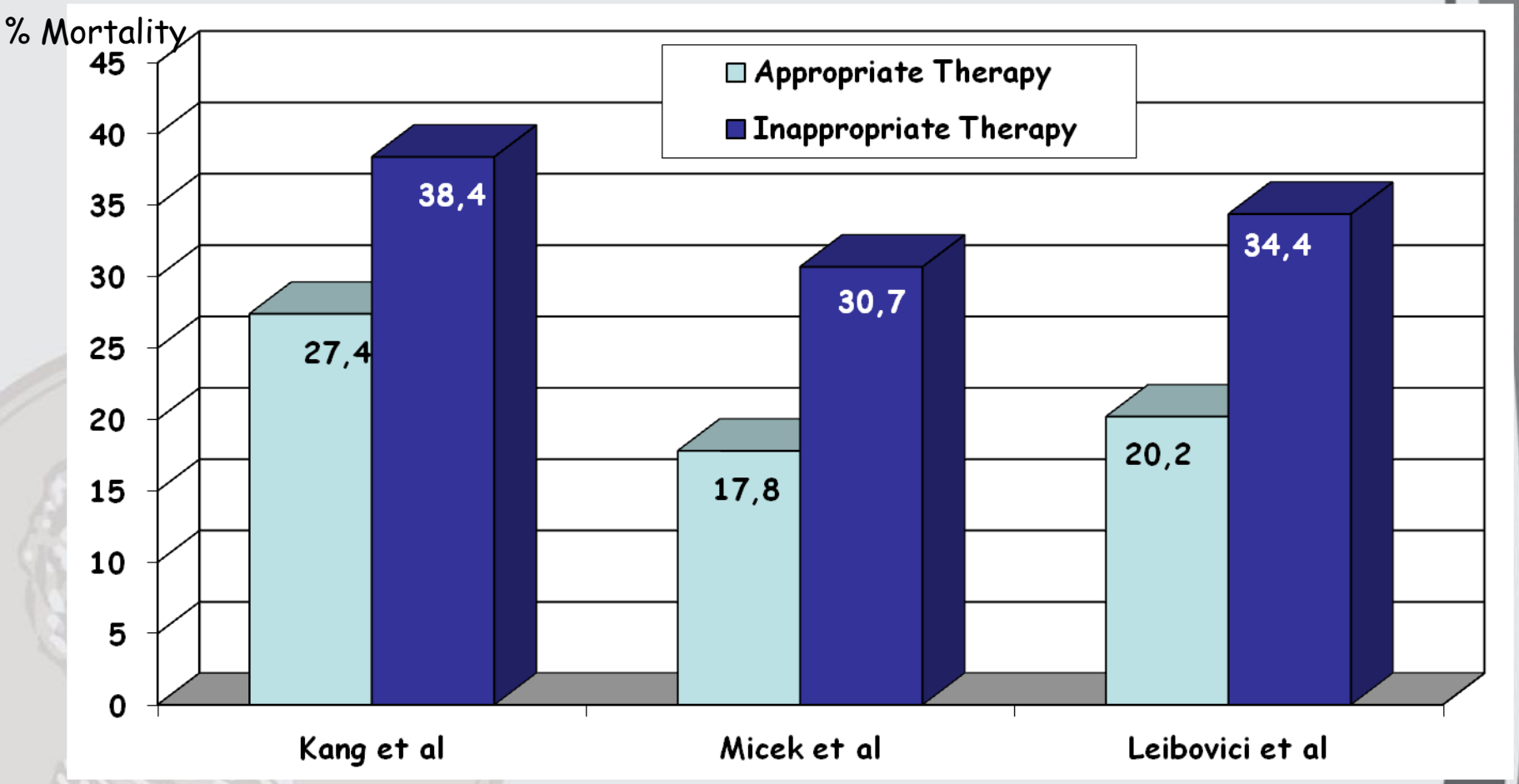
- Mortality
- Morbidity
- Length of hospital stay
- Resistance selection
- Cost burden

The Importance of Initial Empiric Antibiotic Selection



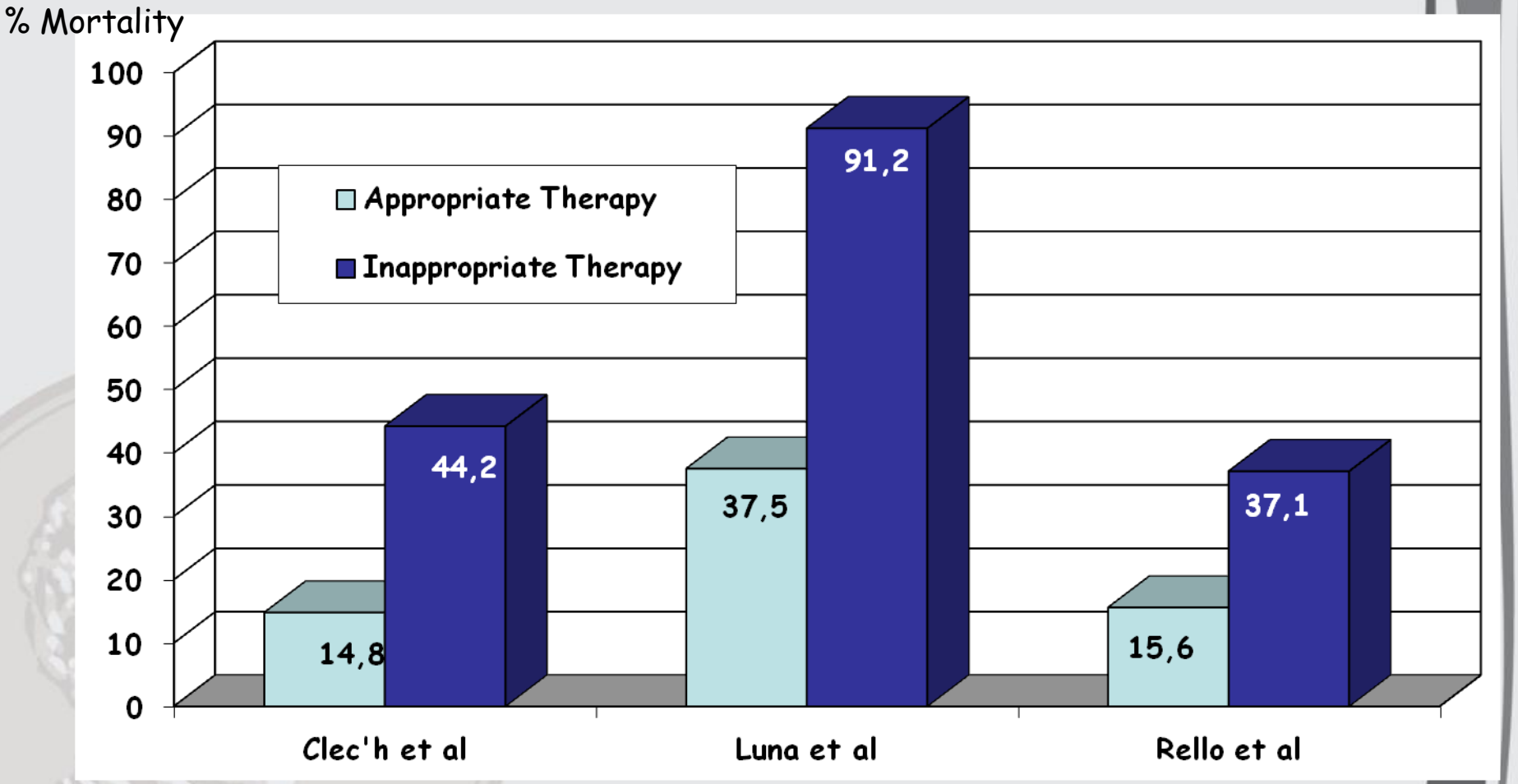
Alvarez-Lerma F. *Intensive Care Med.* 1996;22:387-394.
Rello J, et al. *Am J Respir Crit Care Med.* 1997;156:196-200.
Luna CM, et al. *Chest.* 1997;111:676-685.
Kollef MH, Ward S. *Chest* 1998;113:412-420.
Sanchez-Nieto JM, et al. *Am J Respir Crit Care Med.* 1998;157:371-376.
Ruiz M, et al. *Am J Respir Crit Care Med.* 2000;162:119-125.
Dupont H, et al. *Intensive Care Med.* 2001;27:355-362.

Getting It Right
Bloodstream Infections



Getting It Right

Ventilator-associated Pneumonia



It is a lot more difficult to get it right if the bacteria are multi-drug resistant !!!!!!

Prediction models to identify hospitalized patients at risk of being colonized or infected with multidrug-resistant *Acinetobacter baumannii* Complex

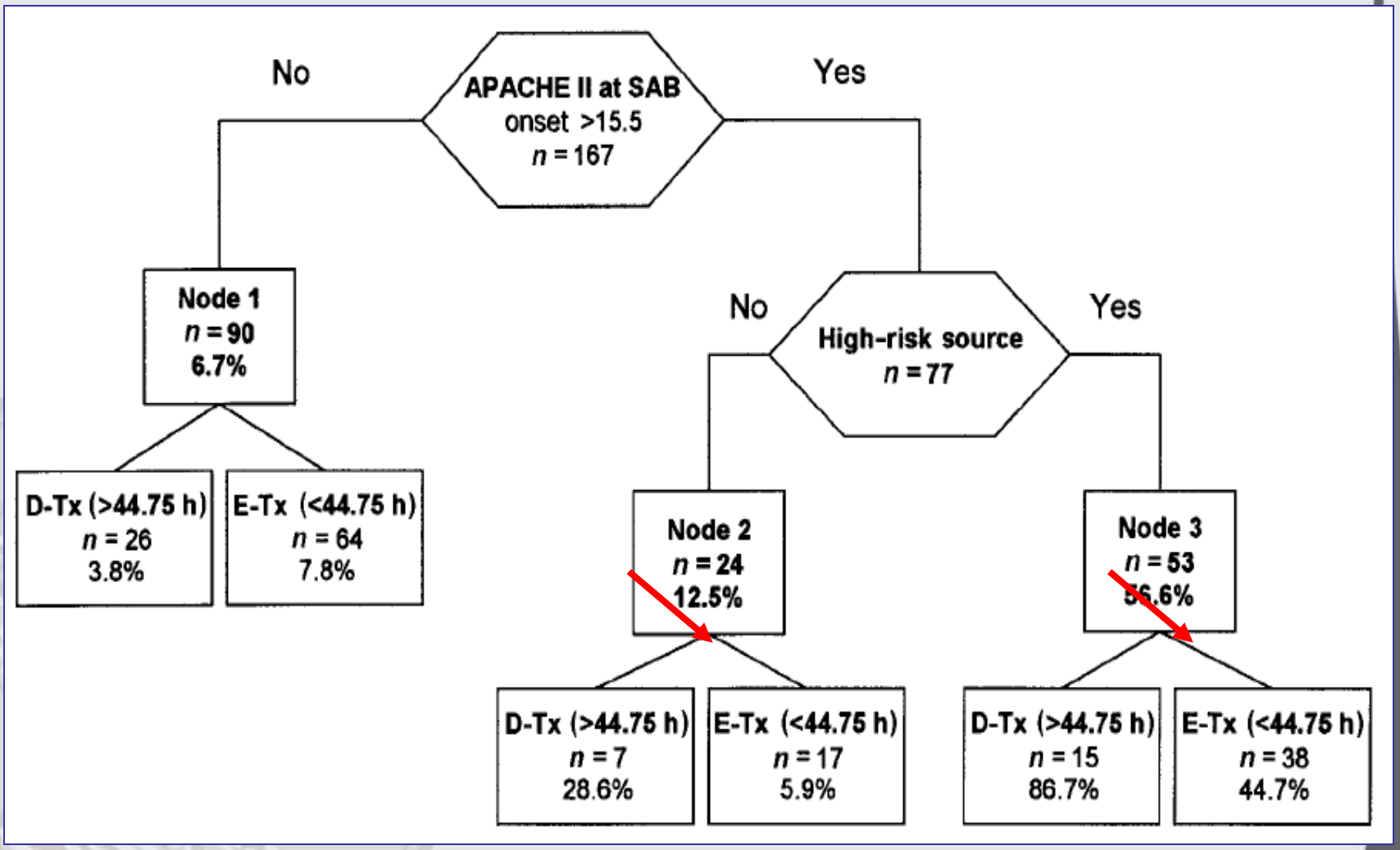
Tacconelli E. JAC 2008

Table 4. Conditional regression analysis predicting MDR-*Abc* among patients colonized or infected

Case groups	OR (95% CI)
Colonized patients	
bedridden status	14.2 (3.1–65.8)
previous MRSA[b]	6.3 (1.2–34.3)
ICU admission[a]	5.8 (1.9–18.2)
prior β-lactam therapy[a]	3.6 (1.2–10.4)
Charlson score >3[c]	3 (1.1–7.7)
Infected patients	
central venous catheter	17.7 (4.3–71.6)
Charlson score >3[c]	17.5 (4.3–73.1)
prior MRSA[b]	12.7 (1.9–83.1)
prior β-lactam therapy[a]	9 (2.4–33.5)
surgery[a]	6 (1.6–22.1)

Outcomes Analysis of Delayed Antibiotic Treatment for Hospital-Acquired *Staphylococcus aureus* Bacteremia

Lodise TP et al, Clin Infect Dis 2003



The Lancet Infectious Diseases, Volume 12, Issue 10, Pages 774 - 780, October 2012

Aggressive versus conservative initiation of antimicrobial treatment in critically ill surgical patients with suspected intensive care-unit-acquired infection: a quasi-experimental, before and after observational cohort study

Tjasa Hraniec et al.

Background

Antimicrobial treatment in critically ill patients can either be started as soon as infection is suspected or after objective data confirm an infection. We postulated that delaying antimicrobial treatment of patients with suspected infections in the surgical intensive care unit (SICU) until objective evidence of infection had been obtained would not worsen patient mortality.

Methods

We did a 2-year, quasi-experimental, before and after observational cohort study of patients aged 18 years or older who were admitted to the SICU of the University of Virginia (Charlottesville, VA, USA). From Sept 1, 2008, to Aug 31, 2009, aggressive treatment was used: patients suspected of having an infection on the basis of clinical grounds had blood cultures sent and antimicrobial treatment started. From Sept 1, 2009, to Aug 31, 2010, a conservative strategy was used, with antimicrobial treatment started only after objective findings confirmed an infection. Our primary outcome was in-hospital mortality. Analyses were by intention to treat.

Findings

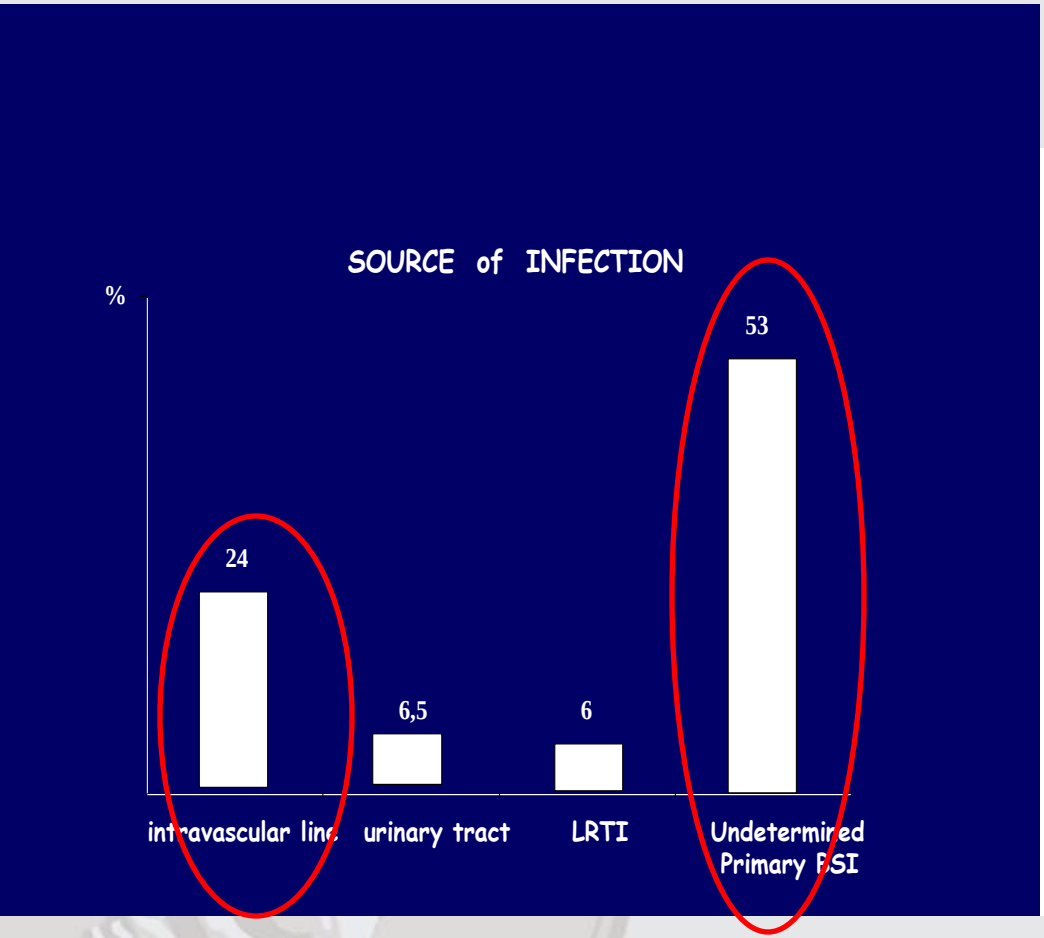
Admissions to the SICU for the first and second years were 762 and 721, respectively, with 101 patients with SICU-acquired infections during the aggressive year and 100 patients during the conservative year. Compared with the aggressive approach, the conservative approach was associated with lower all-cause mortality (13/100 [13%] *vs* 27/101 [27%]; p=0·015), more initially appropriate therapy (158/214 [74%] *vs* 144/231 [62%]; p=0·0095), and a shorter mean duration of therapy (12·5 days [SD 10·7] *vs* 17·7 [28·1]; p=0·0080). After adjusting for age, sex, trauma involvement, acute physiology and chronic health evaluation (APACHE) II score, and site of infection, the odds ratio for the risk of mortality in the aggressive therapy group compared with the conservative therapy group was 2·5 (95% CI 1·5—4·0).

Interpretation

Waiting for objective data to diagnose infection before treatment with antimicrobial drugs for suspected SICU-acquired infections does not worsen mortality and might be associated with better outcomes and use of antimicrobial drugs.

Funding . National Institutes of Health.

Nosocomial Bloodstream Infections in US Hospitals: Analysis of 24,179 Cases from a Prospective Nationwide Surveillance Study



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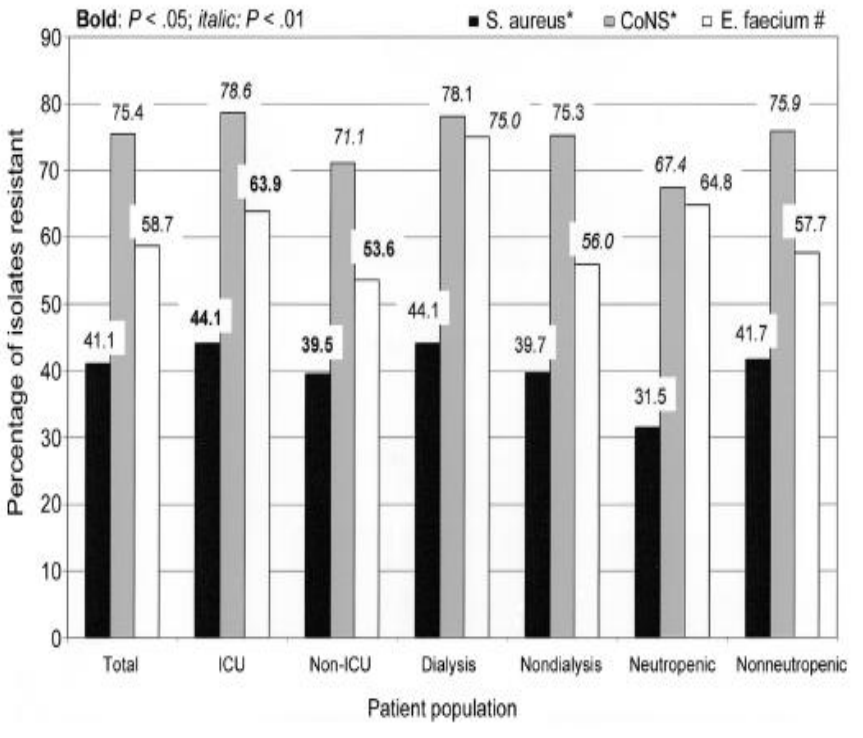


Wisplinghoff H et al. Clin Infect Dis 2004

Studio GiViTi, 2004
Mortalità e Infezioni in ICU

TABELLA III. — *Mortalità e infezione.*

	Mortalità (%) in TI	in H
Pazienti con solo infezioni acquisite in TI	24, 8	32, 2
Pazienti con solo infezioni acquisite pre-TI	35, 4	44, 6
Paz. con infezioni acquisite pre-TI e in TI	32, 5	44, 9
Infezione	19, 8	30, 2
Sepsi	21, 1	31, 6
Sepsi grave	45, 6	52, 9
Shock settico	75, 1	79, 0

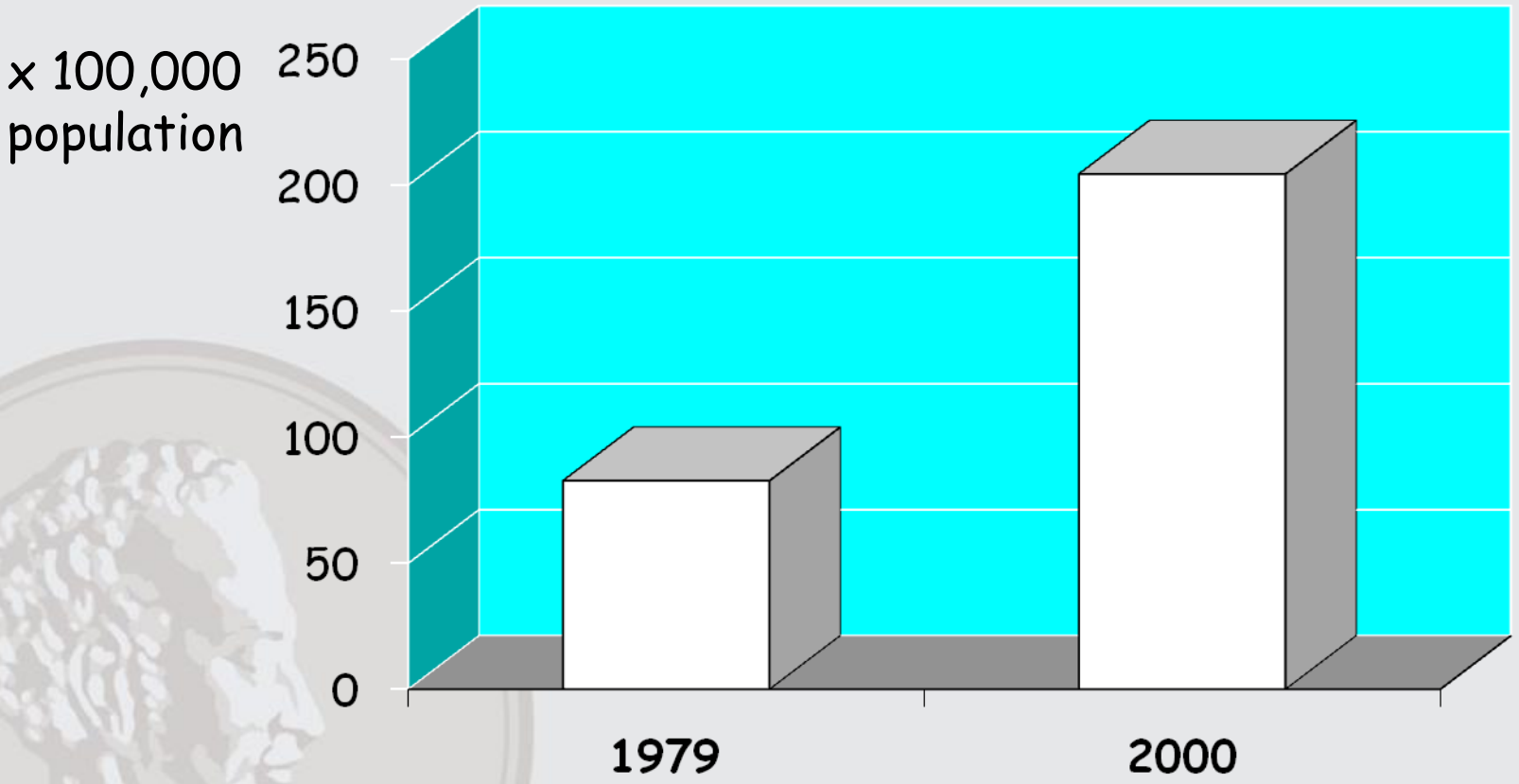
TABELLA IV. — *Microorganismi responsabili delle infezioni.*

	N	%
staphilococco	822	29,7
— aureus	533	19,3
— coagulasi negativi	289	10,4
Streptococco	75	2,7
— pneumoniae	44	1,6
Enterococco	202	7,3
KES	290	10,5
Pseudomonas	448	16,2

P.Malacarne et al.: "La Sorveglianza delle Infezioni in Terapia Intensiva", Minerva Anest. 2004

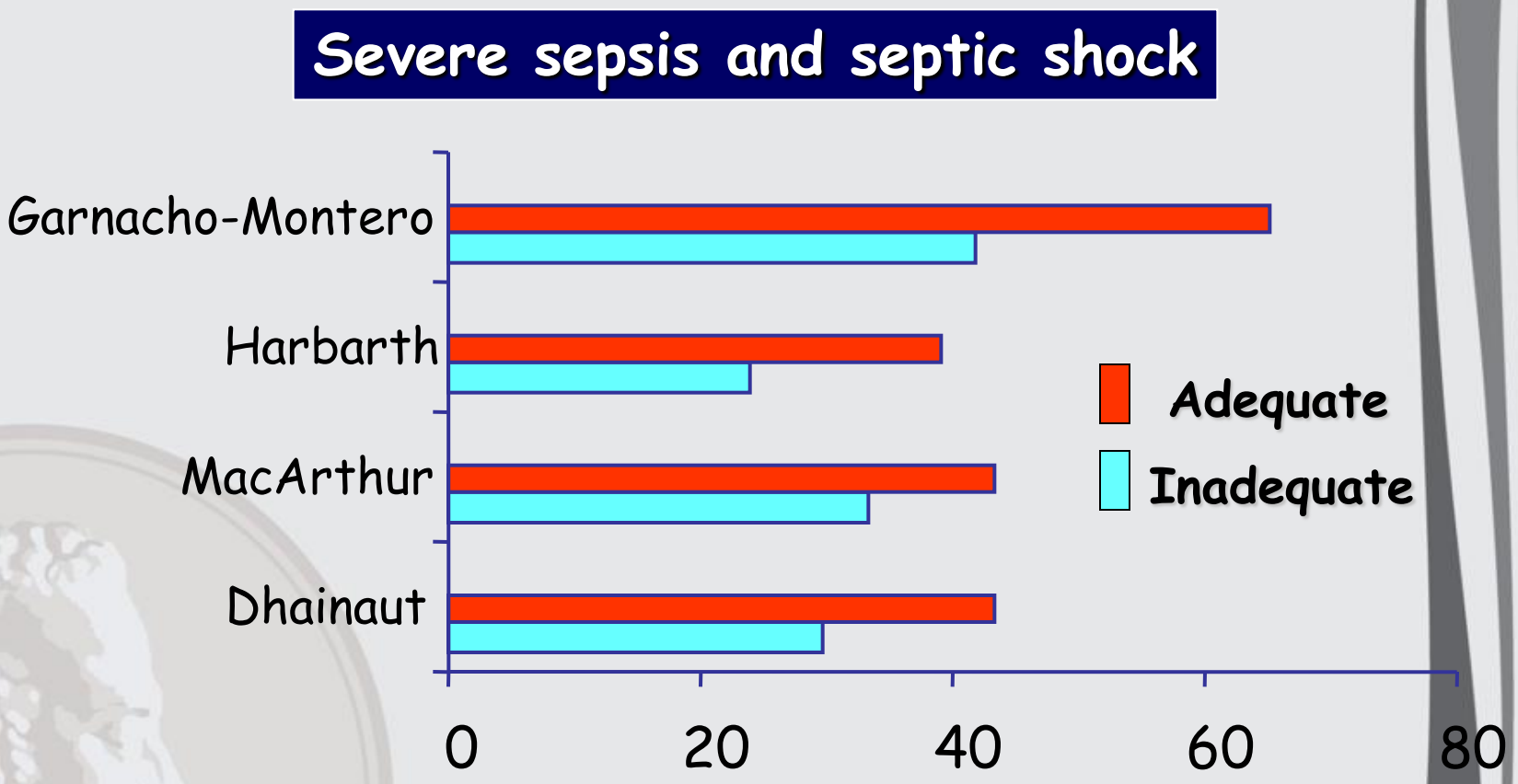
Bacteremias: a leading cause of death

U.S.



Bearman GM et al. Arch Med Res, 2005

Mortality Impact of Inadequate Therapy

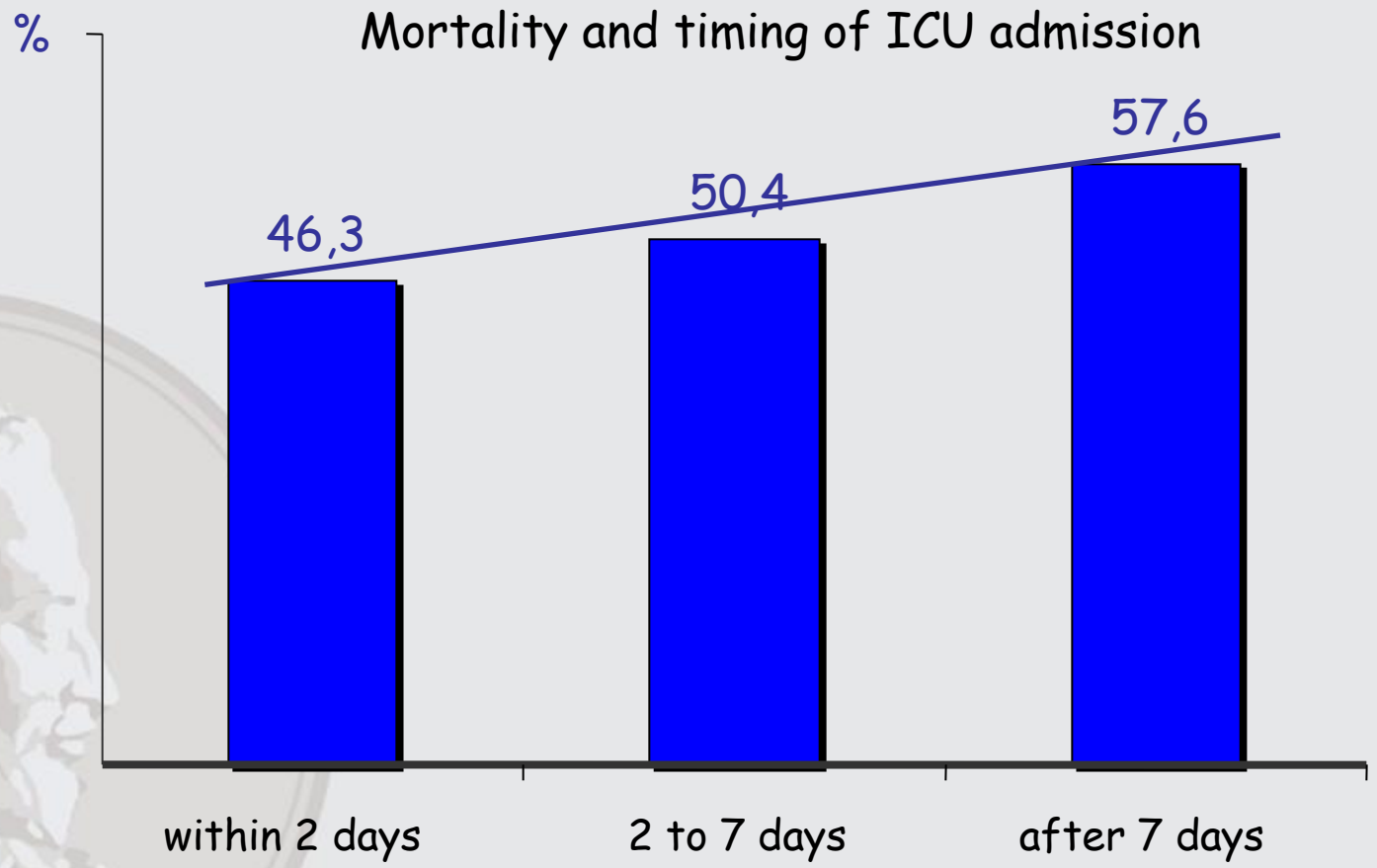


Garnacho-Montero, et al. Crit Care Med 2003
Harbarth, et al. Am J Med 2003
MacArthur, et al. Clin Infect Dis 2004
Dhainaut, et al. Crit Care Med 2003

CAP on the intensive care unit: secondary analysis of 17,869 cases in the ICNARC Case Mix Programme Database

ICU mortality 34.9%

Ultimate hospital mortality 49.4%



Woodhead M et al, Crit Care 2006

Stratifying Risk Factors for Multidrug-Resistant Pathogens in Hospitalized Patients Coming From the Community With Pneumonia

Stefano Aliberti,[1,2] Marta Di Pasquale,[2] Anna Maria Zanaboni,[3] Roberto Cosentini,[4] Anna Maria Brambilla,[4] Sonia Seghezzi,[4] Paolo Tarsia,[2] Marco Mantero,[1] and Francesco Blasi[2]

CID 2012

Table 4. Scoring System to Evaluate the Presence of Multidrug-Resistant Pathogens in Patients With Pneumonia From the Community Who are Hospitalized

Variable	Score
No risk factors for MDR pathogen (including comorbidities)	0
≥1 of the following: cerebrovascular disease, diabetes, COPD, antimicrobial therapy in preceding 90 days, immunosuppression, home wound care, home infusion therapy (including antibiotics)	0.5
Residence in a nursing home or extended-care facility	3
Hospitalization for ≥2 days in the preceding 90 days	4
Chronic renal failure	5

Table 5. Independent Predictors for In-Hospital Mortality in the Study Population

Variable	OR (95% CI)	*P* Value
Hospitalization for ≥2 days in the preceding 90 days	1.63 (1.04–2.54)	.034
Residency in a nursing home or extended-care facility	2.83 (1.54–5.21)	.001
Pneumonia severity index	2.19 (1.58–3.03)	<.001
Severe CAP	2.52 (1.61–3.93)	<.001

Abbreviations: CAP, community-acquired pneumonia; CI, confidence interval; OR, odds ratio.

LOWER RESPIRATORY INFECTIONS (LRI)

MOSTLY SEEN IN ICU RISK FACTORS

- ✓ TRACHEOSTOMY,
- ✓ ENDOTRACHEAL INTUBATION, VENTILATOR,
- ✓ CONTAMINATED AEROSOLS, BAD EQUIPMENT,
- ✓ CONDENSATE IN VENTILATOR TUBING,
- ✓ ANTIBIOTICS,
- ✓ SURGERY,
- ✓ OLD AGE ,
- ✓ COPD,
- ✓ IMMUNOSUPPRESSION

Definitions: The ATS/IDSA Guidelines

HAP

- Pneumonia occurring ≥48 hours post-hospital admission

VAP

- Pneumonia occurring >48-72 hours postintubation

HCAP

- Includes HAP and VAP
- Pneumonia in patients
  - Hospitalized for ≥2 days in an acute care facility within 90 days of infection, residing in a nursing home or LTC facility
  - Attending a hospital or hemodialysis clinic
  - Receiving immunosuppressive therapy or wound care within 30 days of infection

HAP=hospital-acquired pneumonia
HCAP=healthcare-associated pneumonia
LTC=long-term care; VAP=ventilator-associated pneumonia

Am J Respir Crit Care Med 2005

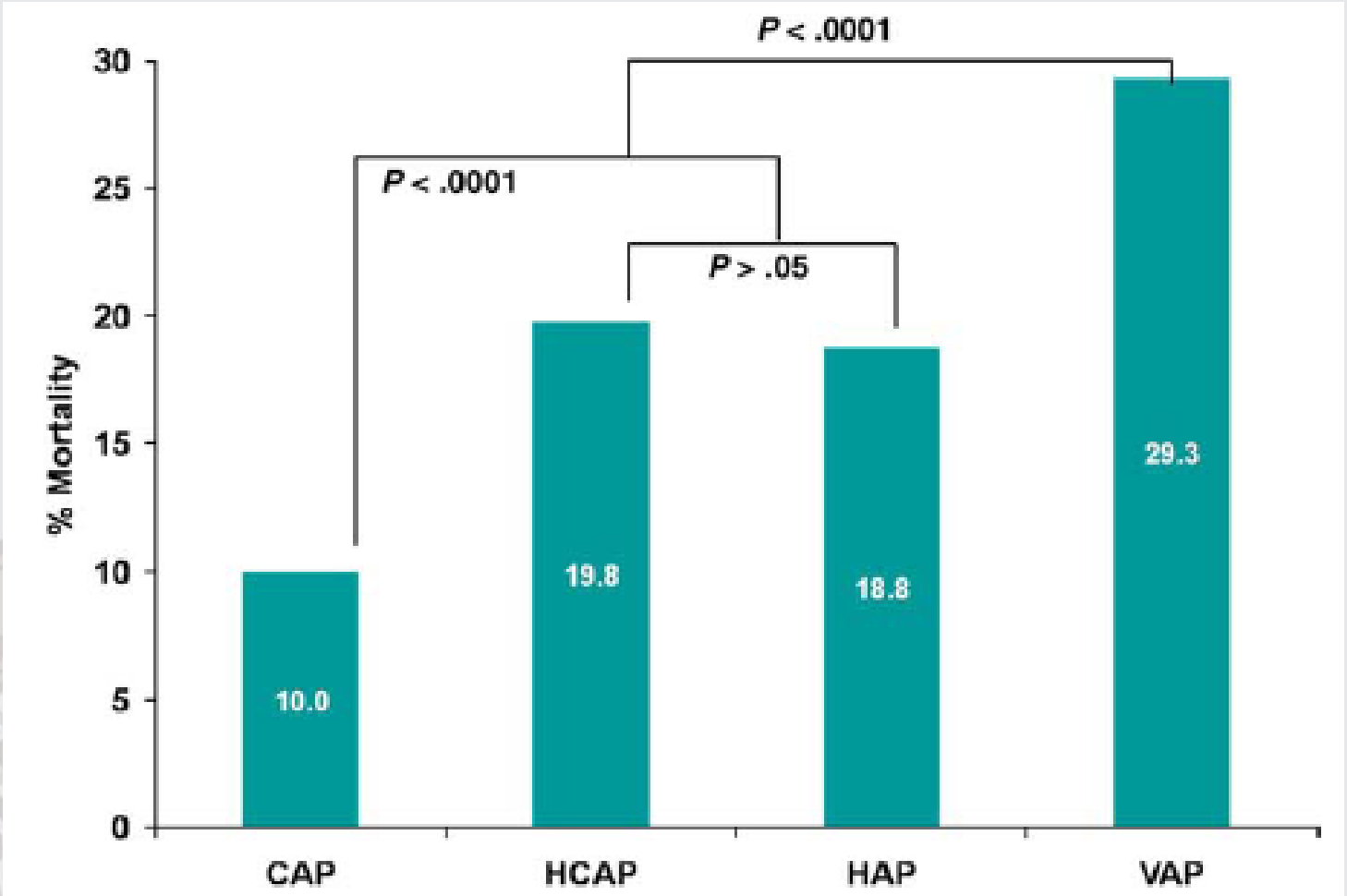


Fig. 1 Mortality rate by pneumonia category. Adapted from *Chest*. 2005;128:3854-3862.

Ventilator-associated pneumonia (VAP)

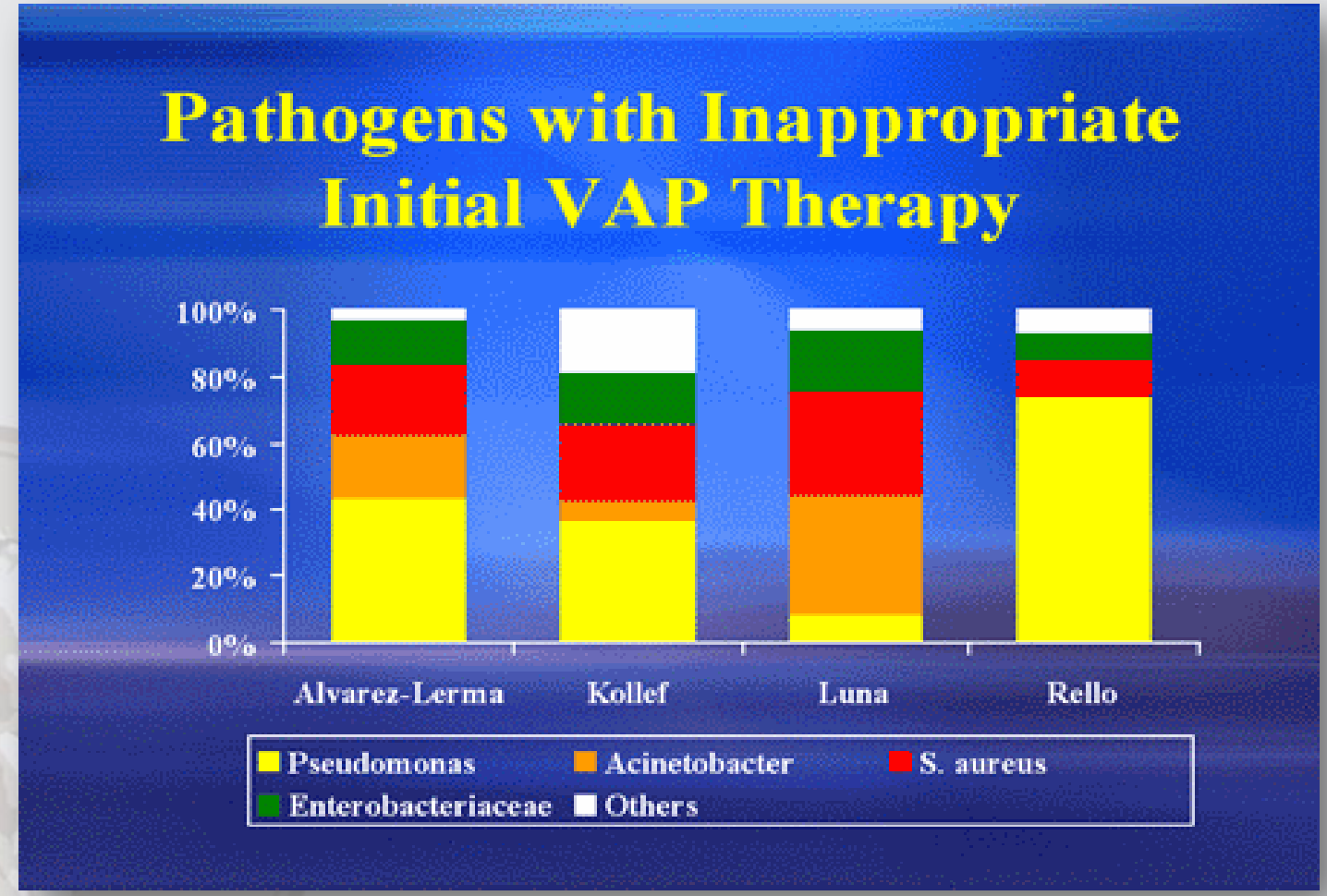
- Incidence : 30 - 200 x 1000 ICU admissions

  5.8 - 34.4 cases x 1000 ventilation-days

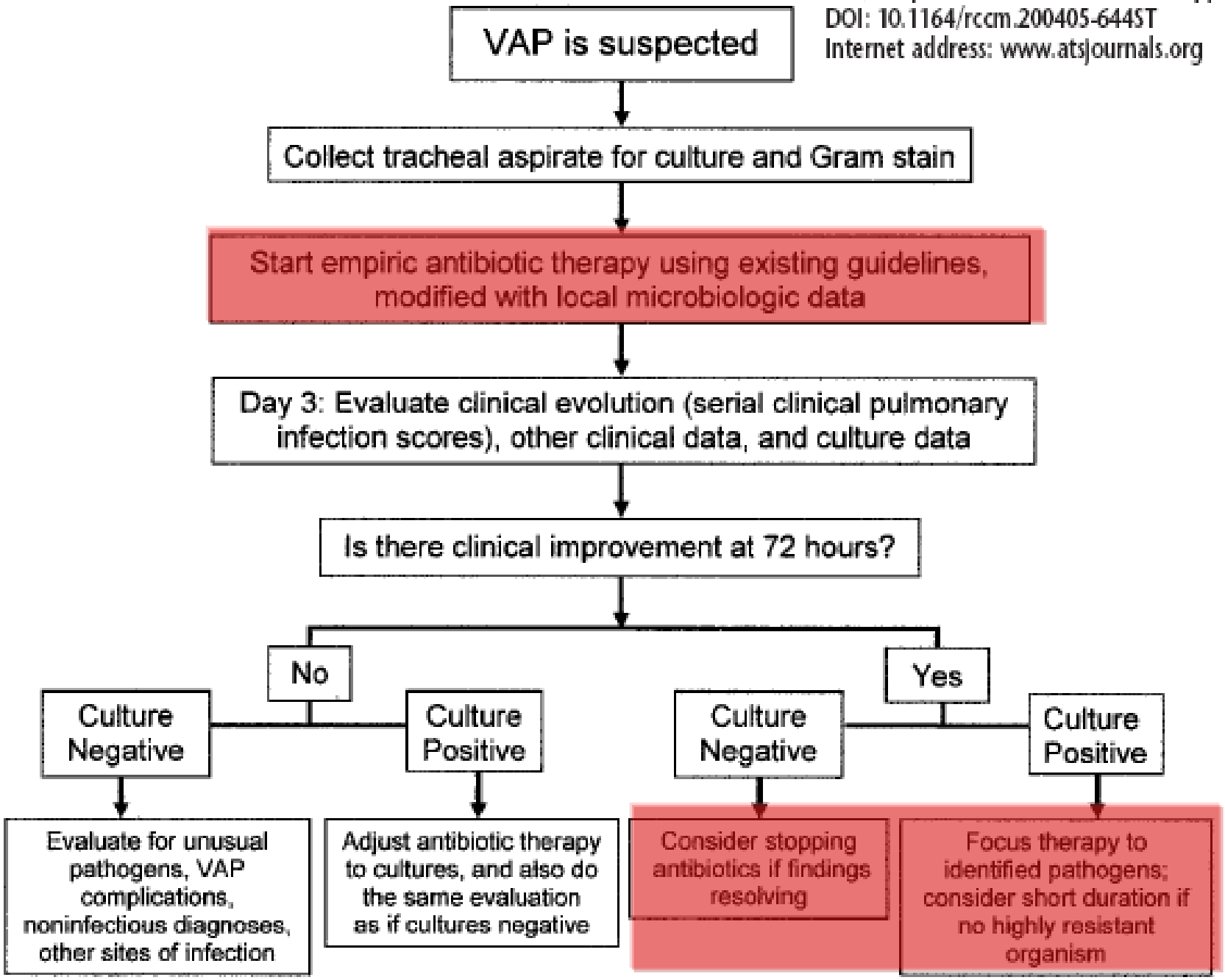
- Global mortality: 30%
- Costs: $ 5.800 - $ 18.000

FR mortality	*Odds Ratio (range)* **Mandell, 2000**
AGE	1,1-4,6
NEOPLASM	1,6
COMORBILITY	4,8-8,8
BILATERAL PNEUMONIA	6,3
ARDS	11,9
SEPTIC SHOCK	2,8
MDR MICRORGANISMS	1,5-8,7
INADEGUATE ATB THERAPY	5,8-32,5
PREVIOUS ATB THERAPY	9,2

VAP: inadeguate antibiotic therapy



Am J Respir Crit Care Med Vol 171. pp 388–416, 2005
DOI: 10.1164/rccm.200405-644ST
Internet address: www.atsjournals.org




REPORT: MEDICAL MISTAKES A LEADING CAUSE OF DEATH
SURGERY
POST-OP
POST-"OOPS!"
MORGUE
Does Antibiotic Treatment Influence Clinical Outcomes?

Nosocomial infections in "critical patients"

Inadeguate treatments

Kollef et al, Chest, 1999

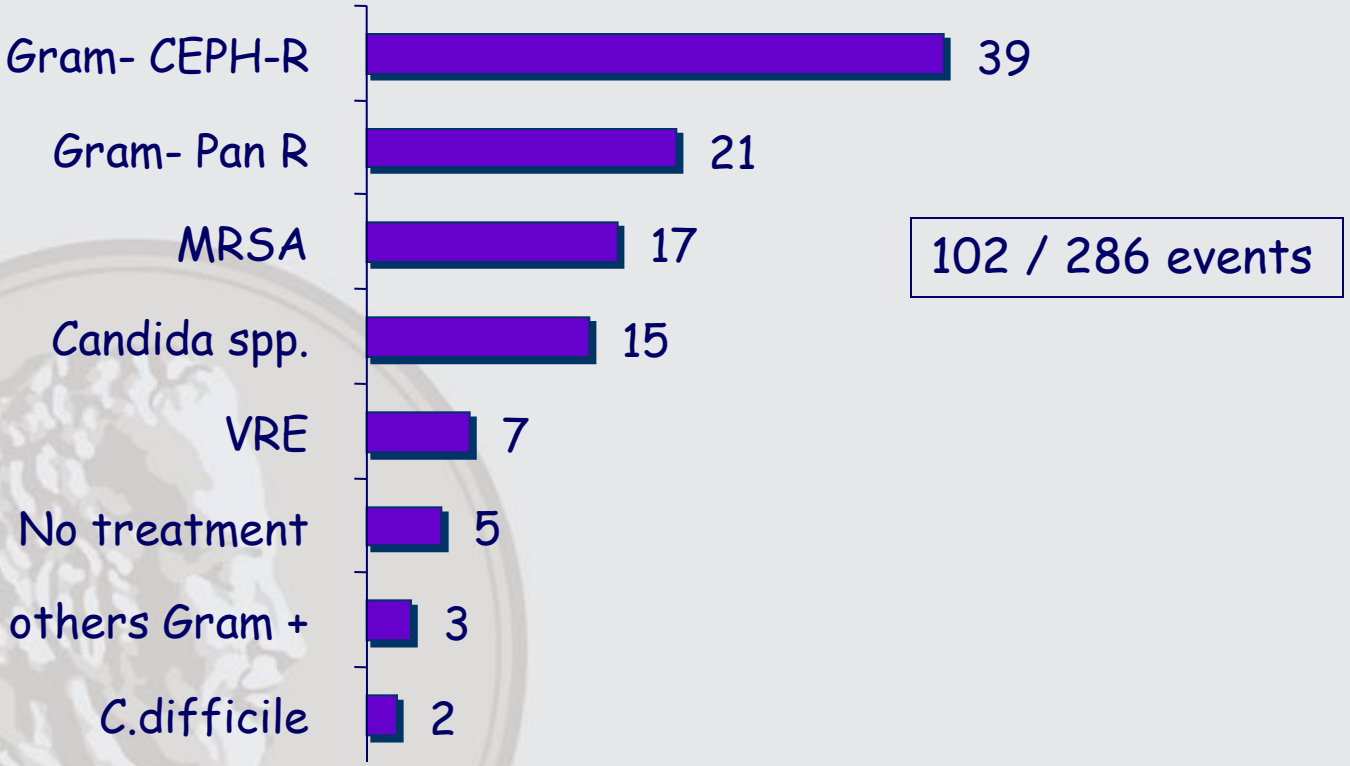
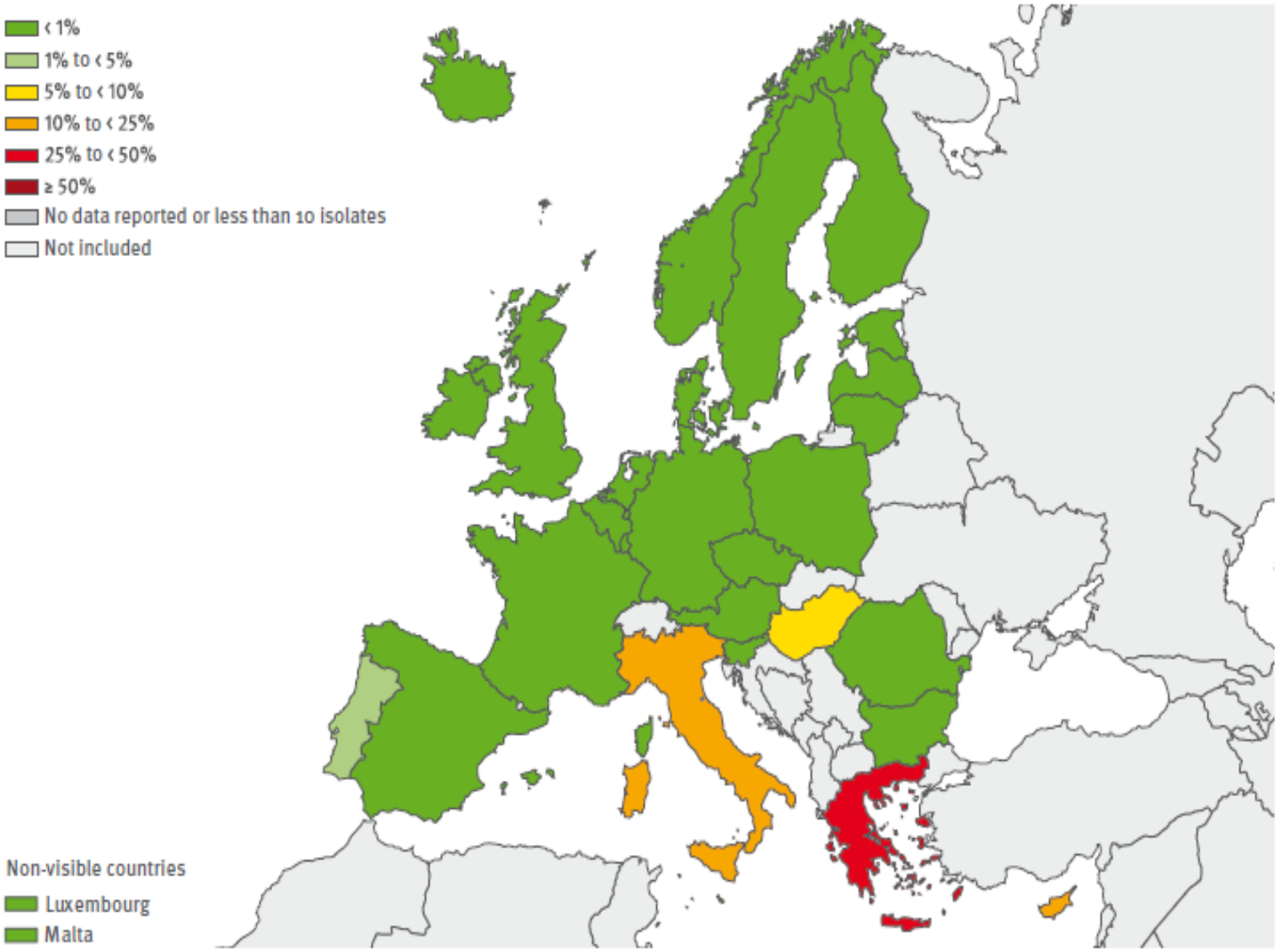


Figure 5.25: *Klebsiella pneumoniae*: proportion of invasive isolates resistant to carbapenems in 2010



Redefining ESKAPE…as ESCAPE

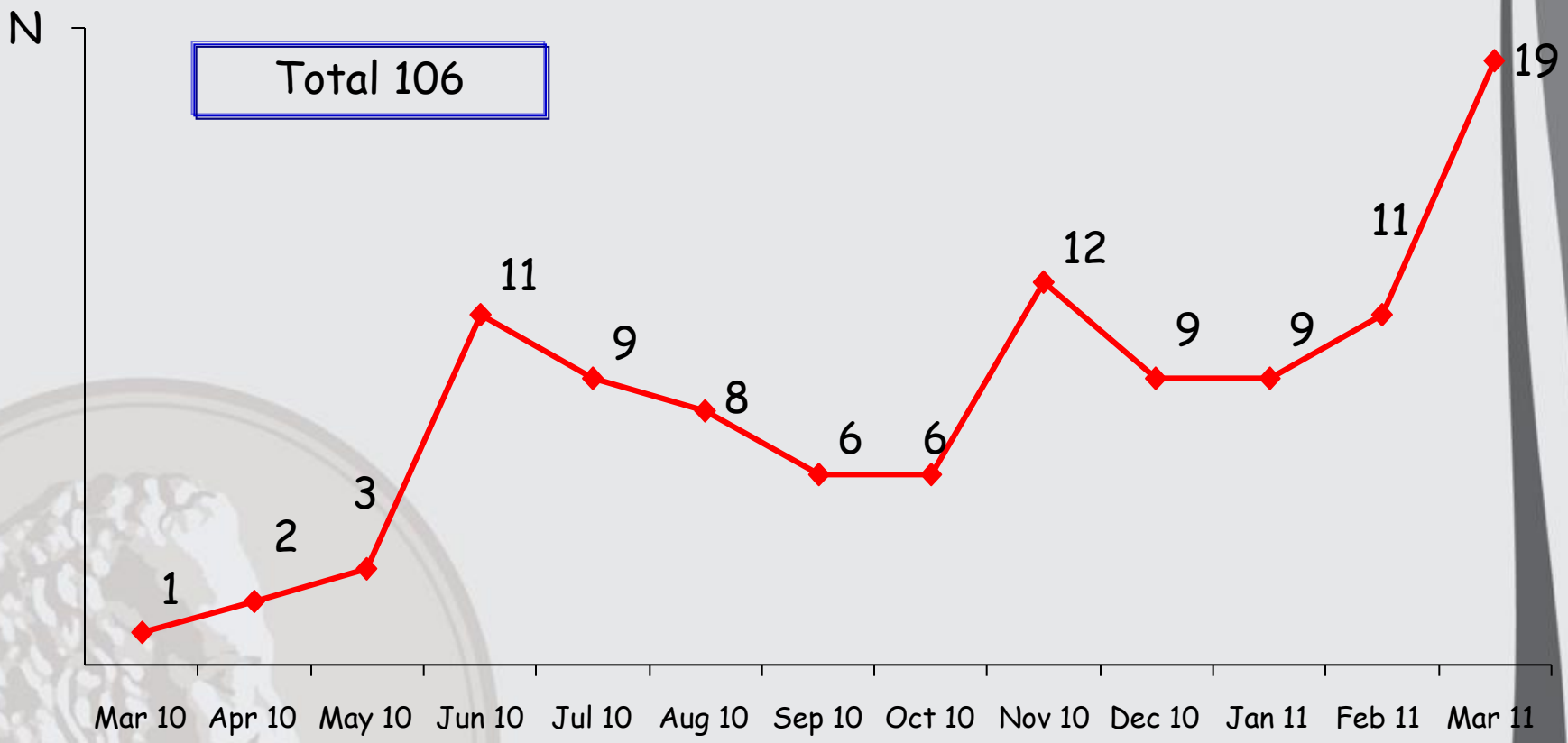
E	*Enterococcus faecium*
S	*Staphylococcus aureus*
C	*Clostridium difficile* → *Acknowledges the growing virulence of C. difficile*
A	*Acinetobacter baumannii*
P	*Pseudomonas aeruginosa*
E	Enterobacteriaceae → *Enterobacteriaceae captures K. pneumoniae, Enterobacter spp., and other resistant species including Escherichia coli and Proteus spp.*

Peterson LR. Clin Infect Dis. 2009

S.Orsola-Malpighi teaching Hospital – University of Bologna

Monthly KPC isolates

Mar 2010- Mar 2011



Patient risk factors for outer membrane permeability and KPC-producing carbapenem-resistant *Klebsiella pneumoniae* isolation: results of a double case–control study

G. B. Orsi · A. Bencardino · A. Vena · A. Carattoli · C. Venditti · M. Falcone · A. Giordano · M. Venditti

Infection 2013

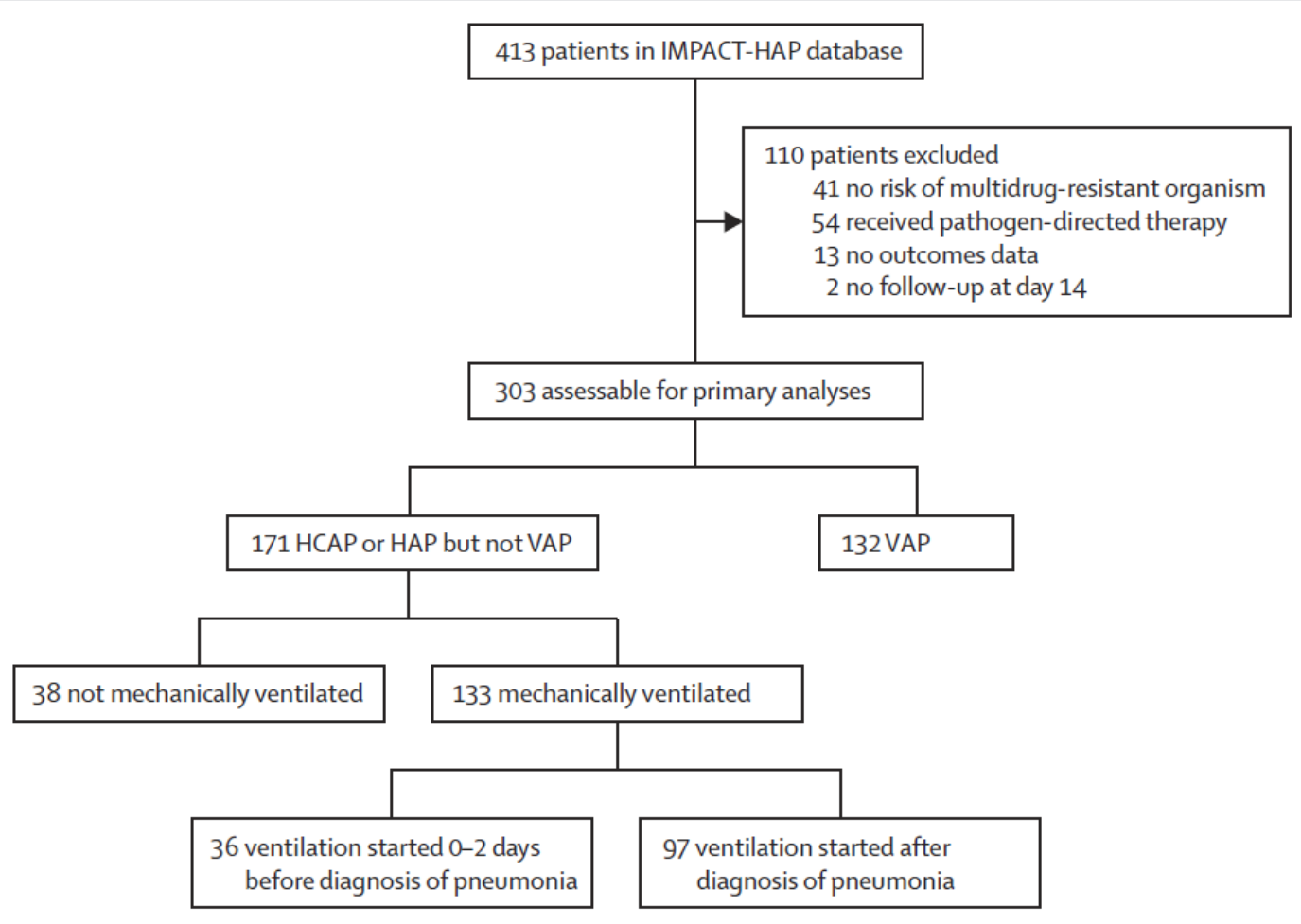
Table 4 Multivariate analysis of risk factors for *K. pneumoniae* acquisition

	Porin-ER-*Kp* vs. controls, OR (95 % CI)	*p*-value	KPC-CR-*Kp* vs. controls OR (95 % CI)	*p*-value
Acute renal failure	7.17 (1.33–38.6)	0.022	–	–
Endoscopy	6.12 (1.46–25.6)	0.013	6.71 (1.25–36.00)	0.026
Second-generation cephalosporins	25.7 (3.20–206.8)	0.0023	–	–
Third-generation cephalosporins	2.24 (0.80–6.31)	0.017	–	–
Carbapenems	19.10 (4.34–83.9)	<0.001	7.74 (1.70–35.02)	0.008

Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study

Kett DH et al, Lancet Infect Dis 2011

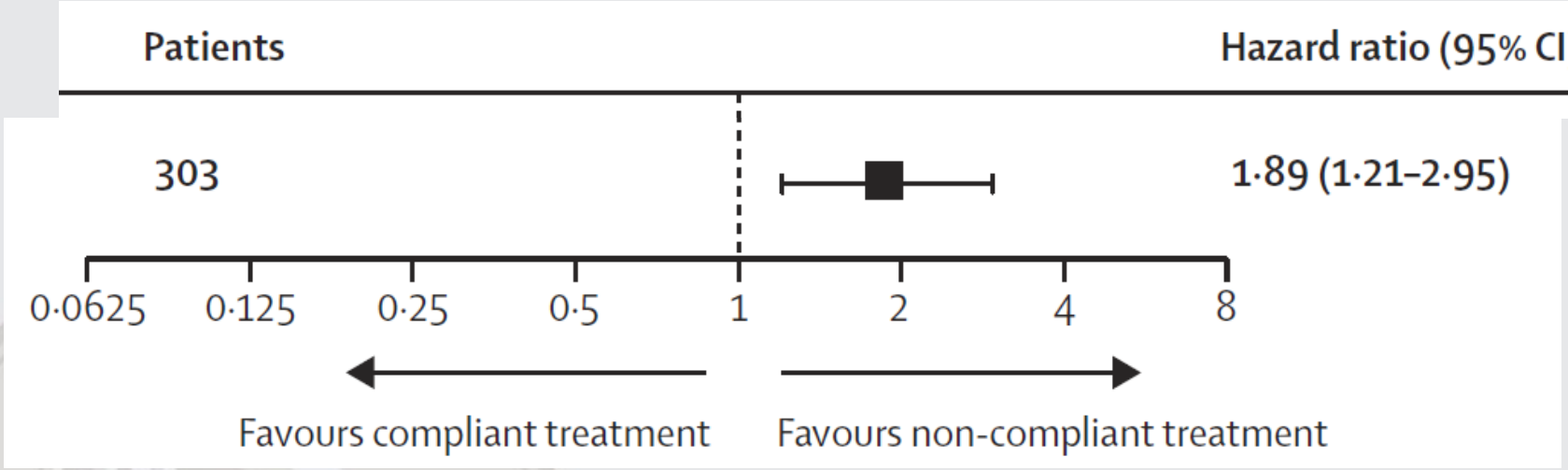
A performance-improvement initiative in four academic medical centres in the USA with protocol-based education and prospective observation of outcomes was implemented. Patients were assessed for severity of illness and followed up until death, hospital discharge, or day 28; 303 Patients in ICU, at risk for MDR pneumonia and treated empirically were included.



Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study

Kett DH et al, Lancet Infect Dis 2011; 11: 181–89

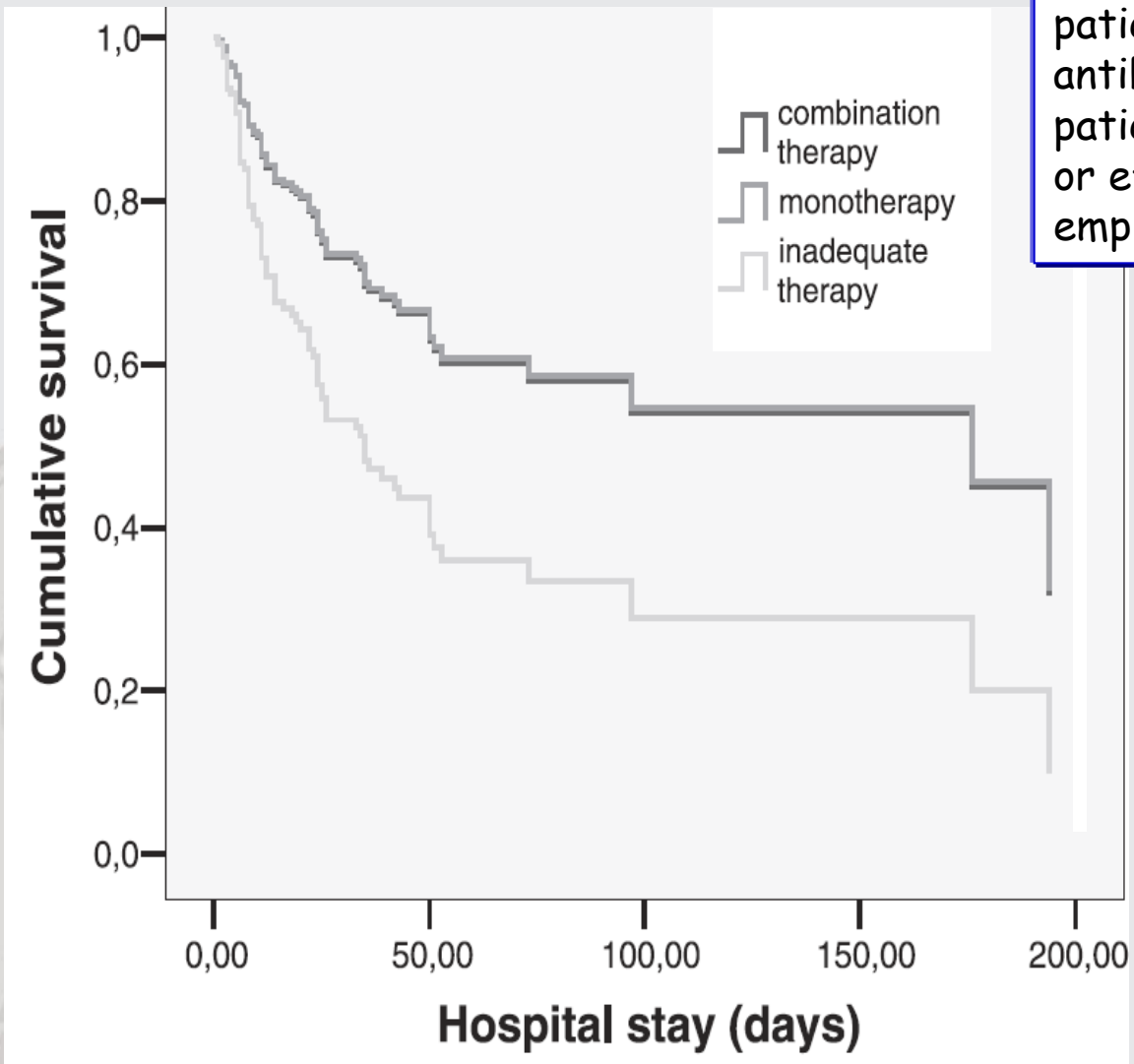
Guideline-compliant empirical treatment outcomes for 28-day mortality



Reasons for non-compliance were failure to use a secondary anti-Gram-negative drug –mainly AG - (154 patients) or, less commonly, failure to use either a primary anti-Gram negative drug (24 patients) or anti-MRSA drug (24 patients).

Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: An observational, multicenter study comparing monotherapy with combination antibiotic therapy

Garnacho-Montero J et al, Crit Care Med 2007



Cumulative survival curves of patients with inappropriate empirical antibiotic therapy compared with patients with effective monotherapy or effective combined therapy in the empirical therapy

Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults (Review)

Richard Pugh[1], Chris Grant[2], Richard PD Cooke[3], Ged Dempsey[2]

THE COCHRANE COLLABORATION®

We considered all randomised controlled trials (RCTs) comparing fixed durations of antibiotic therapy, or comparing a protocol intended to limit duration of therapy with standard care, for HAP (including patients with VAP) in critically ill adults.

Authors' conclusions

We conclude that for patients with VAP not due to NF-GNB, a short fixed-course (seven or eight days) antibiotic therapy may be more appropriate than a prolonged course (10 to 15 days). Use of an individualised strategy (incorporating clinical features or serum procalcitonin) appears to safely reduce duration of antibiotic therapy for VAP.

Which therapy??

A big therapy?????

Would you like to easily improve your antimicrobial stewardship ?

Buy a skilled infectivologist

And give him the change to work

MIND ME

M microbiology guides therapy wherever possible

I indications should be evidence-based

N narrowest spectrum required

D dosage appropriate to the site and type of infection

M minimise duration of therapy

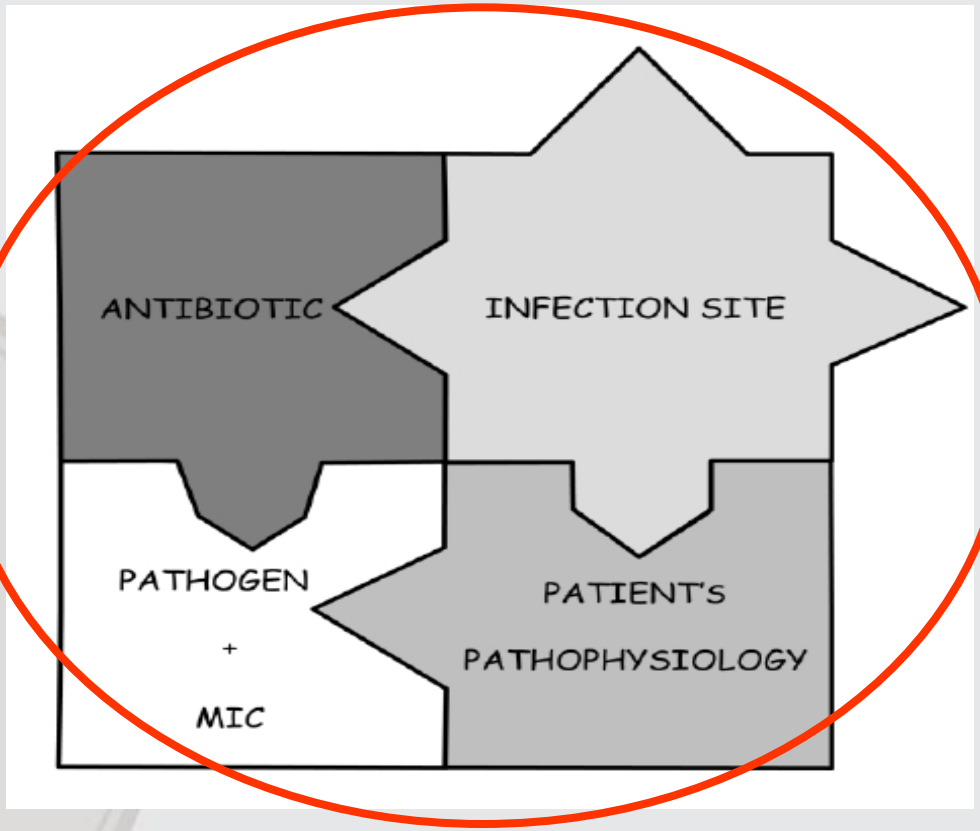
E ensure monotherapy in most situations

Factors in Selecting Initial Appropriate Therapy

- **Patient features:** Choose empiric therapy based on site and severity of infection, and physician assessment of the likelihood for deterioration and mortality.
- **Local susceptibility and epidemiology:** Choose empiric therapy to cover the likely infecting pathogens based on local patterns while considering prior antibiotic therapy.
- **Initial antibiotic therapy dosing and duration:** Choose initial empiric therapy that will deliver enough antibiotic to the site of infection and be well tolerated (consider antibiotic penetration).
- **Combination vs. monotherapy:** Initial antibiotic choice should give broad enough coverage, avoid emergence of resistance, and have the potential for synergy if necessary.

INVITED ARTICLE REVIEWS OF ANTI-INFECTIVE AGENTS
Louis D. Saravolatz, Section Editor

The Antimicrobial Therapy Puzzle: Could Pharmacokinetic-Pharmacodynamic Relationships Be Helpful in Addressing the Issue of Appropriate Pneumonia Treatment in Critically Ill Patients?



Pea F , Viale P Clin Infect Dis 2006

Inadequate Antimicrobial Therapy Promotes the Development of Resistant Organisms

Difficult-to-treat pathogens generally require:

- Combination therapy (2 or even 3 antimicrobials)
- Utilisation of alternative routes of administration (aerosolised or intrathecal antibiotics)
- Prolonged antibiotic courses
- Frequently, the use of more toxic antibiotics

A Systematic Review of the Methods Used to Assess the Association between Appropriate Antibiotic Therapy and Mortality in Bacteremic Patients

Jessina C. McGregor,[1] Shayna E. Rich,[2] Anthony D. Harris,[2,4] Eli N. Perencevich,[2,4] Regina Osih,[3] Thomas P. Lodise, Jr.,[5] Ram R. Miller,[2] and Jon P. Furuno[2]

[1]Oregon State University College of Pharmacy, Portland; Departments of [2]Epidemiology and Preventive Medicine and [3]Medicine, University of Maryland School of Medicine, and [4]Veterans Affairs Maryland Health Care System, Baltimore; and [5]Albany College of Pharmacy, Albany, New York

Clinical Infectious Diseases 2007;45:329–37

Table 4. Key recommendations for future studies of the association between appropriate antibiotic therapy and mortality among bacteremic patients.

Recommendations
Appropriate antibiotic therapy should be assessed separately for empiric and definitive therapy. Empiric antibiotic therapy is that which is administered until the point at which culture and antibiotic susceptibility test results are known. Definitive antibiotic therapy refers to the therapy administered subsequent to the receipt of antibiotic susceptibility test results.
The definition for appropriate antibiotic therapy should take into consideration the in vitro antibiotic susceptibility test results and, when available, current clinical practice guidelines regarding the dosing, route, and pattern of administration.
Mortality should be measured in a manner that best represents the underlying construct within the biologically plausible window of effect. Statistical analyses should be used to account for loss to follow-up (e.g., because of hospital discharge).
Analyses should control for the effects of confounding factors but typically should not control for intermediate factors in the causal pathway. Patient severity of illness is an important confounder of the association between appropriate antibiotic therapy and patient mortality. Severity of illness should be measured before the onset of bacteremia and should be controlled for in final statistical analyses.
All studies should provide a comprehensive description of their study population, study design, the definition of all variables collected, and methods of data analysis.

Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department

Gaieski DF et al, Crit Care Med 2010

Table 6. In-hospital mortality: Time from triage to appropriate antibiotics

				Adjusted			
Cutoffs	Number	Mortality, %	Difference, %	OR	95% CI	*p*	Probability of Death
≤1 hr	41	19.5	13.7	0.30	0.11–0.83	.02	.13 vs. .29
>1 hr	220	33.2					
≤2 hrs	124	28.2	5.4	0.54	0.29–1.03	.06	.22 vs. .31
>2 hrs	137	33.6					
≤3 hrs	172	27.9	9.2	0.53	0.27–1.01	.05	.23 vs. .34
>3 hrs	89	37.1					
≤4 hrs	200	28.5	10.8	0.62	0.31–1.24	.18	.25 vs. .34
>4 hrs	61	39.3					
≤5 hrs	218	30.7	1.8	0.82	0.37–1.79	.62	.27 vs. .29
>5 hrs	43	32.6					

Initial empiric antibiotic therapy in ICU

- Broad spectrum therapy
- Combination
- Bactericidal
- PK-PD
- High dose
- IV
- Continuous or extended infusion
- Adequate duration

KEY POINTS for a CORRECT ANTIMICROBIAL MANAGEMENT

1. PREVENT INFECTIONS

2. DIAGNOSE INFECTIONS

3. CHOICE ANTIMICROBIALS ← The risk adjusted approach

   based on risk factors

   based on microbiological findings

4. USE ANTIMICROBIALS WISELY ← The population tailored approach

CHOICE of ANTIMICROBIALS: the infectivologist skills

- consider	microorganism-related risk factors
	site-related microorganisms
	microorganism-related severity (mortality)
- know	the epidemiology of resistances
	the significance of colonization
- give	PK/PD knowledge
- use correctly	combination regimens
	new drugs
- apply	a correct descalation approach
- don't forget	eradication of primary//secondary site
- guide	the pre-analytic phase of microbiology
	the anti-Resistance "Unit Strategies"

RISK ADJUSTED APPROACH to choice therapy

Severity of illness (SIRS / PIRO scale)

Organ disfunction (SOFA score)

Age & Co-morbidities (Mc Cabe score)

Community vs Hospital acquisition

Site-related

Microorganism-related

risk factors

} DRUGS' CHOICE

Resistance-related

Physio-pathological status

Renal efficiency

Site of infection

} REGIMENS' CHOICE

Paziente critico *ospedalizzato* con sospetta infezione

TERAPIA EMPIRICA - Criteri microbiologici

Presenza di device vascolare	MRSE / MRSA / *Candida spp.* / Enterococchi
Ventilazione Assistita	MRSA / *P. aeruginosa* / *Enterobacter spp.*
Patologia addominale	Enterobacteriaceae / Anaerobi / Enterococchi
Patologia genito-urinaria	*E. coli* / Enterococchi / *P. aeruginosa*
Cardiochirurgia	MRSA / MRSE / Anaerobi / Candida spp.
Neurochirurgia	MRSA / MRSE / *S. pneumoniae*
Traumi cranio-faciali	*S. pneumoniae* / Anaerobi
Prolungata esposizione ad ATB	*Acinetobacter spp.* / *Candida spp.*/ Gram- MDR
Prolungata ospedalizzazione	*P.aeruginosa* / *S. maltophilia* / Enterobacteriaceae Enterococchi / MRSA / *Candida spp.*

A stewardship program about the COMBINATION

- USE COMBINATION
  routinely against selected microorganisms, clinical conditions and patients

- NARROW THE ANTIMICROBIAL SPECTRUM AS SOON AS POSSIBLE
  using sensitivity data and clinical outcome

- AVOID COMBINATION
  using drugs with overlapping spectrum

- CHOOSE FOR THE COMBINATION
  different antibiotic classes

- USING A COMBINATION
  don't reduce the daily dose of singular drugs

- CHOOSE FOR COMBINATION
  Drugs with the best evidence

- AVOID THE ROUTINELY USE OF COMBINATION REGIMENS
  based on traditions, compulsivity, poor evidence

DOSE OPTIMIZATION

Optimization of antimicrobial dosing based on individual patient characteristics, causative organism, site of infection, and pharmacokinetic and pharmacodynamic characteristics of the drug is an important part of antimicrobial stewardship (A-II).

STREAMLINING OR DE-ESCALATION OF THERAPY

Streamlining or de-escalation of empirical antimicrobial therapy on the basis of culture results and elimination of redundant combination therapy can more effectively target the causative pathogen, resulting in decreased antimicrobial exposure and substantial cost savings (A-II).

PARENTERAL TO ORAL CONVERSION

A systematic plan for parenteral to oral conversion of antimicrobials with excellent bioavailability, when the patient's condition allows, can decrease the length of hospital stay and health care costs (AI).

Development of clinical criteria and guidelines allowing switch to use of oral agents can facilitate implementation at the institutional level (A-III).

CORRELAZIONI PK-PD ANTIBIOTICI

BETA-LATTAMINE, GLICOPEPTIDI, OXAZOLIDINONI

- Attività battericida tempo-dipendente (Cmin > MIC)
- PAE solo sui Gram-positivi
- $t_{1/2\beta}$ = 1h (PenG, Ampi, Amoxi, Oxa); 6h (Vanco, Linezolid); 8h (CTX); 30-70h (Teico)
- Concentrazioni oltre 5 volte la MIC non aumentano efficacia
- Obiettivo: mantenere concentrazioni sopra la MIC

t > MIC

NECESSITÀ PLURIFRAZIONAMENTO DELLA DOSE FINO ALL'INFUSIONE CONTINUA

UniUD2004

CORRELAZIONI PK-PD ANTIBIOTICI

AMINOGLICOSIDI, FLUOROCHINOLONI

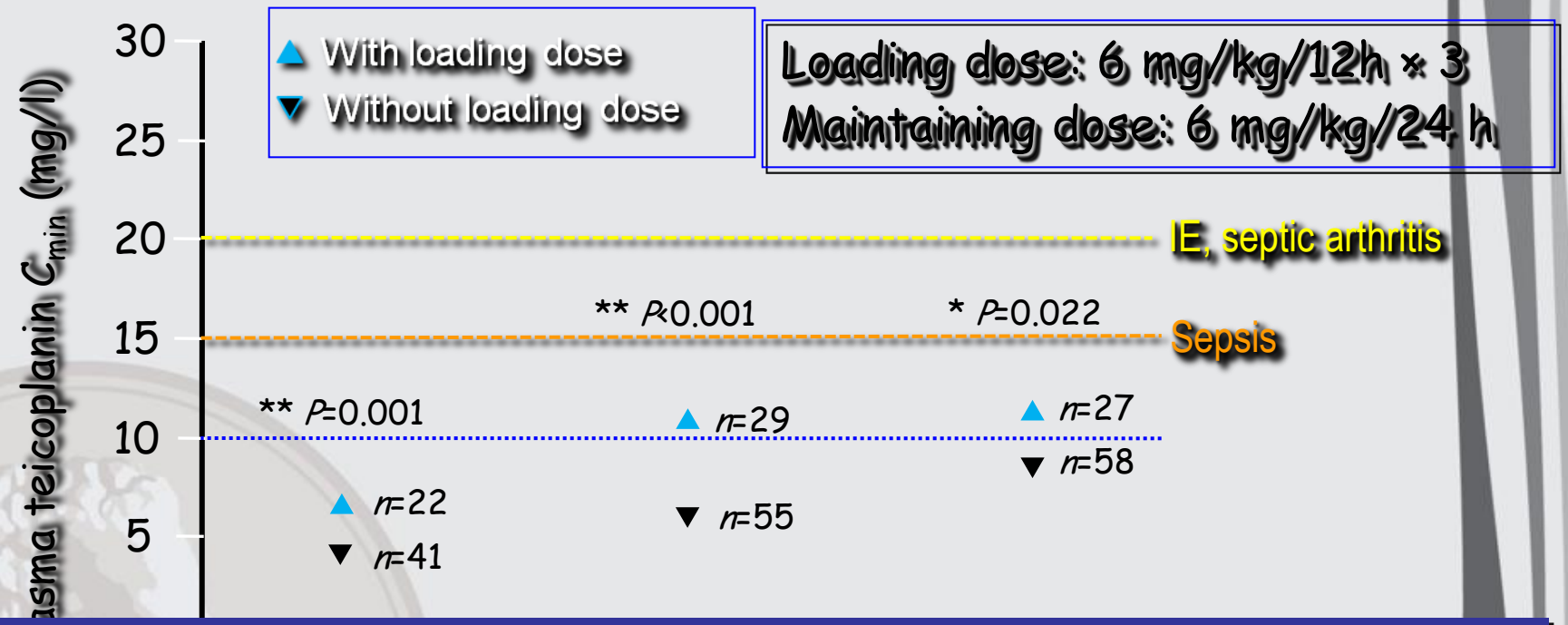
- Attività battericida concentrazione-dipendente
- >> PAE
- $t_{1/2\beta}$ = 2-4h (aminoglicosidi); 4h (cipro); 7h (levo); 9h (moxi)
- Concentrazioni 8 - 10 volte la MIC prevengono resistenza
- OBIETTIVO: OTTENERE ELEVATI LIVELLI MASSIMI E/O AUC

C_{max}/MIC > 10

AUC/MIC > 125

UTILITÀ MONO - BISOMMINISTRAZIONE GIORNALIERA

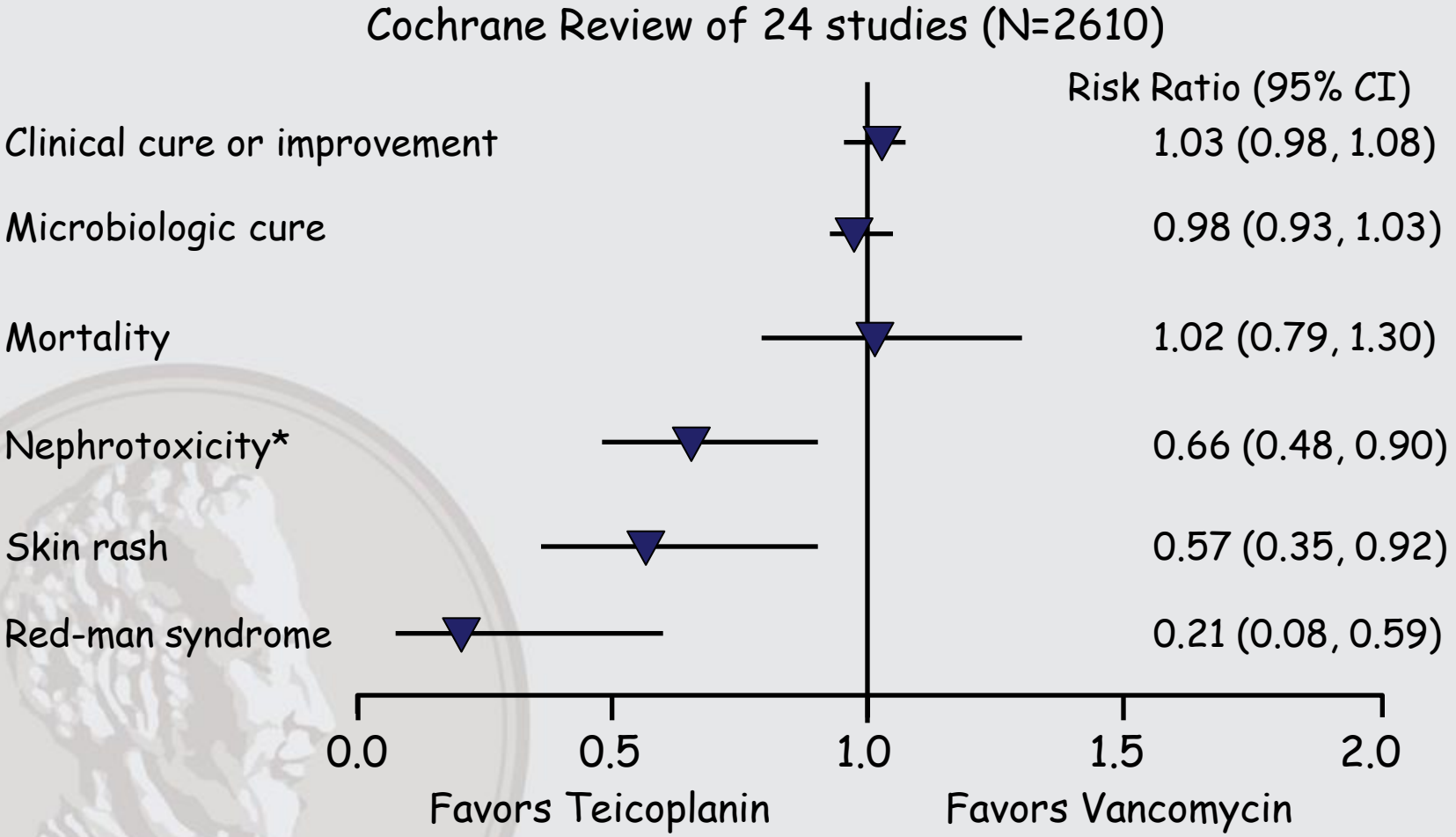
Even with a loading dose, 4 days of therapy are required to achieve trough teicoplanin concentrations of 10 mg/l



However, target concentrations for patients with sepsis, IE or septic arthritis will not be achieved

Pea F et al. J Antimicrob Chemother 2003

Teicoplanin vs Vancomycin for Proven or Suspected Gram-positive Infection



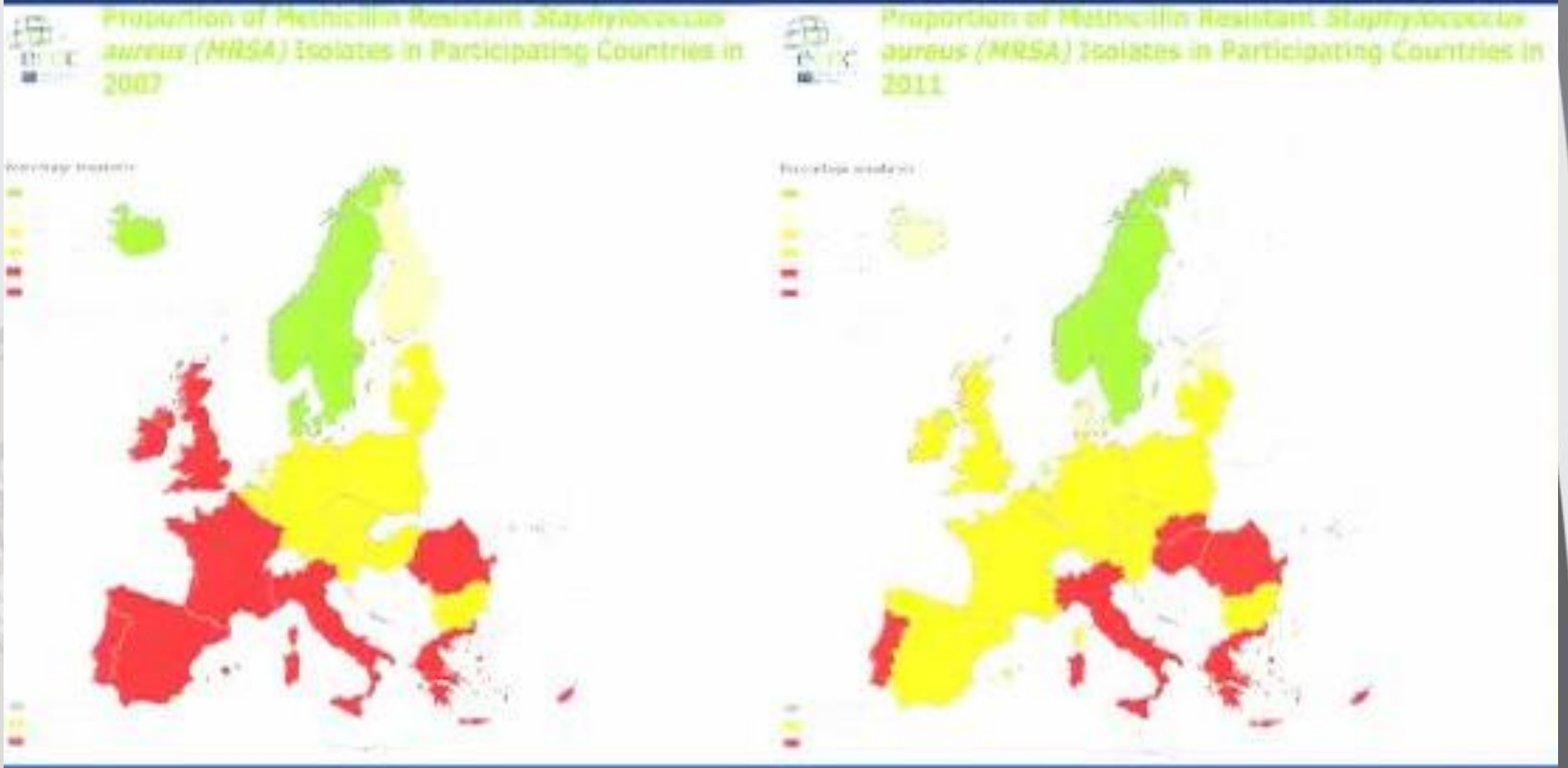
* Nephrotoxicity difference was a consistent finding: Present when vancomycin monitoring was used to guide dosing; present with or without aminoglycosides

Cavalcanti AB et al. Cochrane Database Syst Rev. 2010.

Tissue penetration (% tissue/serum)

Tissue	Vancomycin	Linezolid
Bone	7–13%	60%
CNS	0–18%	70%
ELF	11–17%	450%
Muscle	30%	94%
Perit. dial fluid	20%	61%

MRSA, 2007 vs 2011 in Europe



EARS-NET

American Journal of Emergency Medicine (2007) **25**, 880–886

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The
American Journal of
Emergency Medicine

www.elsevier.com/locate/ajem

Original Contribution

Risk factors associated with methicillin-resistant *Staphylococcus aureus* infection in patients admitted to the ED

Alain Viallon MD[a,*], Olivier Marjollet MD[a], Philippe Berthelot MD[b], Anne Carricajo MD[c], Stéphane Guyomarc'h MD[a], Florianne Robert MD[a], Fabrice Zeni MD[a], Jean Claude Bertrand MD[a]

American Journal of Emergency Medicine (2007) 25, 880–886

The
American Journal of
Emergency Medicine

www.elsevier.com/locate/ajem

Table 2 Comparison of comorbidity factors and other risk factors for contracting MRSA in patients with MRSA and MSSA infections

	MRSA (n = 93)	MSSA (n = 145)	*P*
McCabe score, n (%)			
A	53 (57)	112 (77)	.008
B	39 (42)	31 (21)	
C	1 (1)	2 (2)	
Chronic diseases, n (%)			
Cardiovascular	69 (74)	74 (51)	.001
Pulmonary	25 (27)	19 (13)	.007
Neurologic	33 (35)	22 (15)	.001
Hepatic	13 (14)	15 (10)	NS
Renal insufficiency	13 (14)	6 (4)	.07
Cancer	17 (18)	18 (12)	NS
Diabetes	37 (40)	33 (23)	.004
Psychiatric	12 (13)	11 (8)	NS
Risk factors for contracting MRSA, n (%)			
Institutional care or home nursing	70 (75)	64 (44)	.0001
Implantable device	34 (37)	23 (16)	.0001
Chronic wound	31 (33)	39 (27)	NS
No. of hospital stays during the last 12 mo	1	0	.0001
Interquartile	0-2	0-0.5	

Mortality of *S. aureus* bacteremia and infectious diseases specialist consultation. A study of 521 patients in Germany *Rieg S et al, J Infect 2009*

Multivariate logistic regression analysis of factors potentially associated with in-hospital mortality

Factor/characteristic	OR (95% CI)	p-Value
Age 60 years	2.4 (1.4-4.2)	<0.01
McCabe non-fatal	0.28 (0.1-0.4)	<0.01
MRSA 0.97	2.6 (1.4-4.9)	<0.01
Endocarditis	2.8 (1.4-5.7)	<0.01
ICU admission/stay	5.8 (3.5-9.7)	<0.01
ID specialist consultation	0.6 (0.4-1.0)	0.045

Adequacy of Antimicrobial Treatment and Outcome of *S. aureus* Bacteremia in 9 Western European Countries.

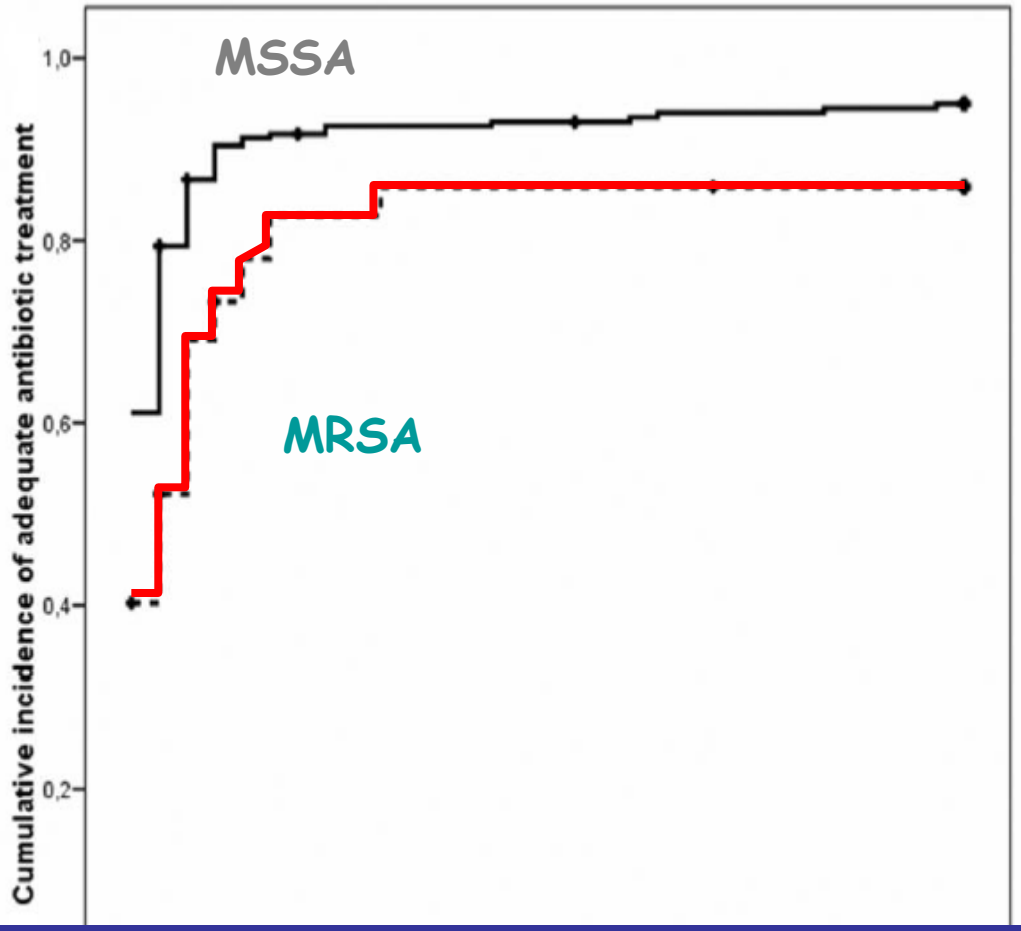
Ammerlaan H et al, Clin Infect Dis 2009

INADEQUATE TREATMENTS	
ATB started > 2 days	53
Uncorrected choice	35
Inadequate route of administration	15
No treatment	7
Total	94 (28%)

Covariate	Alive (n = 254)	Death (all cause) (n = 80)	OR (95% CI)[a]	P[b]
Teaching (vs nonteaching) hospital	197 (77.6)	55 (68.8)	…	.11
Age, median years (IQR)	66.0 (54–76.0)	74.5 (62.5–83)	1.06 (1.03–1.10)	<.001
Male (vs female)	170 (66.9)	54 (67.5)	…	.93
Modified Charlson comorbidity score, median value (IQR)	3.0 (0–5)	4.0 (2–6)	2.09 (1.21–3.63)	.001
Immunocompromised (vs nonimmunocompromised)	32 (12.6)	8 (10.0)	…	.53
Secondary (vs primary) bacteremia	94 (37.0)	28 (35.0)	…	.75
Length of stay before onset of SAB, median days (IQR)	2.0 (0–10)	2.0 (0–9.5)	…	.67
Hospital-acquired (vs community-acquired) bacteremia	119 (46.9)	39 (48.8)	…	.80
Severe sepsis or septic shock (vs sepsis) at onset of SAB	77 (30.3)	49 (61.3)	2.68 (1.52–4.75)	<.001
ICU hospitalization (vs non-ICU) at onset of SAB	44 (17.3)	29 (36.3)	2.89 (1.48–5.64)	<.001
Inadequate (vs adequate) empirical treatment	74 (29.1)	20 (25.0)	0.69 (0.36–1.32)	.57
MRSA (vs MSSA)	57 (22.4)	20 (25.0)	0.98 (0.50–1.94)	.64
Age × modified Charlson comorbidity score (interaction term)[c]	…	…	0.99 (0.98–0.999)	<.001

Adequacy of Antimicrobial Treatment and Outcome of *S. aureus* Bacteremia in 9 Western European Countries.

Ammerlaan H et al, Clin Infect Dis 2009



Prevalence of inadequate treatment

MSSA	21%	P <.001
MRSA	52%	

Adequate antimicrobial therapy was defined as intravenous administration of at least 1 antibiotic to which the isolate showed in vitro susceptibility that was initiated within 2 days after onset of SAB.

YES ! We can come back to the S/I/R era

NO ! We can move to a true comprehensive management

IS IT SUFFICIENT

IN THE CLINICAL PRACTICE ?

Adequate antimicrobial therapy was defined as intravenous administration of at least 1 antibiotic to which the isolate showed in vitro susceptibility that was initiated within 2 days after onset of SAB.

"CORRECT ANTIBIOTIC THERAPY" WHAT DOES IT MEAN ?

Viale P & Pea F Crit Care Med 2007;35:991

The patient point of view

- A TARGETED PHYSIOPHATOLOGICAL DAILY SCHEDULA
- A SEVERITY RELATED APPROACH

"CORRECT ANTIBIOTIC THERAPY" WHAT DOES IT MEAN ?

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The patient point of view

- A TARGETED PHYSIOPHATOLOGICAL DAILY SCHEDULA
- A SEVERITY RELATED APPROACH

The microorganism point of view

- A GOOD MICROBIOLOGICAL / EPIDEMIOLOGICAL CHOICE

The drug point of view

- A CORRECT PHARMACOKINETICAL CHOICE and ADMINISTRATION
- A SITE RELATED INTERPRETATION OF "IN VITRO" SUSCEPTIBILITY

EMPIRIC THERAPY – 10 CRUCIAL QUESTIONS

1. Clinical severity
2. Community vs Hospital acquired
3. Specific site related microorganisms
4. Variables able to change microorganisms and resistance pattern
5. Specific Risk Factors for specific resistance pattern
6. Area related Microbial ecology
7. Site-related PK/PD of antibiotics
8. Physiopathological conditions and antimicrobial disposition
9. The best daily schedule and administration modality
10. Drug-drug interactions

Development of Reduced Vancomycin Susceptibility in Methicillin-Susceptible *Staphylococcus aureus*

Satish K. Pillai,[1,2] Christine Wennersten,[1] Lata Venkataraman,[1] George M. Eliopoulos,[1,2] Robert C. Moellering, Jr,[1,2] and Adolf W. Karchmer[1,2]

[1]Division of Infectious Diseases, Beth Israel Deaconess Medical Center, and [2]Harvard Medical School, Boston, Massachusetts

Background. Most cases of reduced vancomycin susceptibility in *Staphylococcus aureus* reported in the literature have been in methicillin-resistant strains. We report the development of reduced vancomycin susceptibility in a series of clonally related, methicillin-susceptible *S. aureus* (MSSA) clinical isolates. This isogenic series permitted us to determine whether the evolution of reduced vancomycin susceptibility in MSSA is similar to that seen in MRSA.

Methods. Differences in vancomycin population analysis profiles; chemical autolysis; vancomycin, oxacillin, and daptomycin minimum inhibitory concentrations; and bactericidal activities were examined.

Results. Progressive vancomycin resistance correlated with increasing daptomycin nonsusceptibility. Chemical autolysis and the bactericidal activity of vancomycin, oxacillin, and daptomycin were reduced in the final, vancomycin-intermediate *S. aureus* isolate, compared with the vancomycin-susceptible MSSA progenitor.

Conclusions. Clinicians should recognize that reduced vancomycin susceptibility can occur in *S. aureus* irrespective of background methicillin susceptibility and that development of intermediate vancomycin susceptibility in MSSA may result in increased tolerance to several classes of anti-staphylococcal antibiotics.

Clinical Infectious Diseases 2009; 49:1169–74

Influence of Vancomycin MIC on the Treatment of MRSA Bacteremia

Soriano A et al, Clin Infect Dis 2008

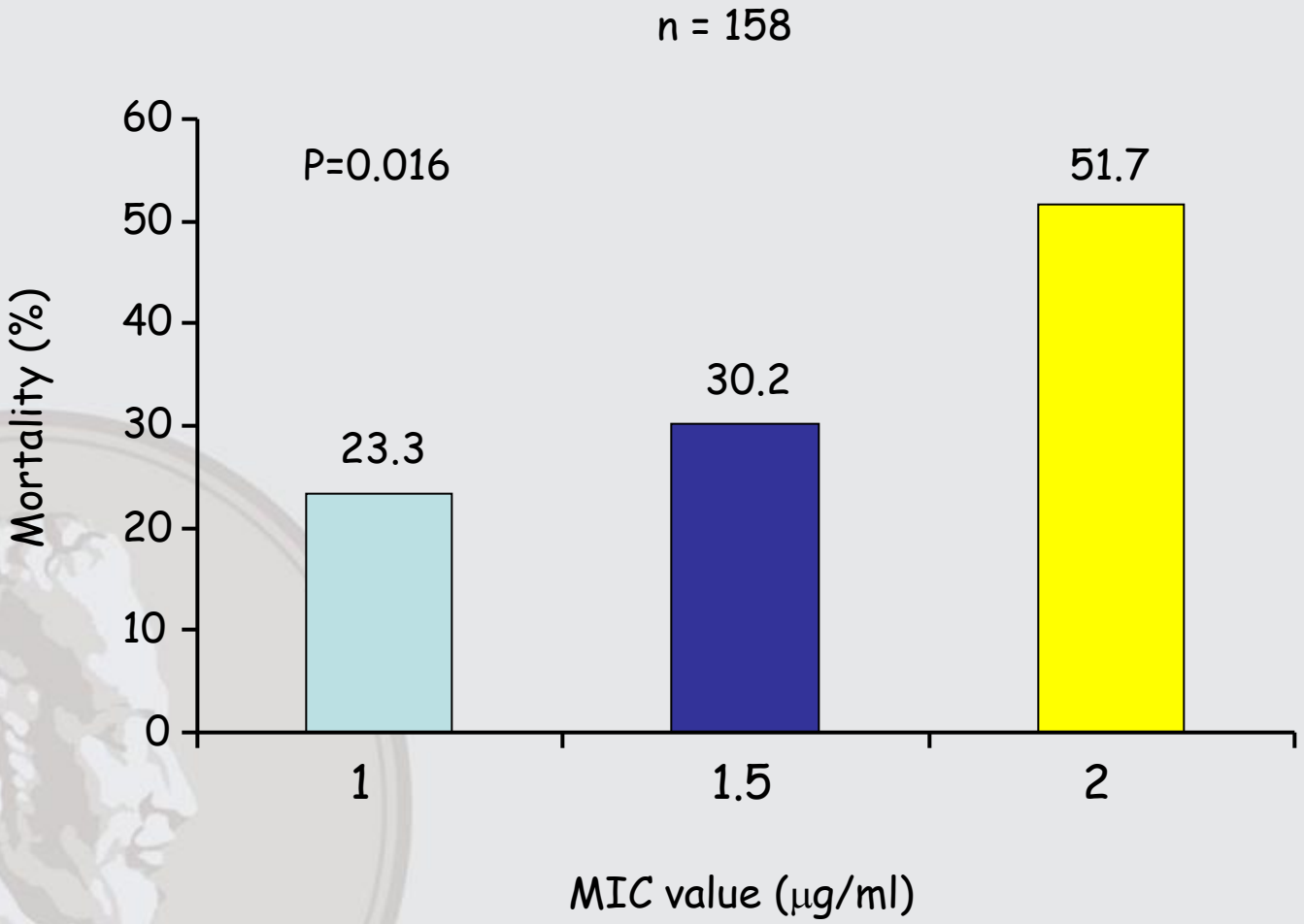
Factor	OR (95% CI)	*P*
Age, per year	1.02 (1.00–1.04)	.013
Receipt of corticosteroids	1.85 (1.04–3.29)	.034
Prognosis of underlying disease		
Nonfatal	1	
Rapidly fatal	1.81 (1.06–3.10)	.029
Ultimately fatal		
Source of bacteremia		
Low risk		
Intermediate risk		
High risk		
Treatment group		
VMIC1	1	
VMIC1.5	2.86 (0.87–9.35)	.08
VMIC2	6.39 (1.68–24.3)	<.001
NA	3.62 (1.20–10.9)	<.001
Shock	7.38 (4.11–13.3)	<.001

Factors independently associated with mortality (logistic regression model)

No information on
- **drug exposure**
- **vancomycin mode of administration**

No stratification for severity status of the patients

Vancomycin MICs and outcome in MRSA pneumonia



Haque N, et al. Chest. 2010

A call form the microbiologist…

Staphylococcus aureus !!!

TWO STEP THERAPEUTICAL APPROACH

MRSA

VANCOMYCIN
TEICOPLANIN

MSSA

OXACYLLIN

Vanco - MIC

< 1 mg/L

VANCOMYCIN
TEICOPLANIN

> 1 mg/L

ALTERNATIVES

ALTERNATIVES: WHERE ?

Continuous vs intermittent infusion of vancomycin in severe Staphylococcal infections: PRCT

Wysocki M et al. Antimicrob Ag Chem 2001; 45(9): 2460-7

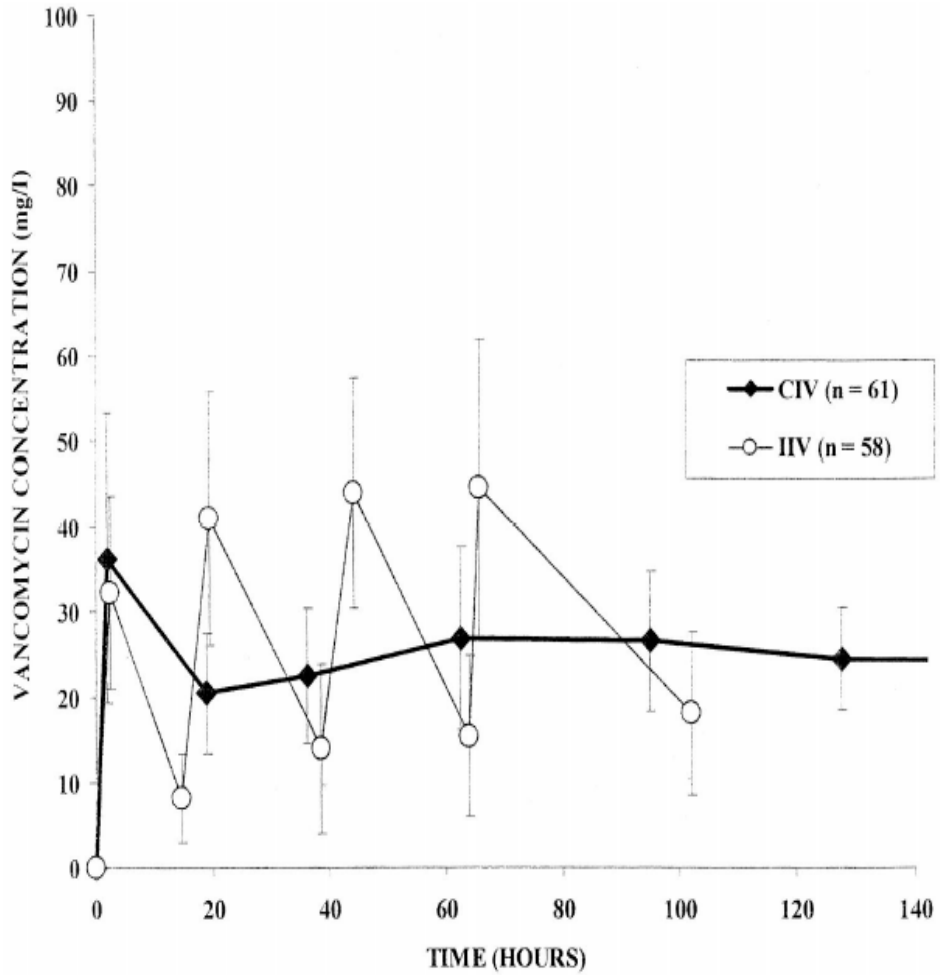
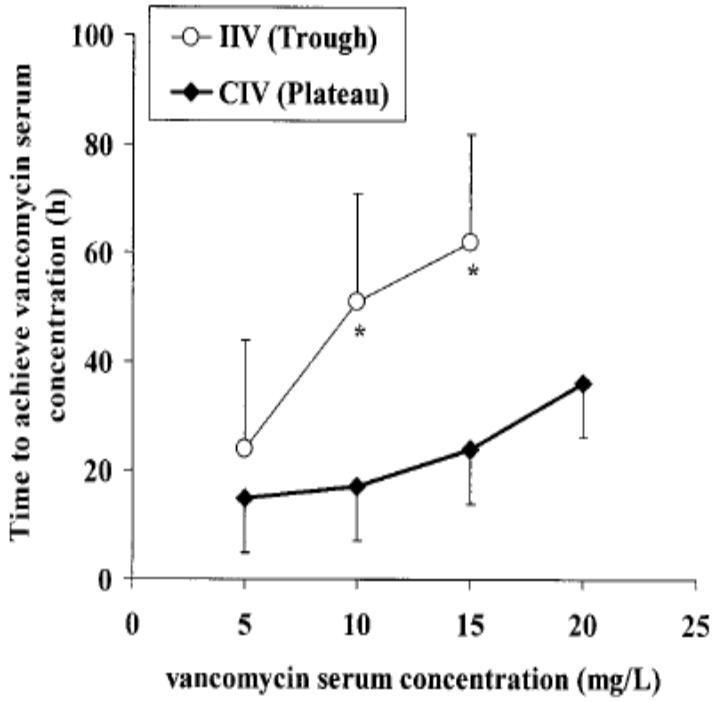
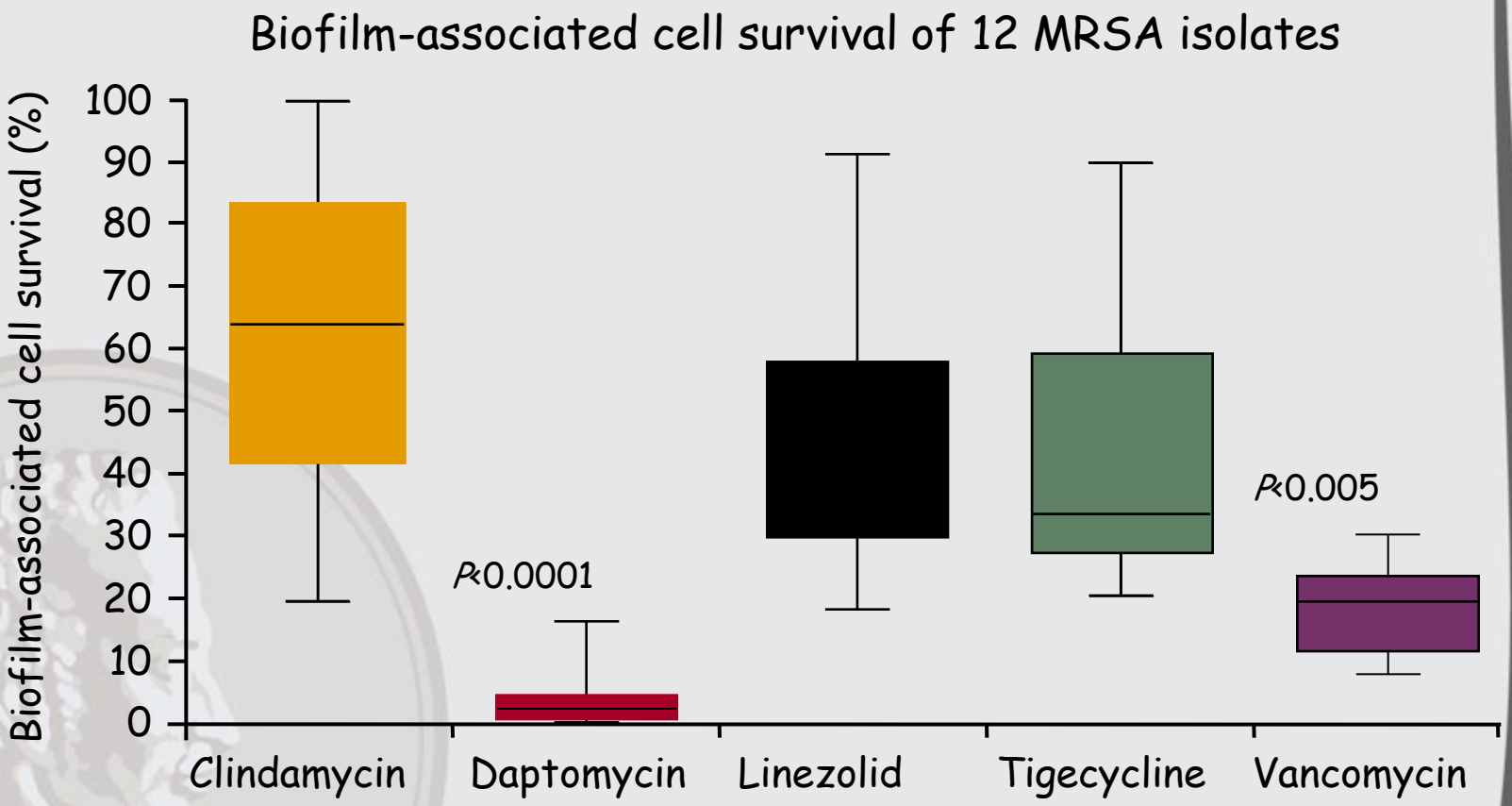


FIG. 3. Changes in serum vancomycin concentrations over time in the two treatment groups. The AUC_{24h} was 577 ± 120 in the CIV group and 653 ± 232 mg/liter/h in the IIV group. The AUC_{24h} and the daily dose given over 10 days of treatment have less variability between patients with CIV than with IIV (variance, 14,621 versus 53,975 $mg^2/liter^2/h^2$ [$P = 0.02$] and 414 versus 818 g^2 [$P = 0.05$], respectively).



In vitro survival of methicillin-resistant *S. aureus* biofilms to antibiotics

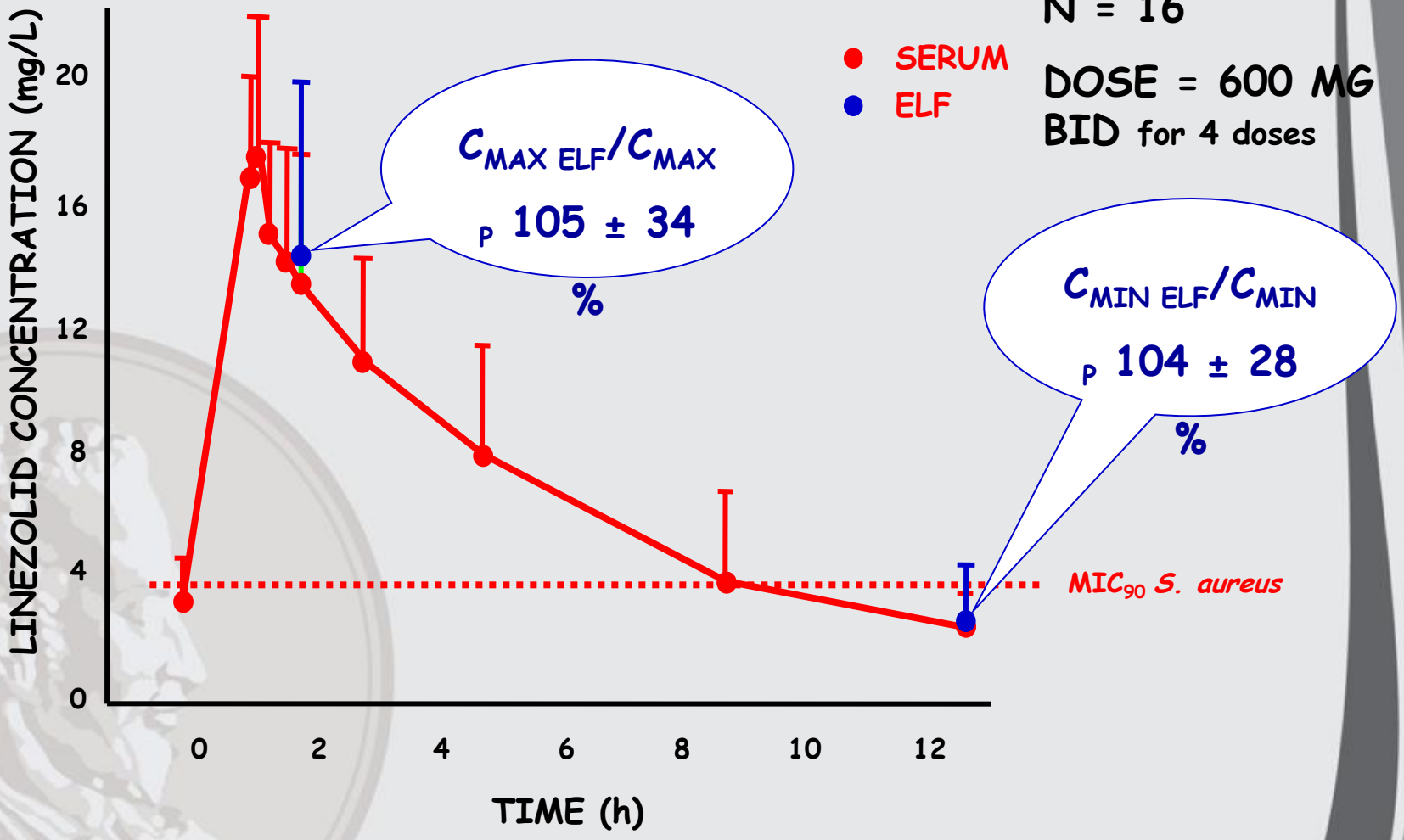


MRSA exposed to antibiotics at concentrations of 64 μg/mL. Each box plot represents the spread of cell survival across the different clinical isolates; error bars are the standard deviation

Smith K et al. Int J Antimicrob Agents 2009

PK and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia

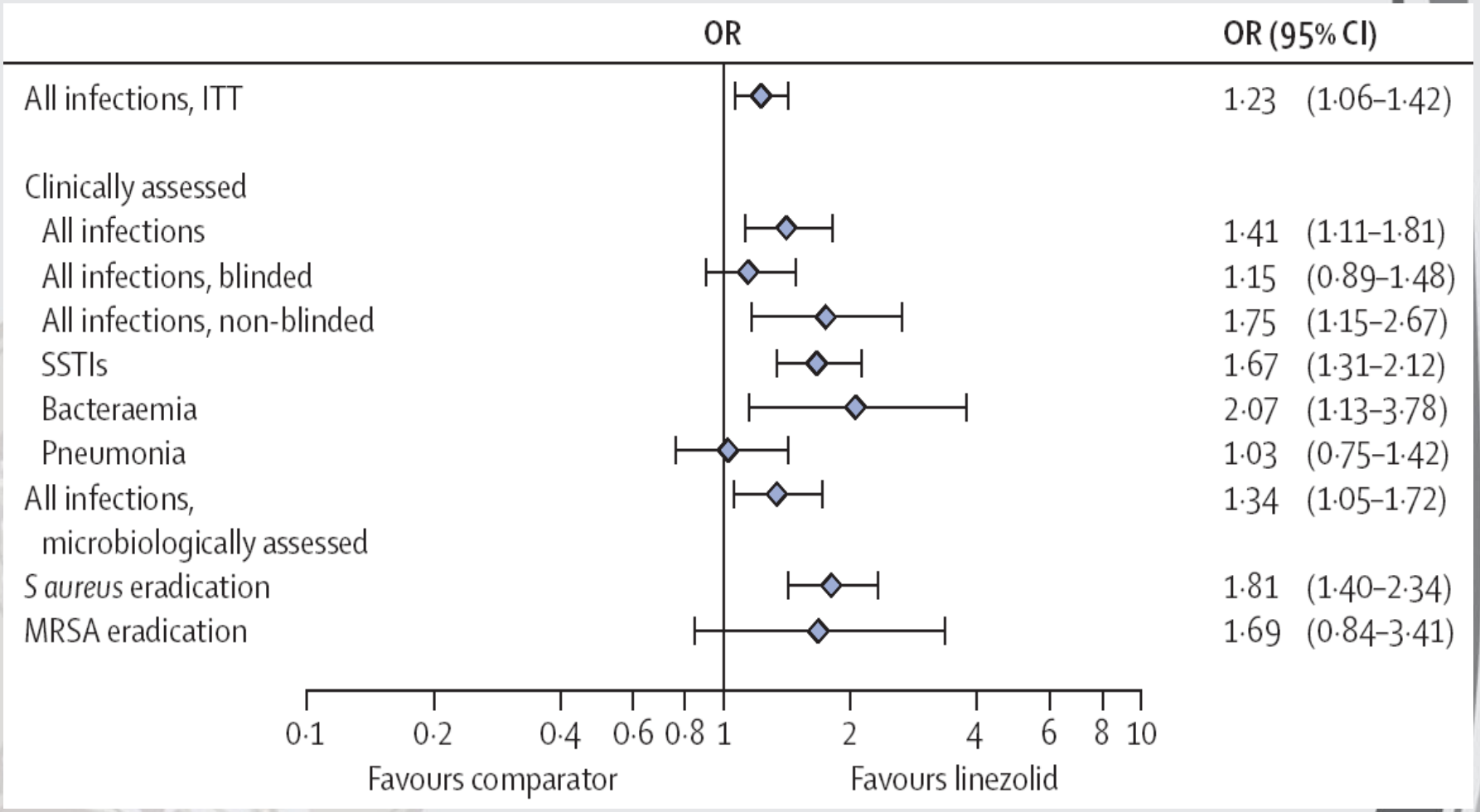
Boselli E et al. Critical Care Med 2005



Linezolid versus glycopeptide or b-lactam for treatment of Gram-positive bacterial infections: meta-analysis of randomised controlled trials

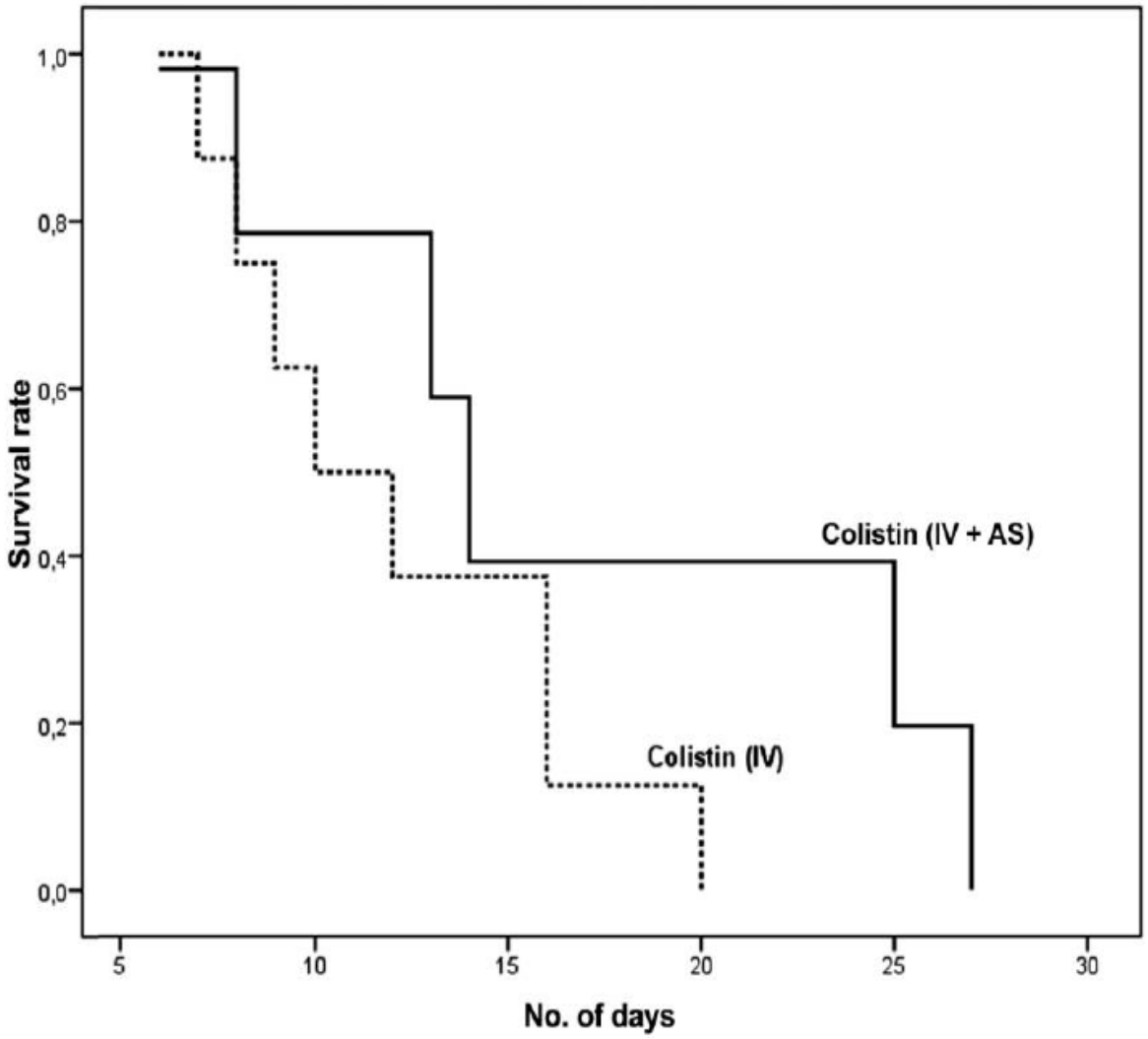
Falagas ME et al Lancet Infect Dis 2008

Comparative effectiveness of linezolid versus comparator antibiotics for the studied outcomes and populations



Aerosolized plus Intravenous Colistin versus Intravenous Colistin Alone for the Treatment of Ventilator-Associated Pneumonia: A Matched Case-Control Study

Kofteridis DP et al, Clin Infect Dis 2010



VAP-related mortality

EXPERT REVIEWS

Treatment of carbapenem-resistant *Klebsiella pneumoniae*: the state of the art

Expert Rev. Anti Infect. Ther. 11(2), 159–177 (2013)

Petrosillo N. , Viale PL et al

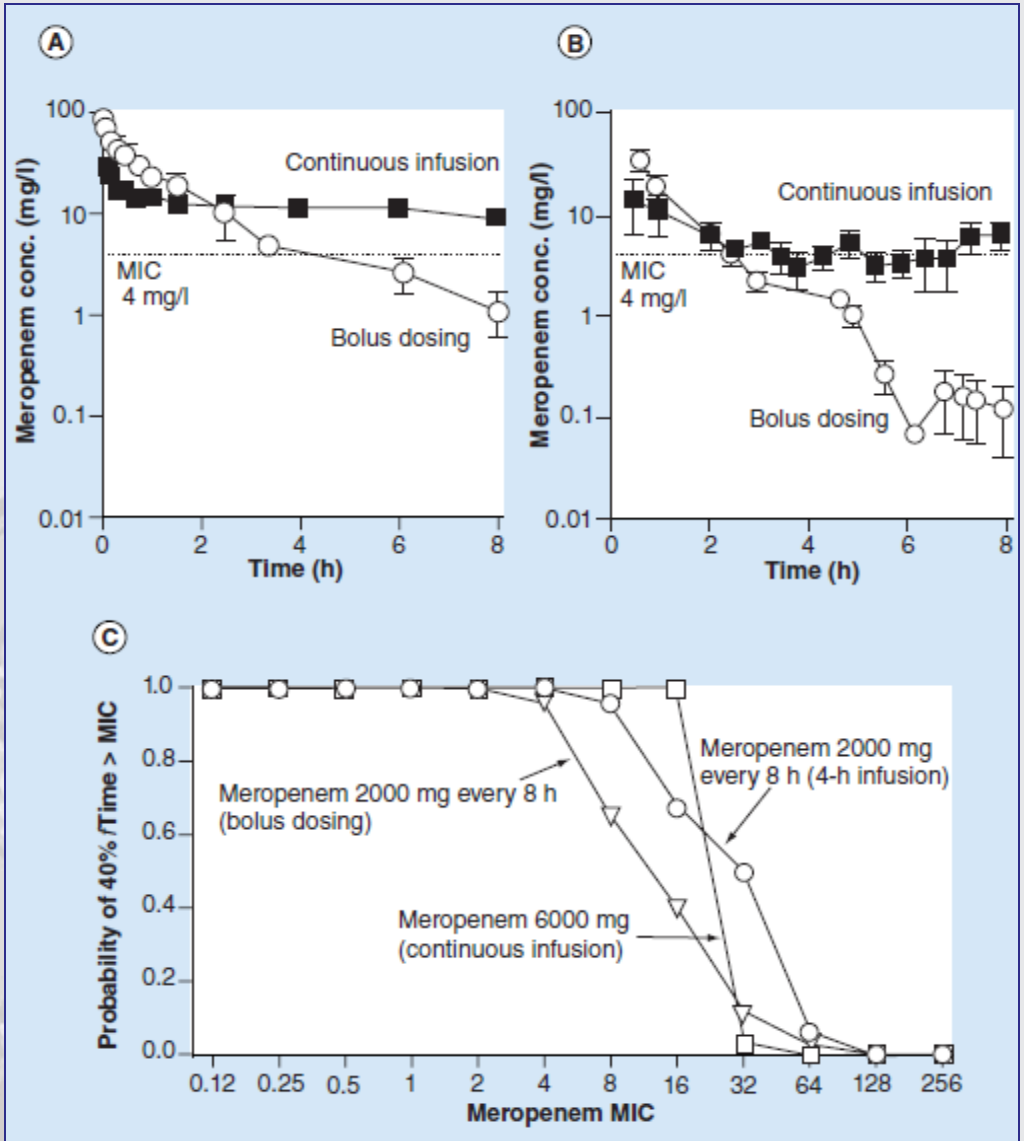


Figure 1. Meropenem concentrations in critically ill patients with sepsis without renal dysfunction administered as intermittent or continuous-infusion regimens of meropenem. (A) Plasma and **(B)** subcutaneous tissue concentrations observed in ten critically ill patients administered 500-mg loading dose, then 1000 mg every 8 h continuous infusion (filled squares); or 1500-mg loading dose followed by 1000 mg every 8 h bolus dose (open circles). **(C)** Monte Carlo dosing simulations, meropenem 6000 mg/day. Pharmacokinetic data from the critically ill patients were used to develop a population pharmacokinetic model to analyze the pharmacokinetic/pharmacodynamic performance of simulated high-dose (6000 mg/day) meropenem regimens over a range of hypothetical pathogen MICs. High-dose extended or continuous-infusion meropenem regimens had high probability pharmacokinetic:pharmacodynamic target attainment up to an MIC of 8–16 mg/l.

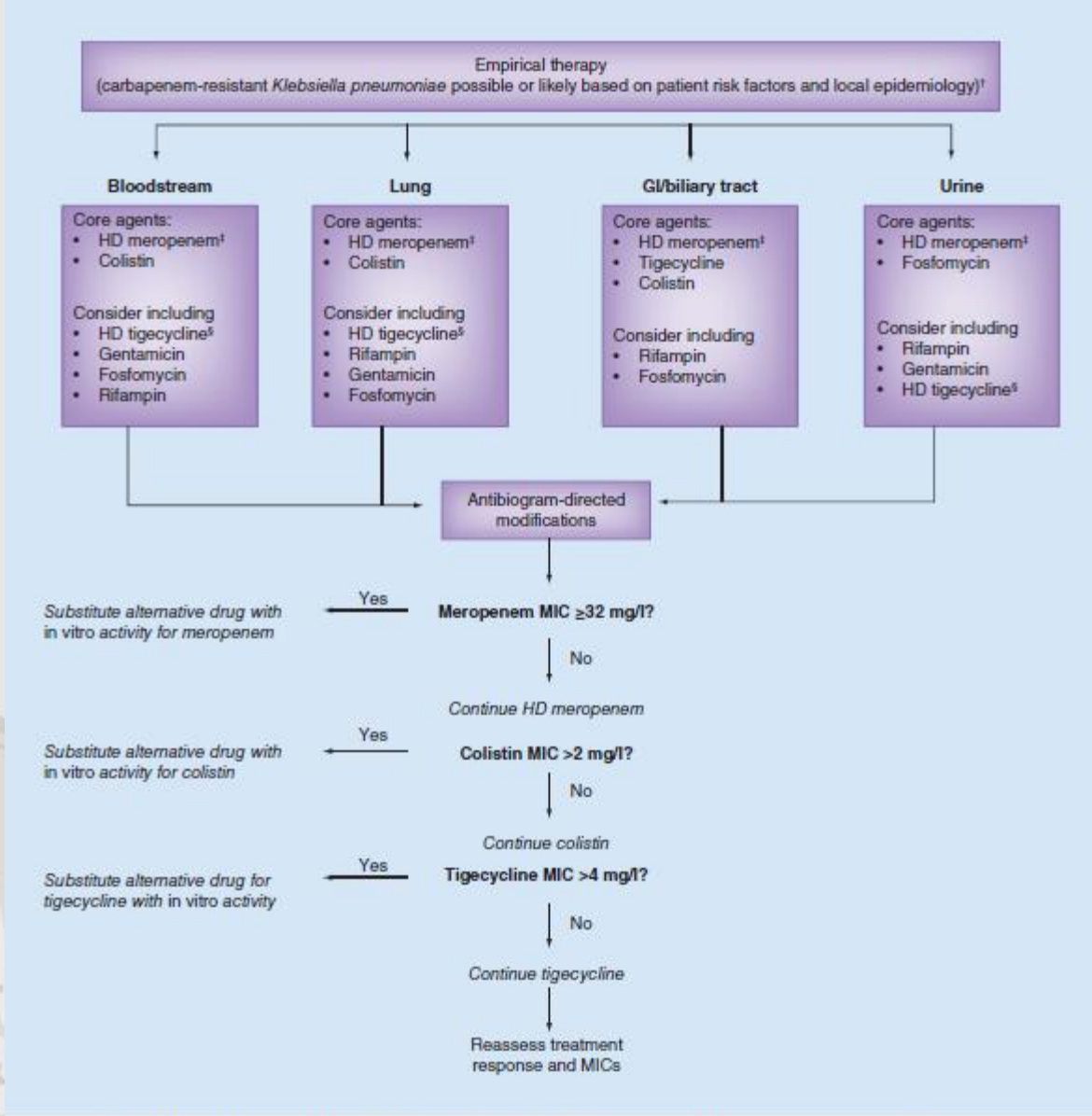


Figure 2. Potential antibiotic combination therapy algorithm for the treatment of carbapenem-resistant *Klebsiella pneumoniae* infections stratified to site of infection and antibiogram results.

†Algorithm would be appropriate for institution where >50% of isolates exhibit carbapenem MICs in the treatable range with HD therapy (MIC <32 mg/ml). Specific drugs used for empirical therapy should be tailored the epidemiology of endemic carbapenem-resistant *Klebsiella pneumoniae* strains.

‡HD meropenem (6 g daily, administered as prolonged infusion).

§HD tigecycline (200 mg loading dose, 100 mg once a day), see text regarding the limitations and evidence supporting the use of HD regimens.

HD: High-dose.

PCT-driven therapy

- La **PCR**, ottimo marker di infiammazione, (Struck et al., 2001), è **più aspecifica:**

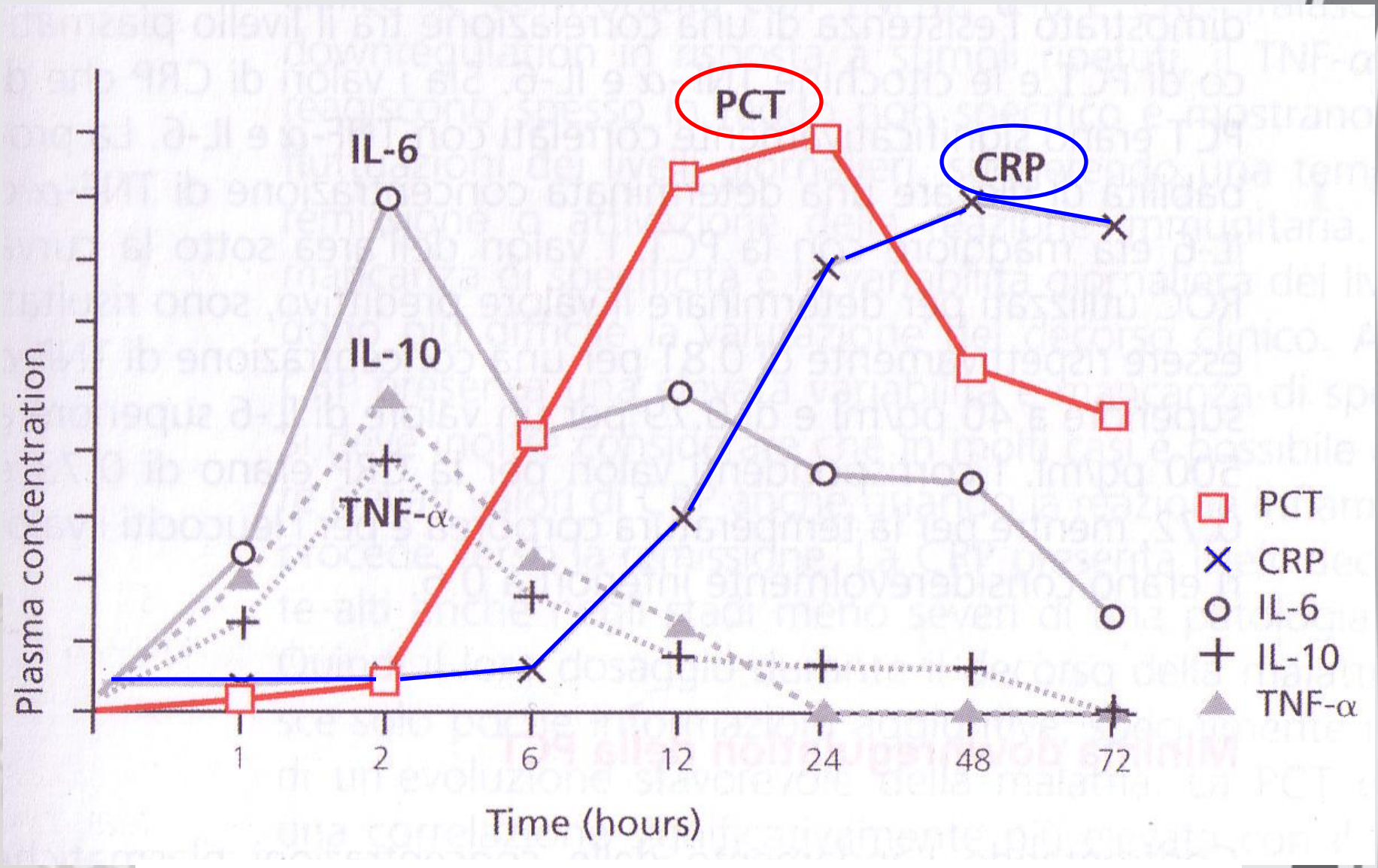
  - può elevarsi sia in corso di infezione virale che batterica

  - **non sembra** essere correlata con l'entità della sepsi (raggiunge i suoi massimi livelli anche nelle sepsi meno gravi, oppure rimane elevata per poco tempo rispetto alla severità della prognosi del paziente) (Tschaikowsky K et al., 2002).

- Una meta-analisi (Simon et al. 2004), ha evidenziato come la PCT sia un marker più accurato rispetto alla PCR nella ***distinzione fra infiammazione batterica*** e ***quella di origine non infettiva:***

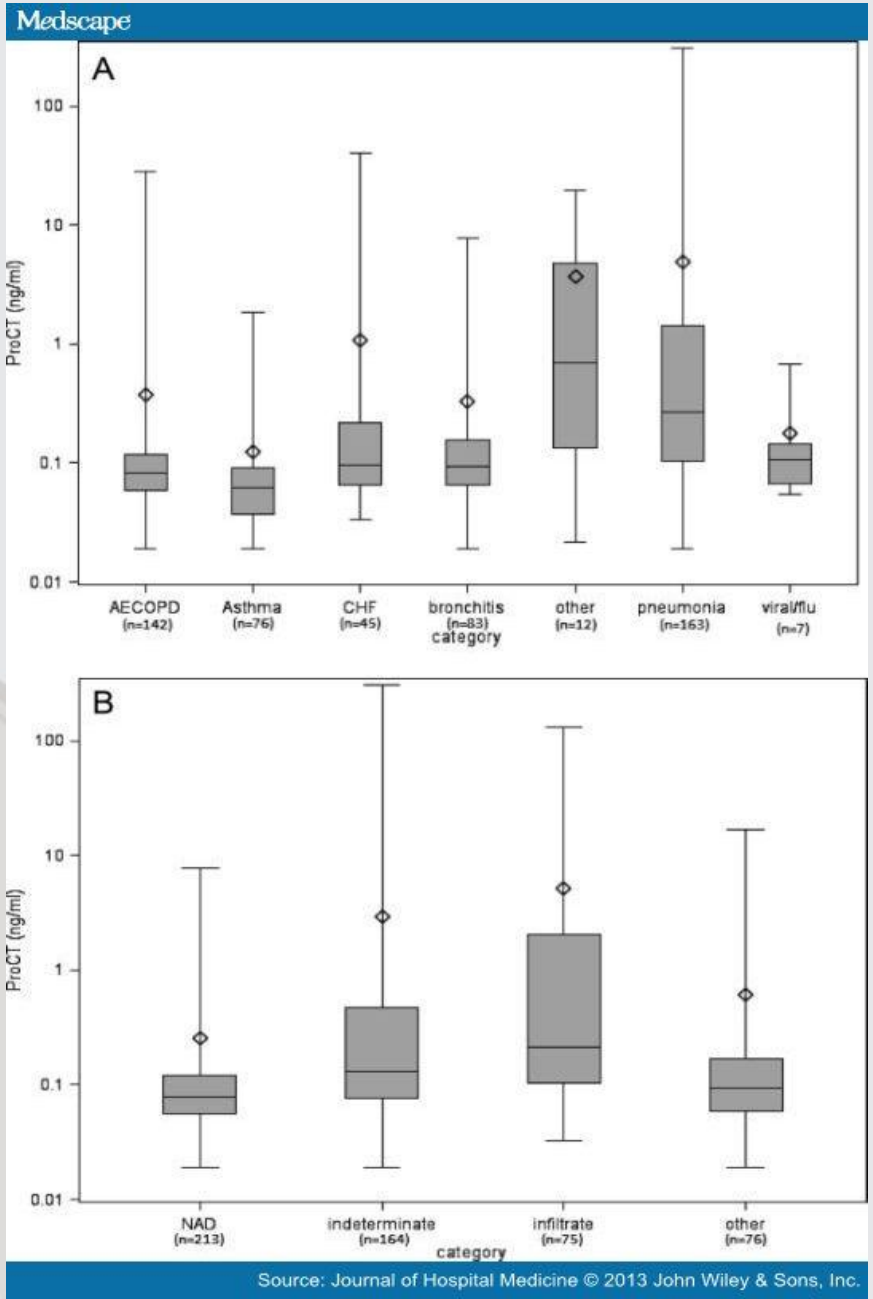
  sensibilità dell'88% vs 75%

  specificità dell'81% vs 67%

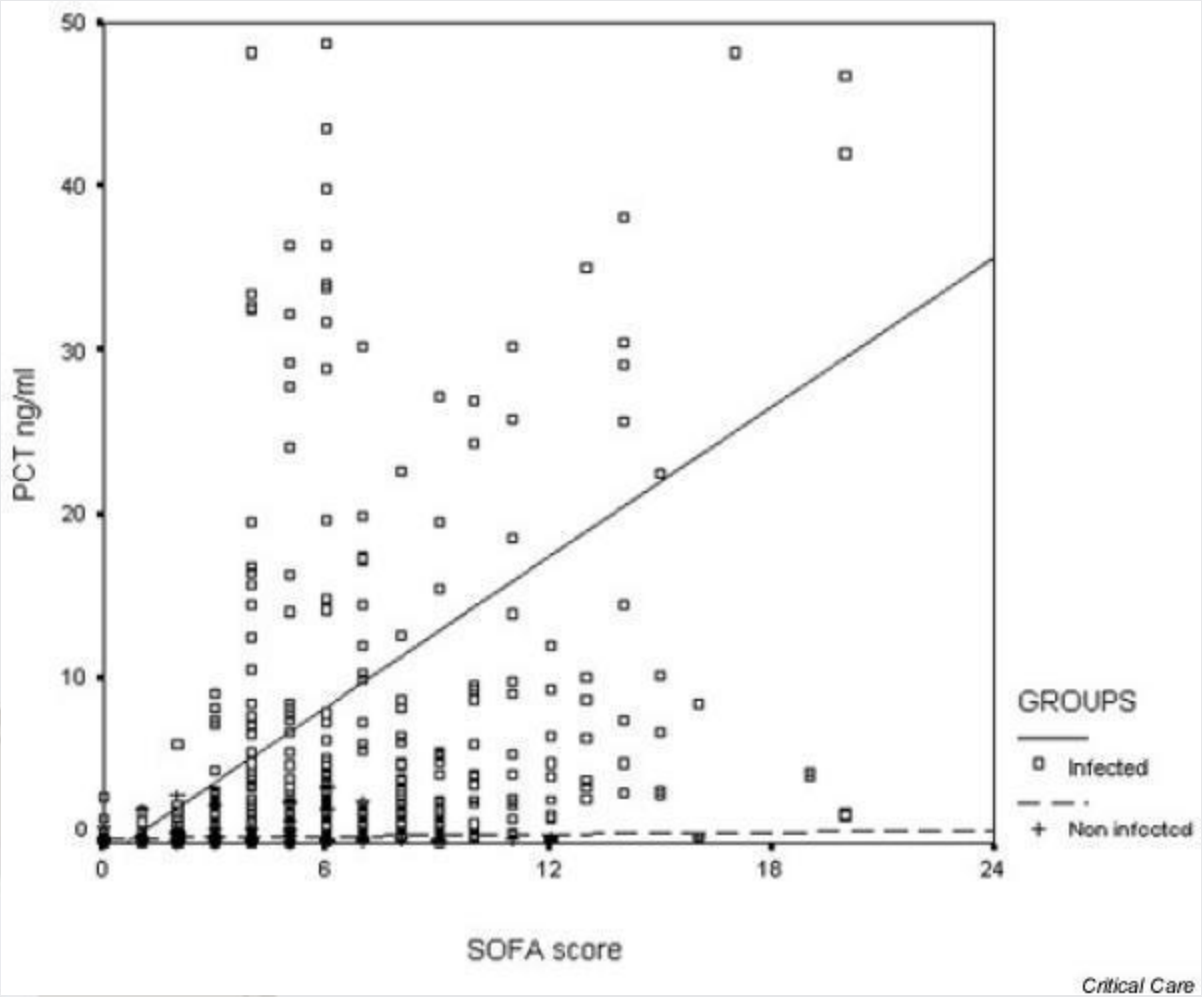


Andamento delle concentrazioni plasmatiche di procalcitonina, proteina C-reattiva e citochine dopo trauma chirurgico (Meissner M, 1999).

Can serum procalcitonin levels help interpret indeterminate chest radiographs in patients hospitalized with acute respiratory illness?



Walsh E. et al
Journal of Hospital Medicine 2013



Procalcitonin (PCT)–sequential organ failure assessment (SOFA) correlation in infected patients (PCT = -0.84 + 1.526 × SOFA score, ng/ml) and noninfected patients (PCT = 0.27 + 0.02 × SOFA score, ng/ml). * $P < 0.02$. □ and solid line, infected and regression line; + and dashed line, noninfected and regression line.

ORIGINAL ARTICLE 10.1111/j.1469-0691.2011.03672.x

Guidelines for the management of adult lower respiratory tract infections - Full version

M. Woodhead[1], F. Blasi[2], S. Ewig[3], J. Garau[4], G. Huchon[5], M. Ieven[6], A. Ortqvist[7], T. Schaberg[8], A. Torres[9], G. van der Heijden[10], R. Read[11] and T. J. M. Verheij[12] Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases

CMI 2011

hospitalization should be seriously considered [A3]. Biomarkers (e.g. CRP or PCT) have a significant potential to improve severity assessment but have not been sufficiently evaluated for the decision to hospitalize [A3].

What should be the duration of treatment?

Recommendation: The duration of treatment should generally not exceed 8 days in a responding patient [C2]. Biomarkers, particularly PCT, may guide shorter treatment duration.

Research

Open Access

Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction

Gian Paolo Castelli[1], Claudio Pognani[1], Michael Meisner[2], Antonio Stuani[1], Daniela Bellomi[3] and Laura Sgarbi[1]

Critical Care 2004

Key messages

- Both CRP and PCT were higher in patients in whom infection was diagnosed at comparable levels of organ dysfunction; CRP was already increased during minor severity of organ dysfunction and sepsis, but did not further increase during more severe stages of the disease.
- PCT on the contrary was low during SIRS and sepsis, but high in patients with severe sepsis/septic shock and higher categories of the SOFA score.
- PCT reacted more quickly than CRP and this kinetic characteristic allows anticipation of a diagnosis of sepsis 24-48 hours before the CRP level would.
- In the trauma patient, when infectious complication occurred, PCT values rose promptly and marked the septic event.

Table 1

Procalcitonin (PCT), C-reactive protein (CRP), lactate and sepsis score values at different categories of the sequential organ failure assessment (SOFA) score and severity of systemic inflammation according to American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) criteria

	SOFA	PCT (ng/ml)	CRP (mg/l)	Lactate (mmol/l)	Sepsis score
Category of SOFA score (number of observations)					
1–6 ($n = 557$)	3 (2/5)	0.37 (0.12/1.2)	101 (53/161)	1.24 (0.96/1.6)	6 (3/10)
7–12 ($n = 156$)	9 (7/10)	2.55 (0.85/9.95)	140 (65/209)	1.74 (1.2/2.43)	13 (10/16)
13–18 ($n = 31$)	14 (13/15)	8.5 (3.3/28.4)	180 (115/219)	3 (2.34/3.83)	21.5 (16.25/25.75)
19–24 ($n = 13$)	19.5 (19/20)	23.24 (2.28/50.92)	154 (9.6/308)	3.7 (3.5/5)	25(24.25/25.75)
Category according to ACCP/SCCM criteria (number of patients)					
No SIRS ($n = 15$)	3 (2–4.5)	0.14 (0.07–0.29)	72 (20–125)	1.26 (0.64–1.38)	3 (0–5.5)
SIRS ($n = 15$)	4 (2.25–8.25)	0.38 (0.16–0.93)*	51 (19.5–80.5)	2.13 (1.14–2.93)*	3.5 (2–8.25)
Sepsis/SS ($n = 71$)	6 (4–9)	3 (1.48–15.26)**	164 (75–222)**	2.2 (1.27–3.74)	11 (7–17)**
Sepsis ($n = 34$)	4.5 (3–6)	1.58 (0.41–3) **	150 (71–209)**	1.37 (1–2.61)	8.5 (3.75–12.25)**
Severe sepsis ($n = 22$)	7 (6–8.25)†	5.58 (1.84–32.93)†	159 (75–209)	2.19 (1.73–2.93)	14.5 (9.25–19.75)†
Septic shock ($n = 15$)	11 (9–15)d	13.1 (6.1–42.2)‡	195 (75–272)	3.7 (2.6–6.4)‡	15 (13.5–19.5)
Trauma patients ($n = 49$)	5 (3–8)	1.4 (0.3–5.1)	40 (16–150)	2.7 (1.7–5)	3 (0–5.3)

All patient groups without trauma were evaluated. Trauma patients were in a separate group. Data presented as median values (lower and upper quartiles). SIRS, systemic inflammatory response syndrome. * $P < 0.05$ versus no systemic inflammatory response syndrome (No-SIRS), ** $P < 0.05$ versus SIRS, † $P < 0.05$ versus sepsis, ‡ $P < 0.05$ versus severe sepsis.

Journal club critique

Procalcitonin-guided antibiotics in severe sepsis

Peter Simon[1], Eric B Milbrandt[2] and Lillian L Emlet[2]

Unfortunately, the main shortcoming of the study is that it was not powered to answer the real question. That is, can antibiotic exposure be safely reduced? Mortality and infection recurrence rates were similar between groups, suggesting that antibiotic use was reduced without harming patients. Yet, as the authors point out, a study powered for these endpoints would require several hundred patients per arm.

Recommendation

The PCT-based protocol in the study does appear to reduce antibiotic exposure in patients with severe sepsis, but issues of assay availability, generalizeability, safety, and cost-effectiveness must be addressed before we can recommend its routine use.

Longitudinal changes in procalcitonin in a heterogeneous group of critically ill patients*

Steven C. Reynolds, MD, FRCPC; Andrew F. Shorr, MD, MPH; John Muscedere, MD, FRCPC; Xuran Jiang, MSc; Daren K. Heyland, MD, MSc, FRCPC

CCM 2012

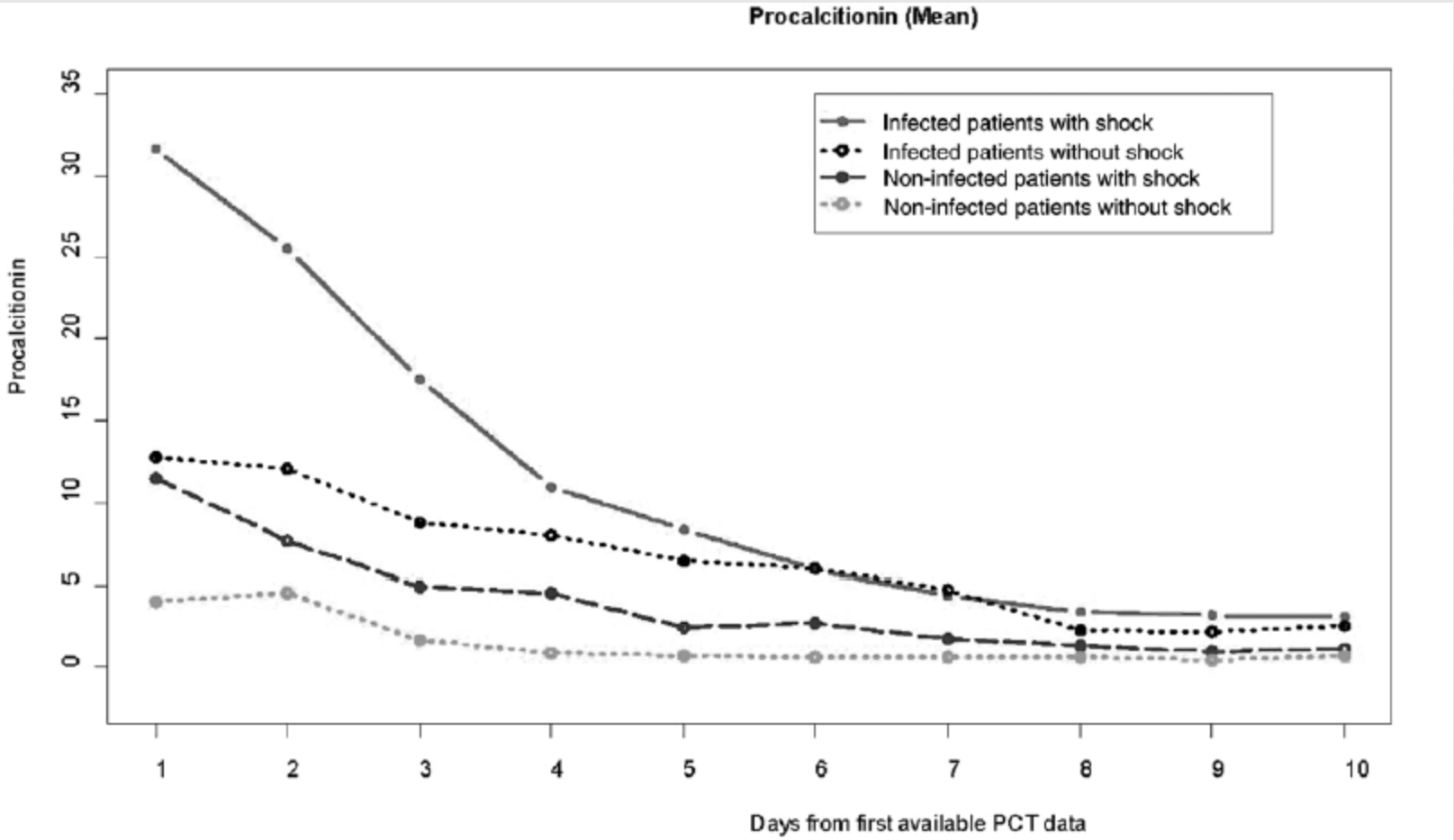


Figure 4. Shock by infection status as determinants of procalcitonin (*PCT*) over time.

CONS

Procalcitonin-guided interventions against infections to increase early appropriate antibiotics and improve survival in the intensive care unit: A randomized trial*

Jens U. Jensen, MD, PhD; Lars Hein, MD; Bettina Lundgren, MD, DMSc; Morten H. Bestle, MD, PhD; Thomas T. Mohr, MD, PhD; Mads H. Andersen, MD; Klaus J. Thornberg, MD; Jesper Løken, MD; Morten Steensen, MD; Zoe Fox, MD, PhD; Hamid Tousi, MD; Peter Søe-Jensen, MD; Anne Ø. Lauritsen, MD; Ditte Strange, MD; Pernille L. Petersen, MD; Nanna Reiter, MD; Søren Hestad, MD; Katrin Thormar, MD; Paul Fjeldborg, MD; Kim M. Larsen, MD; Niels E. Drenck, MD; Christian Østergaard, MD, PhD, DMSc; Jesper Kjær, MSc; Jesper Grarup, DVM; Jens D. Lundgren, MD, DMSc; for The Procalcitonin And Survival Study (PASS) Group

Objective: For patients in intensive care units, sepsis is a common and potentially deadly complication and prompt initiation of appropriate antimicrobial therapy improves prognosis. The objective of this trial was to determine whether a strategy of antimicrobial spectrum escalation, guided by daily measurements of the biomarker procalcitonin, could reduce the time to appropriate therapy, thus improving survival.

Design: Randomized controlled open-label trial.

Setting: Nine multidisciplinary intensive care units across Denmark.

Patients: A total of 1,200 critically ill patients were included after meeting the following eligibility requirements: expected intensive care unit stay of ≥24 hrs, nonpregnant, judged to not be harmed by blood sampling, bilirubin <40 mg/dL, and triglycerides <1000 mg/dL (not suspensive).

Interventions: Patients were randomized either to the "standard-of-care-only arm," receiving treatment according to the current international guidelines and blinded to procalcitonin levels, or to the "procalcitonin arm," in which current guidelines were supplemented with a drug-escalation algorithm and intensified diagnostics based on daily procalcitonin measurements.

Measurements and Main Results: The primary end point was death from any cause at day 28; this occurred for 31.5% (190 of 604) patients in the procalcitonin arm and for 32.0% (191 of 596) patients in the standard-of-care-only arm (absolute risk reduction, 0.6%; 95% confidence interval [CI] −4.7% to 5.9%). Length of stay in the intensive care unit was increased by one day (p = .004) in the procalcitonin arm, the rate of mechanical ventilation per day in the intensive care unit increased 4.9% (95% CI, 3.0–6.7%), and the relative risk of days with estimated glomerular filtration rate <60 mL/min/1.73 m^2 was 1.21 (95% CI, 1.15–1.27).

Conclusions: Procalcitonin-guided antimicrobial escalation in the intensive care unit did not improve survival and did lead to organ-related harm and prolonged admission to the intensive care unit. The procalcitonin strategy like the one used in this trial cannot be recommended. (Crit Care Med 2011; 39:2048–2058)

KEY WORDS: antibiotics; bacterial infection; biomarker guidance; mortality; procalcitonin; sepsis

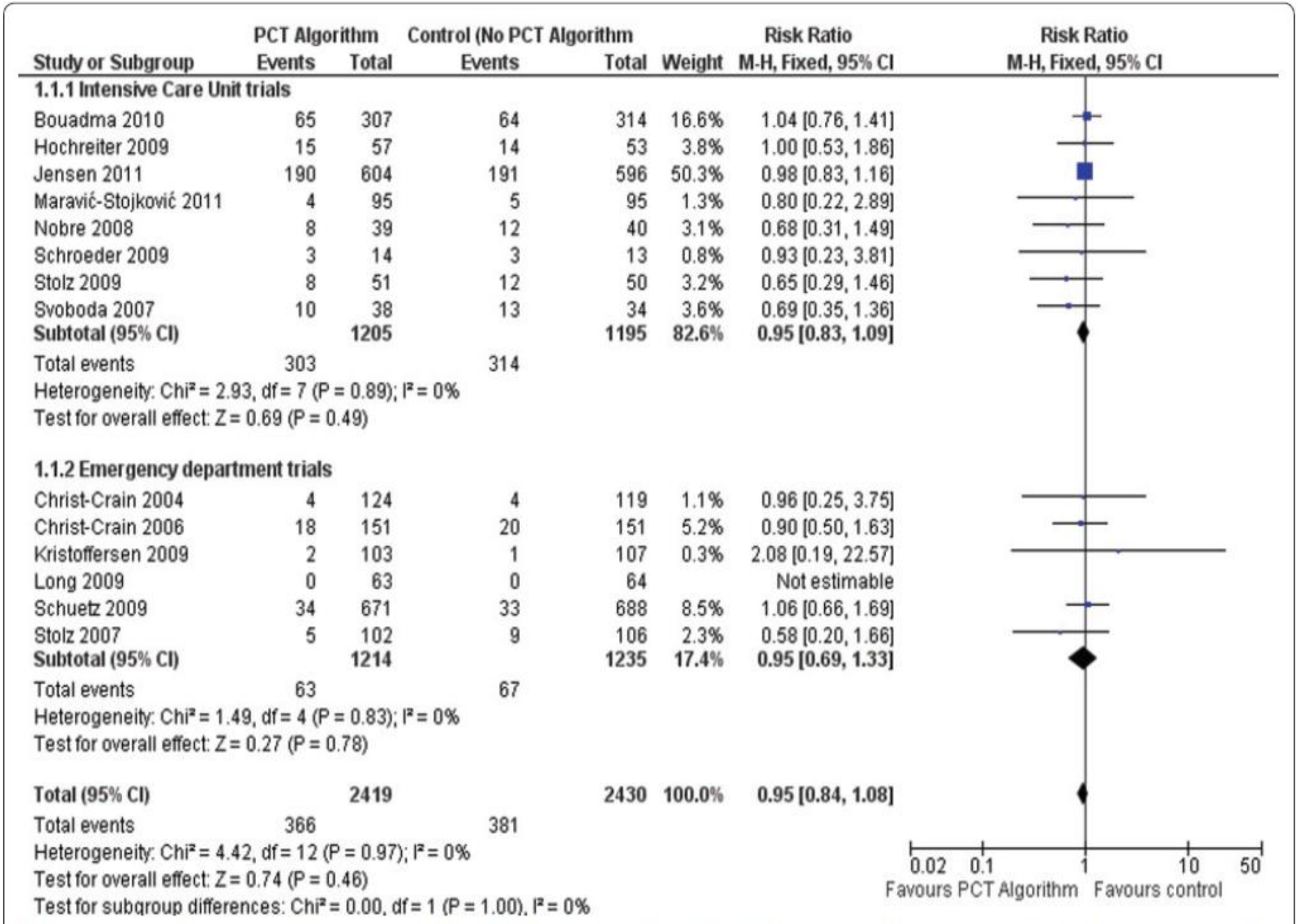


Figure 1. Updated meta-analytic assessment of mortality with procalcitonin-guided treatment versus control. CI, confidence interval; M-H, Mantel-Haenszel test; PCT, procalcitonin.

TAKE HOME MESSAGES:
An Approach to Antibiotic Prescription in ICU

1 .Ask how well the patient is!
In the gravely ill patient (as opposed to the 'not-so-seriously ill'), there is little time for delay, and an error in choice of antibiotics may well cost the patient his/her life. Prolonged ventilation and prior antibiotic use (especially of broad-spectrum agents) predispose to resistance.

2 .Know the organism
Your benchmark for treatment should be treating a known organism with an appropriate dose of antibiotic to which that organism is likely to respond, based on sensitivity testing. This ideal will often not be met. Sometimes you will obtain an organism and its sensitivity on routine microbiological surveillance and then the patient will show features of infection likely to be due to that organism. More often, you will have to rely on empiric therapy. (See also: [Am J Med 1991 301 165-72])

3 .Know the environment
Know the patterns of resistance, and the organisms prevalent in your ICU environment. This helps with antibiotic choice.

4 .Identify the site of infection
Positive blood cultures are simply not good enough. Identify the site of infection (e.g. respiratory tract, urinary tract, a subdiaphragmatic collection, or whatever) and address any surgically remediable pathology right away. The primary treatment of an abscess, for example, is immediate drainage, *not antibiotics*


Grazie per la vostra attenzione!!!!!

Durata suggerita terapia in alcune infezioni

	giorni
Batteriemia	10-14
Colite pseudomembranosa	10
Cistite	3
Pielonefrite	14 (7 se cipro)
Polmonite, pneumococcica	3-5 dallo sfebbramento
Polmonite, pseudo-enterobact.	21-42
Polmonite,stafilococcica	21-28
Legionella-mycoplasma-chlamidie	14-21
Ascesso polmonare	28-42
Meningite, meningococcica	5-7
Meningite, emofilo	7
Meningite, pneumococco	14-21
Sinusite acuta	10-14

Sandford Guide 2002

ANTIBIOTICI IDROFILI

- Beta-lattamine
  - ✓ Penicilline
  - ✓ Cefalosporine
  - ✓ Carbapenemi
  - ✓ Monobactami
- Glicopeptidi
- Aminoglicosidi

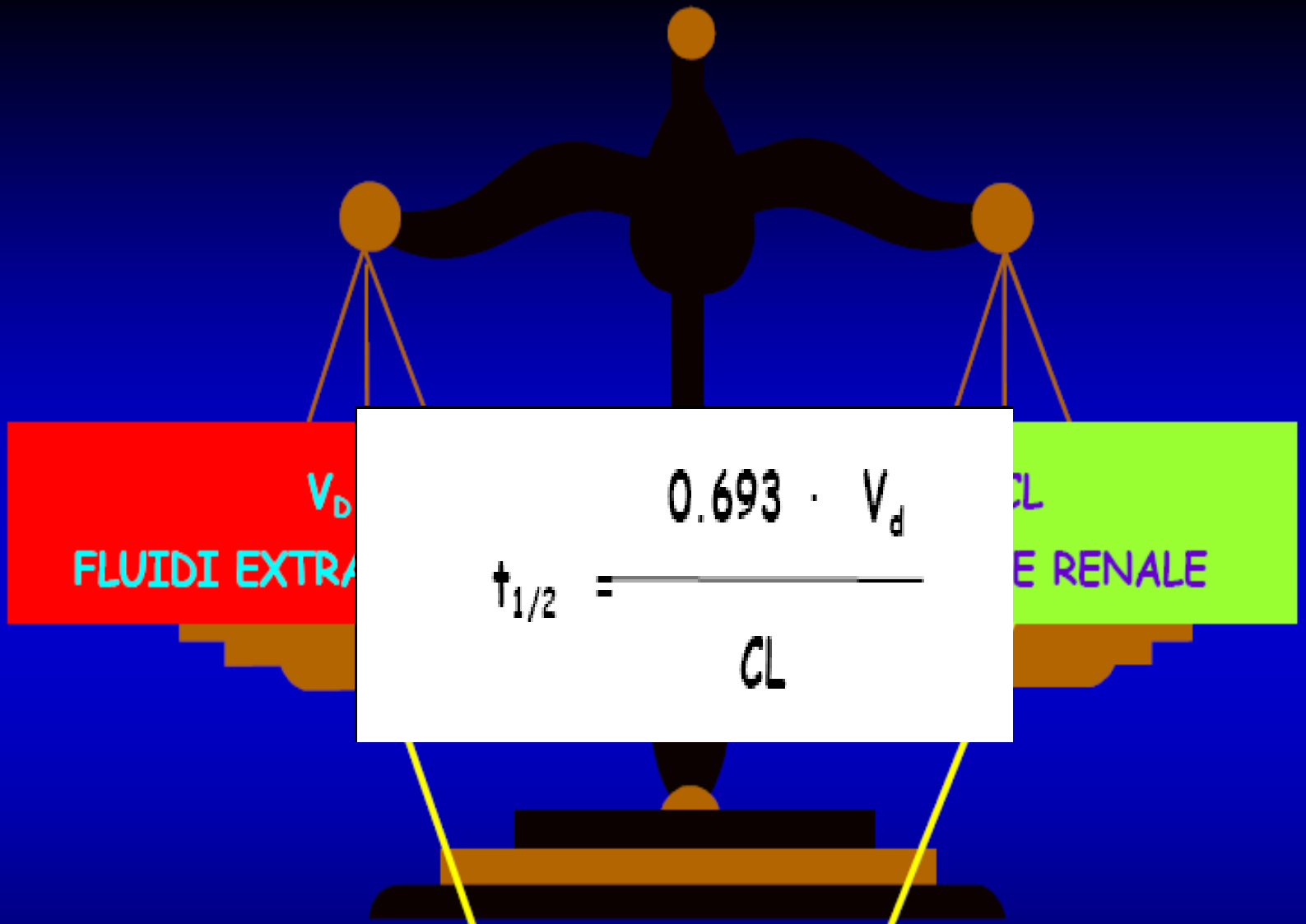
- ✓ Basso volume di distribuzione
- ✓ Incapacità ad attraversare m. plasmatica
- ✓ Inattivi su patogeni intracellulari
- ✓ Eliminazione prevalentemente renale

ANTIBIOTICI LIPOFILI

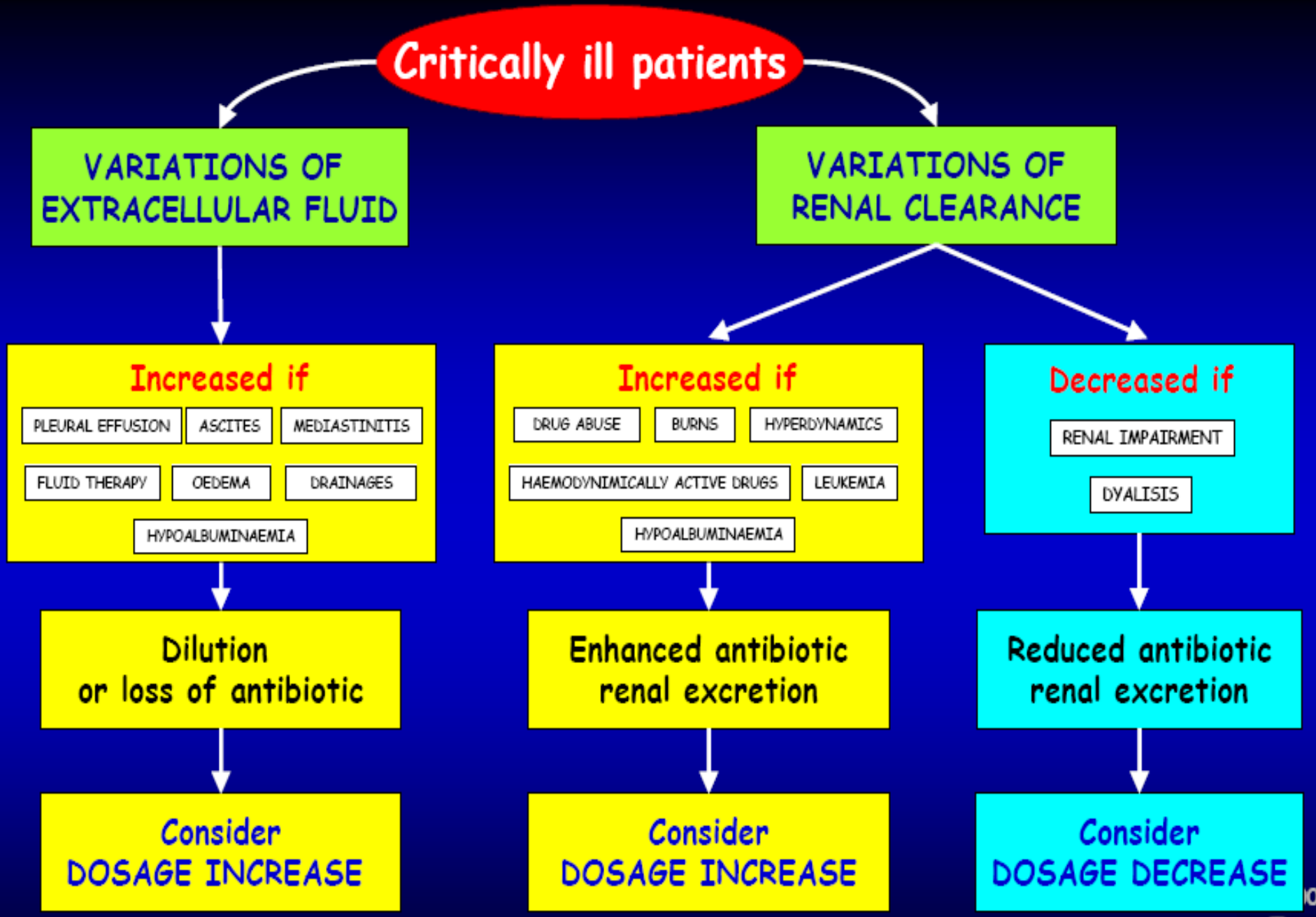
- Macrolidi
- Fluorochinoloni
- Tetracicline
- Cloramfenicolo
- Rifampicina
- Linezolid

- ✓ Alto volume di distribuzione
- ✓ Attraversamento m. plasmatica
- ✓ Attivi su patogeni intracellulari
- ✓ Eliminazione dopo metabolismo epatico

Pea F, Viale P, Furlanut M. *Clin Pharmacokinet* 2005,



Posologie diverse
vs altre popolazioni



Pea F, Viale P, Furlanut M. *Clin Pharmacokinet* 2005;

Rapporto tra concentrazioni intra/extra-cellulari di antibiotici

Antibiotico	%
Betalattamine, aminoglucosidi	<1
Cloramfenicolo	2
Rifampicina	2-5
Fluorchinoloni	20-30
Vancomicina, trimetoprim, teicoplanina	6-12
Clindamicina, eritromicina	1->10
Azitromicina	>50

Fattori legati al paziente

- Presenza di fattori rischio;
- Comorbosità;
- Presenza di allergie farmacologiche;
- Fisiopatologia dell' ospite;
- Pregressi trattamenti antibiotici;
- Colonizzazione;
- Precedenti infezioni

Fattori legati all' infezione

- Tipo d'infezione;
- Gravità della stessa;
- Sorgente dell'infezione (nella sepsi)
- Etiologia generale;
- Patterns nazionali e/o locali di sensibilità

Fattori legati allo antibiotico

- Spettro dell' antibiotico: ampio, comprese le forme MDR;
- Attività battericida;
- Potenza elevata con evidenza di efficacia clinica;
- Profilo farmacocinetico (PK) /farmacodinamico (PD) favorevole;
- Scarsa induzione di resistenze;
- Manegevolezza: effetti indesiderati ed interazioni farmacologiche;
- Costo contenuto (?)

1. Is the microbiological result biologically and clinically compatible with the infection site ?
2. Can the isolate be considered as the etiological agent or more probable as a colonizing strain?
3. Is the chemosensivity pattern possible?
4. Is the resistance definition the only criteria useful to choice drugs?
5. Is the a role for a MIC driven therapy?
6. Is there a role for a daily schedula ad administration modalities be adapted to the MIC value?
7. Which are the antimicrobials with the best PK behavior related to the infection site?
8. Is there physio-pathological conditions interfering with the drug exposition?
9. Which is the best administration modality for the specific patient conditions?
10. How much critical are the potential drug-drug interaction?

Elementi legati al setting assistenziale

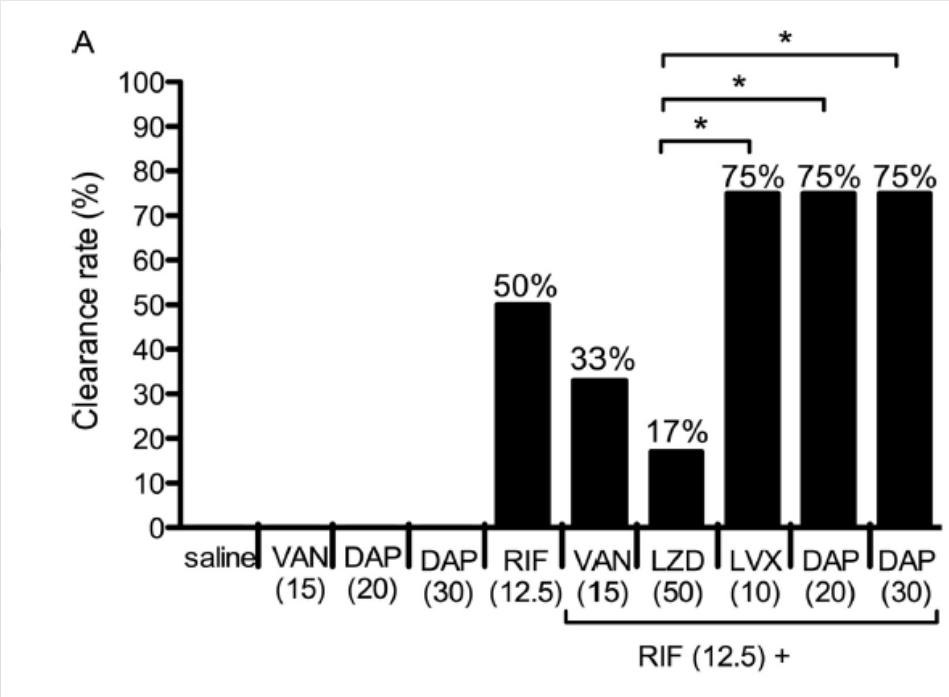
- Tipologia del Reparto di ricovero
- Situazioni epidemiologiche particolari
- Politica terapeutica generale di reparto

Efficacy of Daptomycin in Implant-Associated Infection Due to MRSA: Importance of Combination with Rifampin

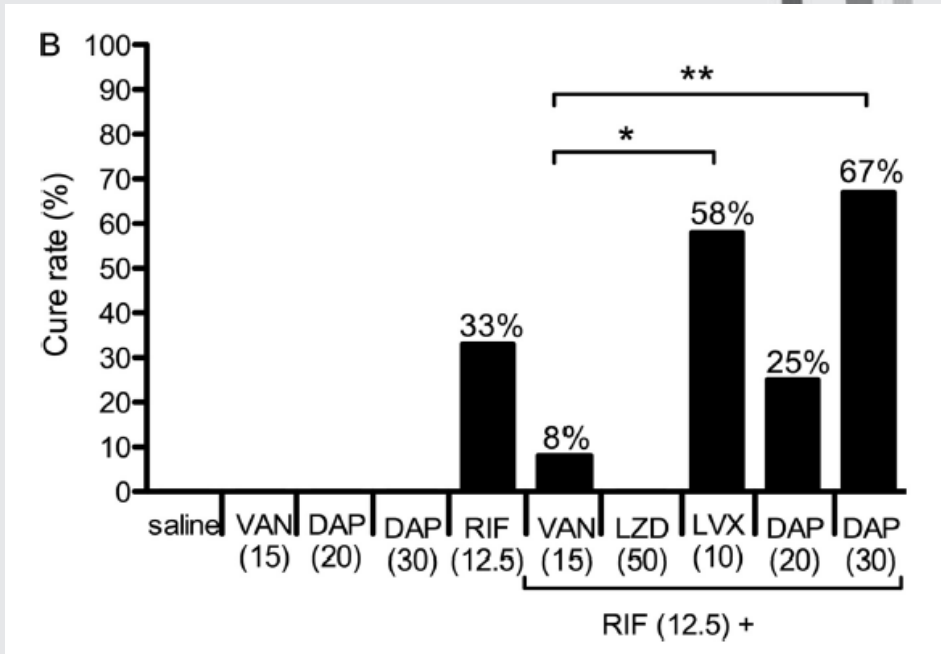
John AK et al, Antimicrob Ag Chemother 2009

Clearance rate of planktonic MRSA and cure rate of adherent MRSA in explanted cages

PLANKTONIC

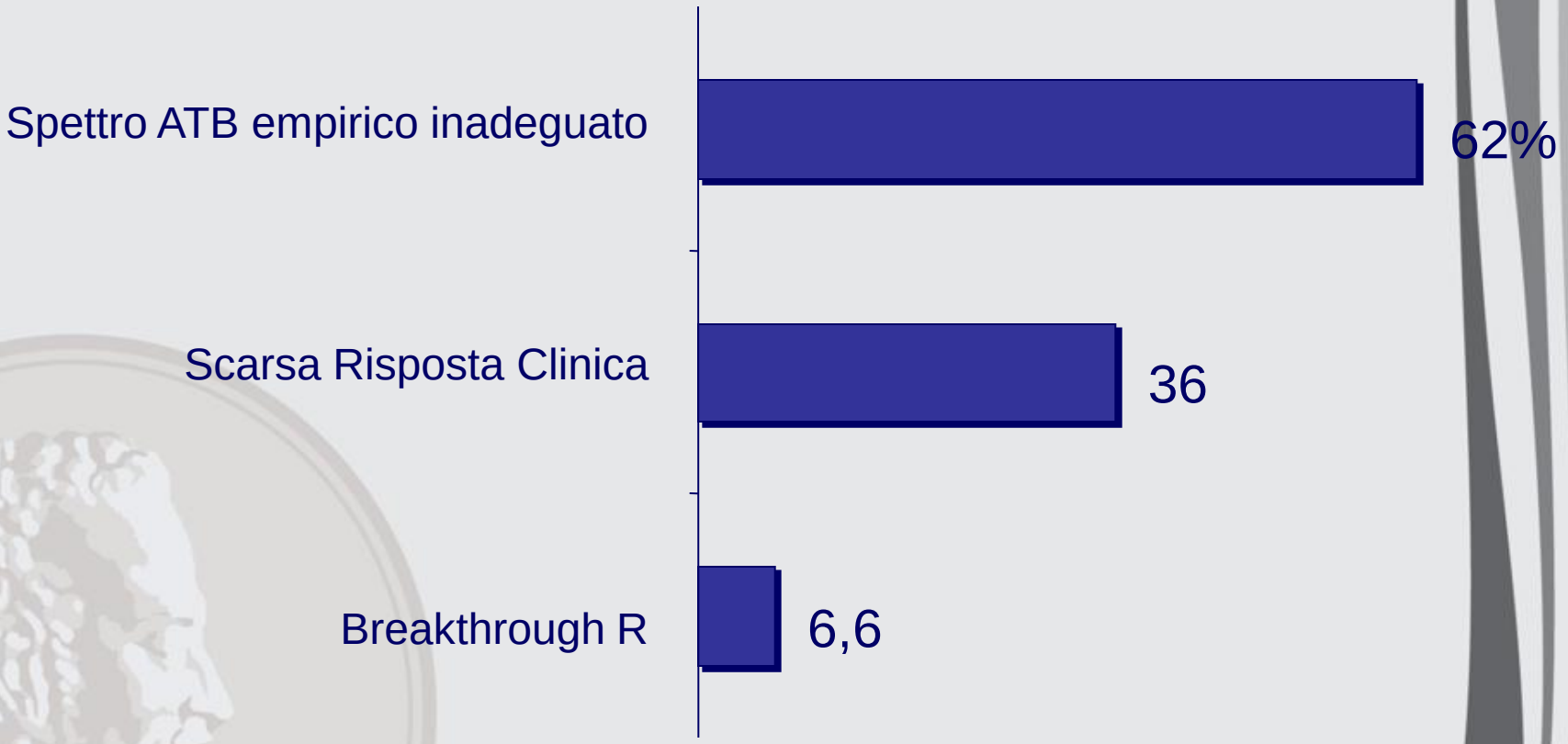


SESSILE



VAP : MOTIVAZIONE VARIAZIONE ATB-TERAPIA

Alvarez-lerma et al, Int Care Med 1996



Influence of Vancomycin MIC on the Treatment of MRSA Bacteremia

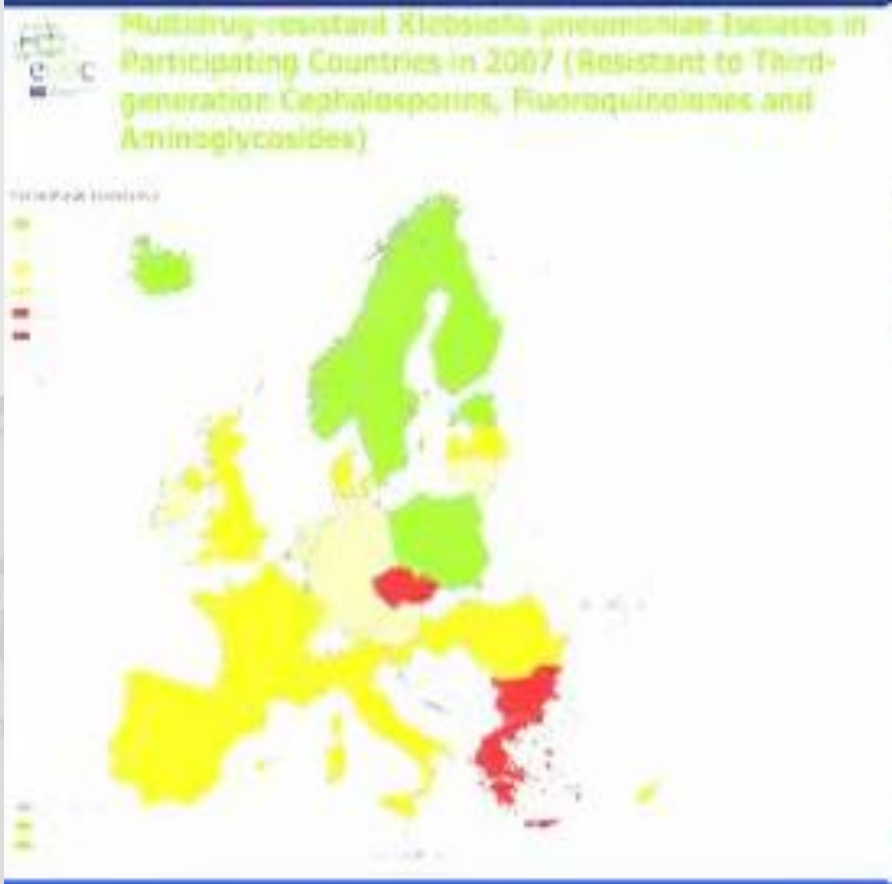
Soriano A et al, Clin Infect Dis 2008; 46:193–200

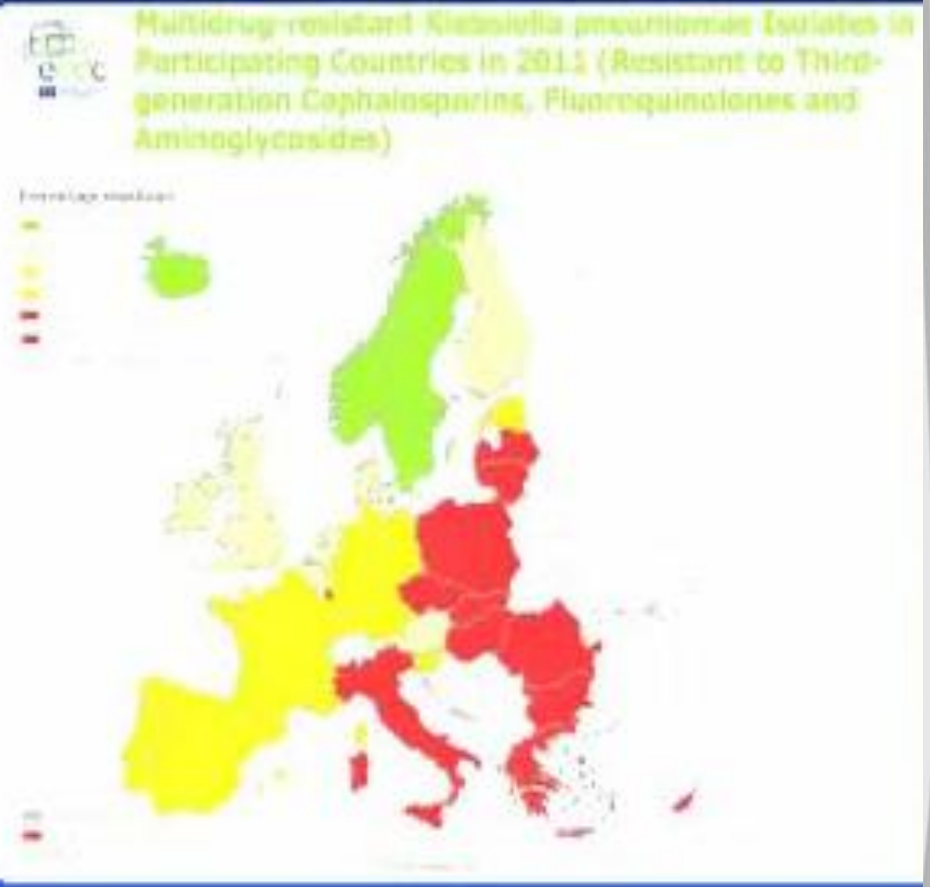
A total of 414 episodes of MRSA bacteremia were prospectively followed-up from 1991 through 2005.
MIC of vancomycin for the first isolate was determined by E-test.Clinical variables recorded were age, comorbidity, prior administration of vancomycin, use of corticosteroids, prognosis of underlying disease, source of bacteremia, the need for mechanical ventilation, shock, and mortality.

A "treatment group" variable was created and defined as follows: (1) receipt of empirical vancomycin and an isolate with a vancomycin MIC of 1 mg/L (38 episodes), (2) receipt of empirical vancomycin and an isolate with a vancomycin MIC of 1.5 mg/L (90 episodes), (3) receipt of empirical vancomycin and an isolate with a vancomycin MIC of 2 mg/L (40 episodes), and (4) receipt of inappropriate empirical therapy (246 episodes).

Univariate and multivariate analyses were performed

MDR *K. pneumoniae* 2007 vs 2011, Europe





EARS-NET

Adequacy of Antimicrobial Treatment and Outcome of *S. aureus* Bacteremia in 9 Western European Countries.

Ammerlaan H et al, Clin Infect Dis 2009

Concerns about the results

Certain antibiotics assumed to be inadequate have some effect in treating MRSA BSI

An external validation of microbiological data was not done.

Although glycopeptides are considered to be adequate for the treatment of MSSA bacteremia, there is evidence that they are inferior to b-lactams for serious MSSA infections

Appropriate dosing of antibiotic treatment was not included in the definition of adequate treatment

Data on adjustments in therapy were not provided

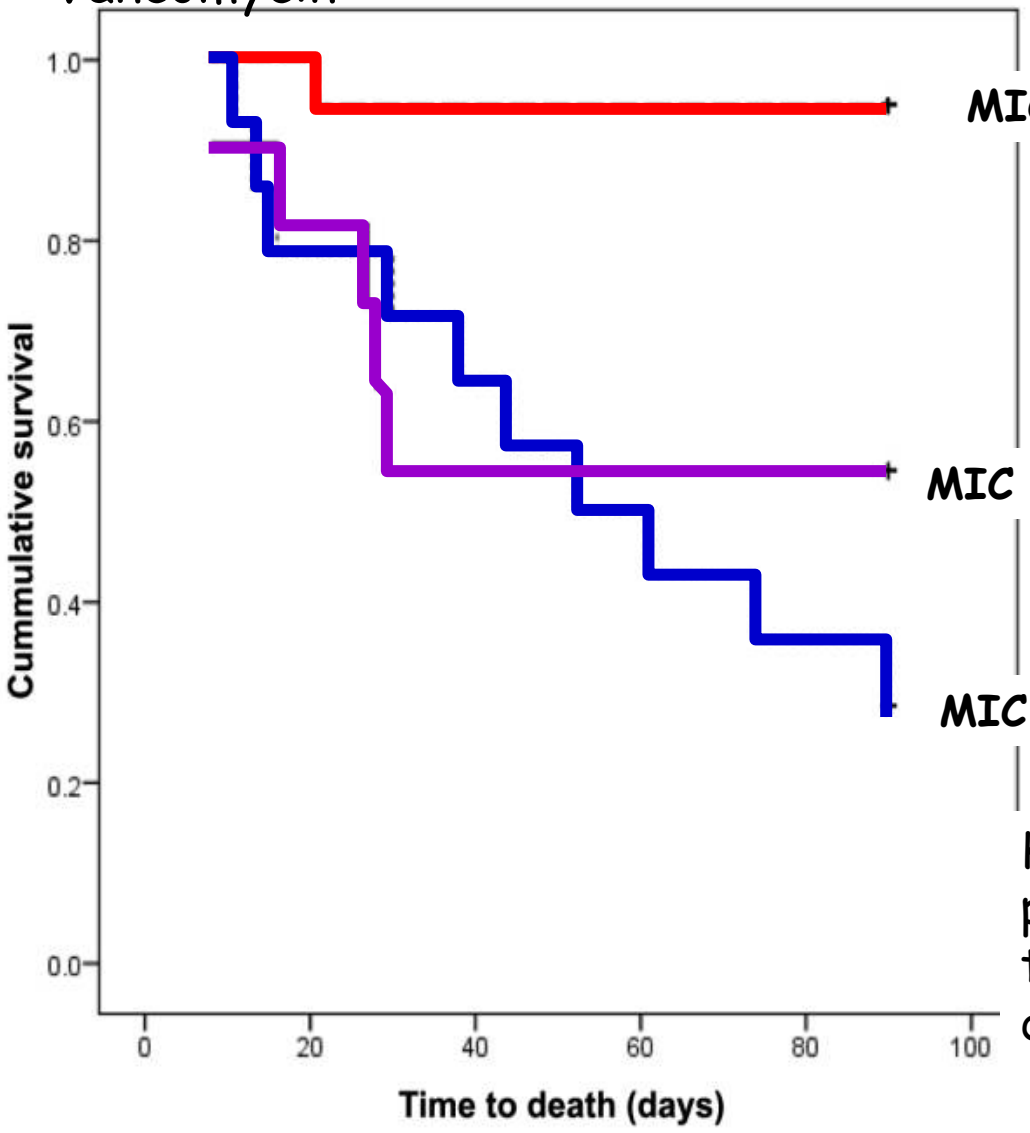
30-day mortality rate may be too crude a measure to identify the effectiveness of antimicrobial therapy. 39% of the deaths in this study occurred in patients in whom there were end-of-life decisions!

On the other hand only a fraction of patients had a critical clinical condition

Bacteremia is the easiest infection to be treated from a PK/PD point of view

Paradoxical Relationship between the Clinical Outcome of *S. aureus* Bacteremia and the Minimum Inhibitory Concentration of Vancomycin

Price J et al, Clin Infect Dis 2009



Kaplan-Meier survival curve for 45 patients with *S.aureus* bacteremia treated with vancomycin related to different MIC ranges of vancomycin

...rnal of Antimicrobial Chemotherapy
...OI: 10.1093/jac/dkg147

JAC

Teicoplanin therapeutic drug monitoring in critically ill patients: a retrospective study emphasizing the importance of a loading dose

TEICOPLANIN TDM IN CRITICALLY ILL PATIENTS:

A RETROSPECTIVE STUDY EMPHASIZING THE IMPORTANCE OF A LOADING-DOSE

Pea F, Brollo L, Viale P, Pavan F, Furlanut M

J Antimicrob Chemother 2003; 51: 971-975

TEICOPLANINA:

DOSE DA CARICO (6 MG/KG OGNI 12 ORE PER ALMENO 3-4 DOSI)

A TUTTI I PAZIENTI

INDIPENDENTEMENTE DALLA FUNZIONE RENALE

Figure 1
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Vancomycin still seems to be the reference drug for most of us, but we can reduce its use

Specific situation	More suitable drug
Pneumonia	Linezolid or ceftobiprole
CNS infection	Linezolid or high-dose vancomycin
Renal failure	Linezolid or daptomycin or ceftobiprole
Bone and joint infection	Teicoplanin or dalbavancin
Endocarditis Right	High-dose vancomycin Daptomycin
Empiric, broad-spectrum coverage Severe infections Non-severe infections (ie wound infection, pericatheter cellulitis)	 Ceftobiprole or linezolid or daptomycin Tigecycline or vancomycin

IDONEE MODALITA' di SOMMINISTRAZIONE

Meropenem in IC

% di guarigione per i 2 diversi schemi terapia
(IC vs dose ripetuta):

- 90.47% IC
- 59.57% dr

IC fa la differenza nel paziente instabile e nell'eziologia da Gram – "difficili"

Il meropenem va ricostituito al momento, non è stabile per > 6 ore.

Lorente Ann Pharmacother 2006

the MIC - related daily schedula ad administration modality

Meropenem by Continuous Versus Intermittent Infusion in VAP due to Gram-Negative Bacilli *Lorente L et al, Ann Pharmacother 2006;40:219-23.*

Table 5. Clinical Cure Rates of Ventilator-Associated Pneumonia

Rate	Continuous Infusion, n (%)	Intermittent Infusion, n (%)	OR (95% CI)	p Value
All cases	38 (90.47)	28 (59.57)	6.44 (1.97 to 21.05)	<0.001
Microorganism				
Pseudomonas aeruginosa	11 (84.61)	6 (40)	8.25 (1.33 to 51.26)	0.02
other	27 (93.10)	22 (68.75)	6.13 (1.21 to 30.98)	0.02
MIC (µg/mL)				
0.25–0.49	21 (100)	23 (76.67)	7.09 (0.72 to 56.38)	0.03
≥0.50	17 (80.95)	5 (29.41)	7.84 (2.26 to 46.09)	0.003

MIC = minimum inhibitory concentration.