Endpoints in HAP/VAP trials: Mortality, Clinical Endpoints, Biomarkers

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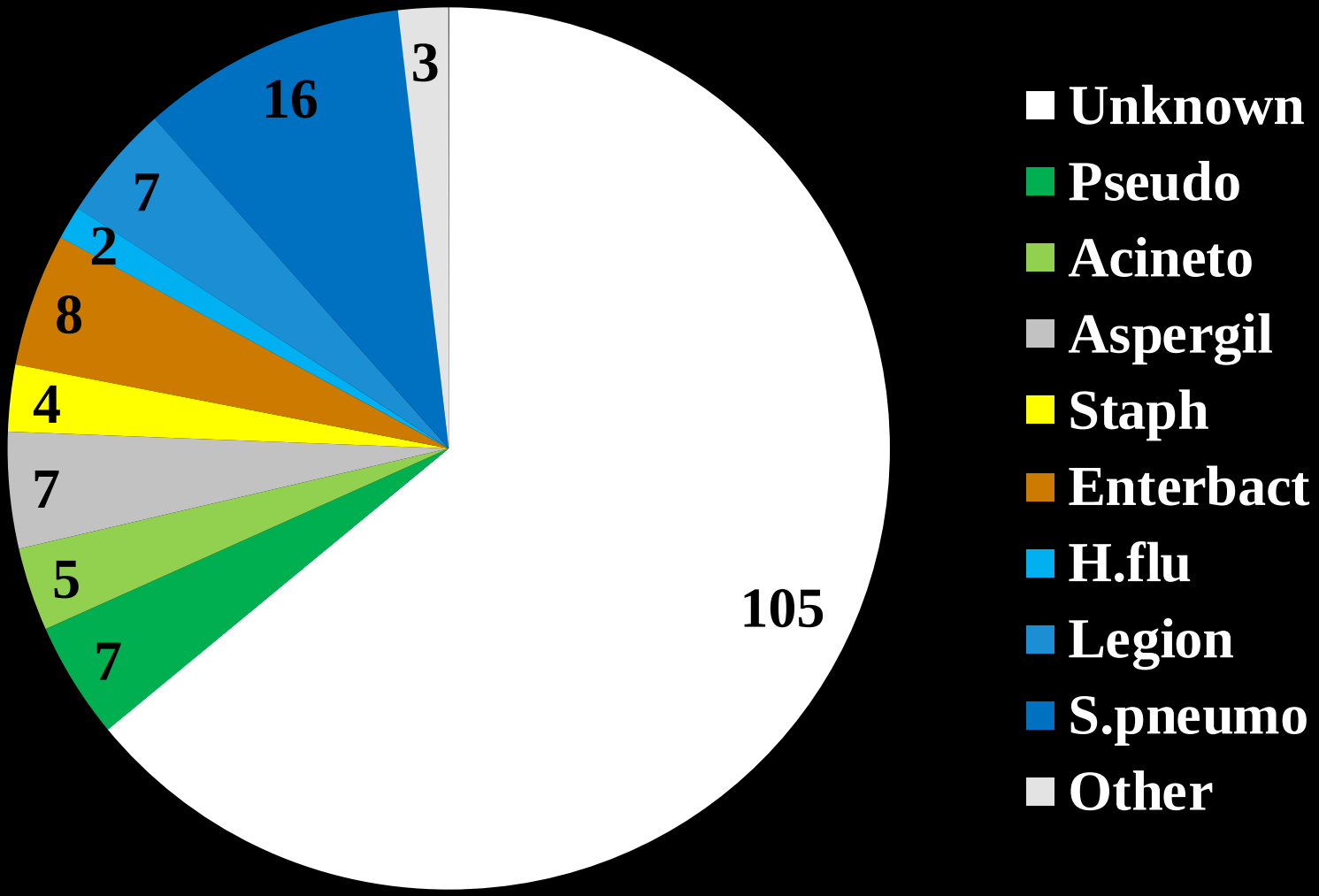
Populations and Pathogens

Etiology of non-ICU HAP



Mortality 26%

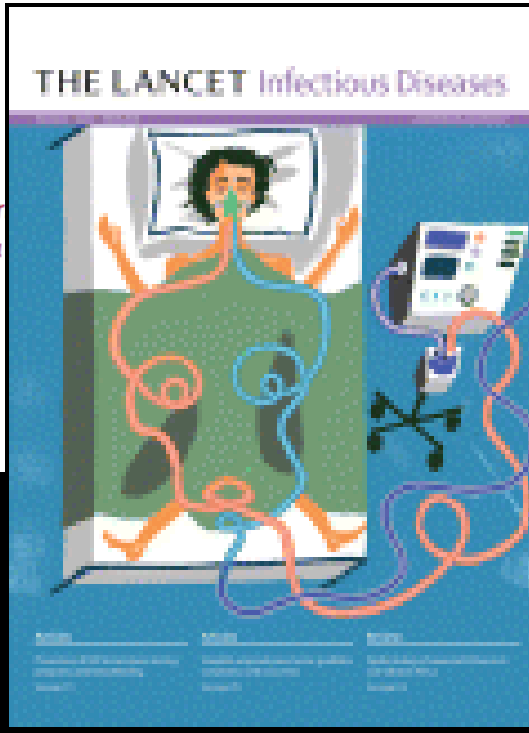
Sopena, Chest, 2005

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

Daniel H Kett, Ennie Cano, Andrew A Quartin, Julie E Mangino, Marcus J Zervos, Paula Peyrani, Cynthia M Cely, Kimbal D Ford, Er
*Julio A Ramirez, and the Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia Investigators**

Summary

Background The American Thoracic Society and Infectious Diseases Society of America provide management of hospital-acquired, ventilator-associated, and health-care-associated pneumonias,

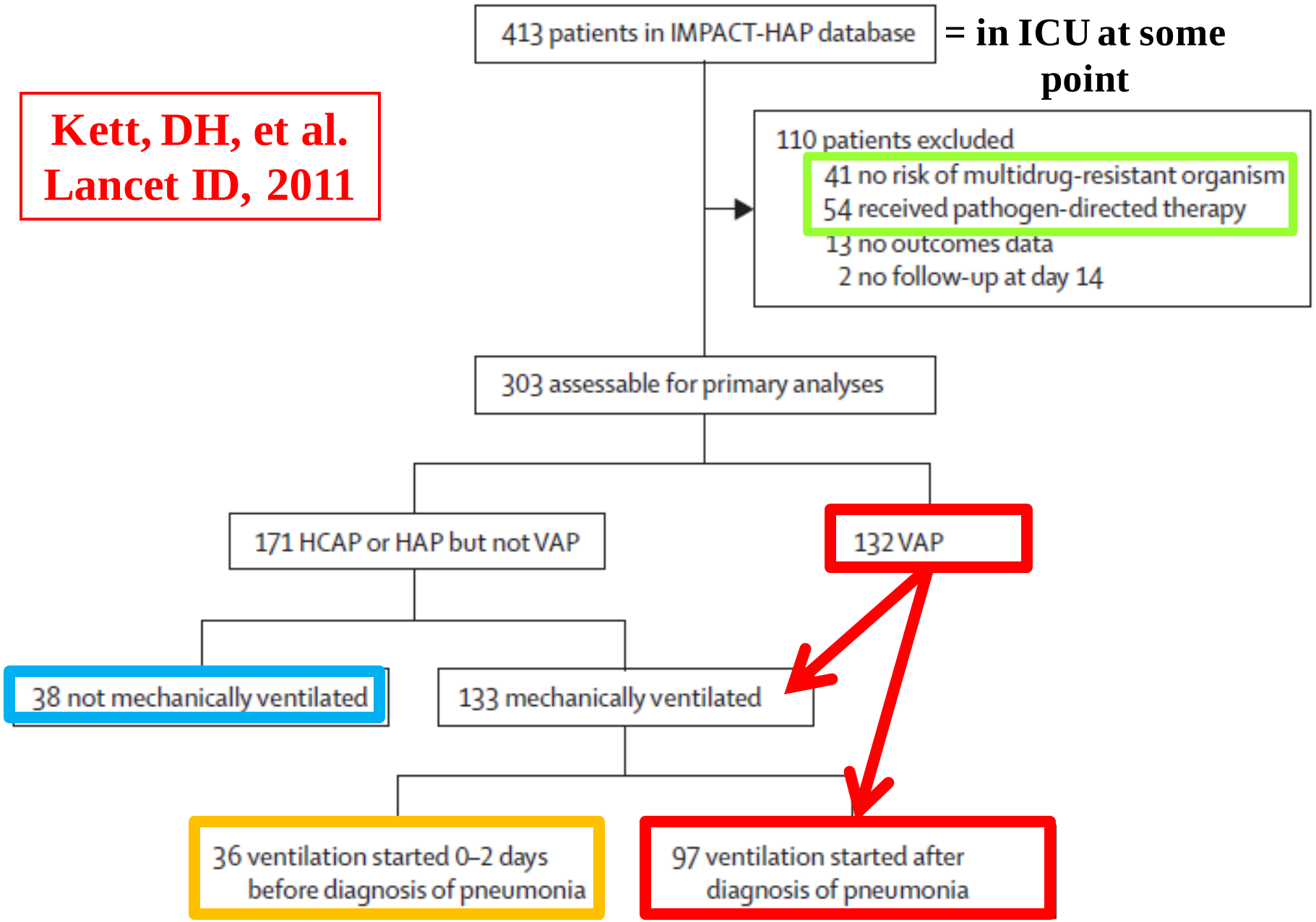


Lancet ID, 2011

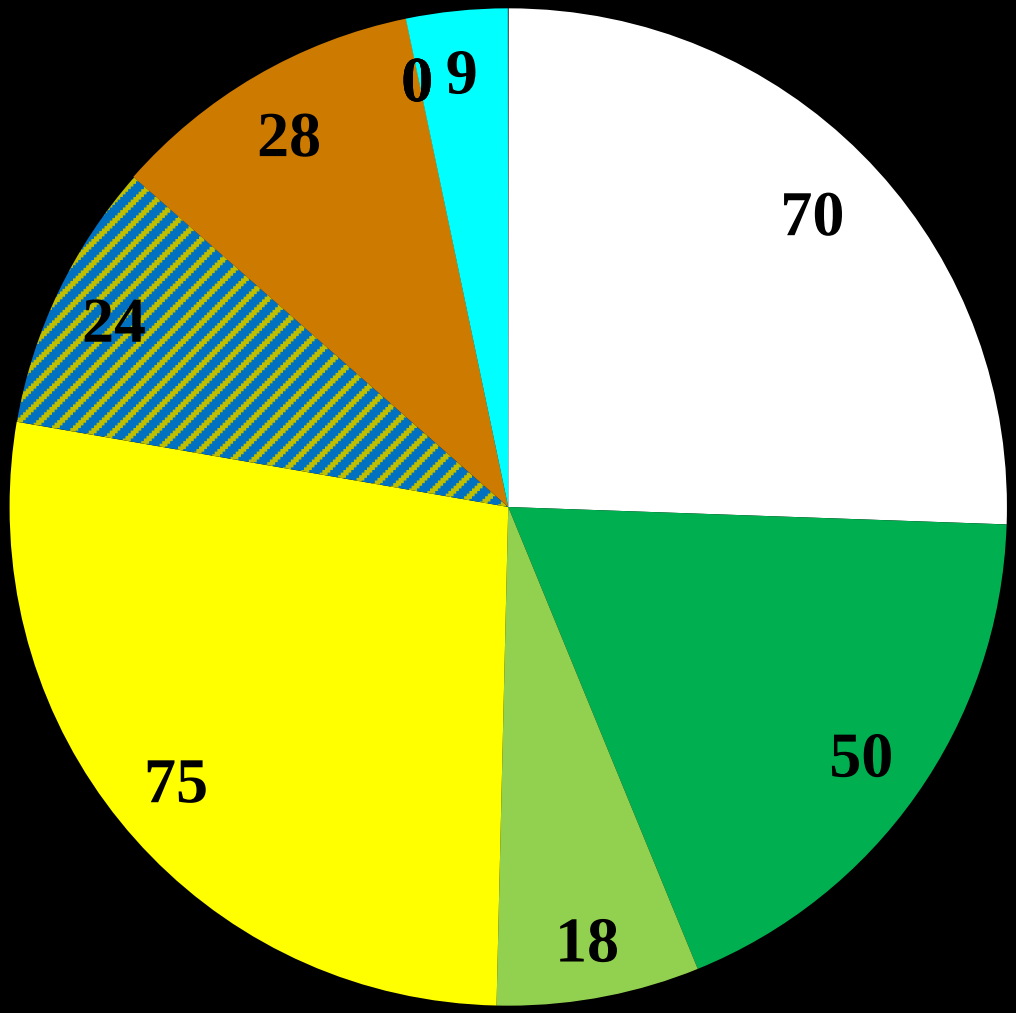
Discussion

In our cohort study, compliance with the ATS–IDSA guidelines[13] was associated with increased mortality.

Kett, DH, et al. Lancet ID, 2011



Etiology of ICU HAP



- Unknown
- Pseudo
- Acineto
- MRSA
- MSSA
- Enterobact
- H.flu
- Legion
- S.pneumo
- Other

Kett, Lancet ID, 2011

Mortality Endpoint

Mortality in ICU HAP/VAP

	Compliant treatment (n=129)			Non-compliant treatment (n=174)		
	Patients	Treatment active	Deaths	Patients	Treatment active	Deaths
MRSA	27 (21%)	25 (93%)	11 (42%)	50 (29%)	38 (76%)	9 (18%)
Pseudomonas spp	33 (26%)	29 (88%)	15 (45%)	17 (10%)	14 (82%)	3 (18%)
Klebsiella spp	11 (9%)	9 (82%)	2 (18%)	16 (9%)	14 (88%)	6 (37%)
MSSA	7 (5%)	7 (100%)	0	17 (10%)	17 (100%)	1 (6%)
Acinetobacter spp	11 (9%)	5 (46%)	0	7 (4%)	4 (57%)	3 (43%)
Escherichia coli	3 (2%)	2 (67%)	2 (67%)	13 (7%)	10 (77%)	3 (25%)
Enterobacter spp	2 (2%)	2 (100%)	1 (50%)	10 (6%)	9 (90%)	3 (30%)
Polymicrobial*	25 (19%)	17 (68%)	9 (36%)	45 (26%)	33 (73%)	12 (27%)
Culture negative	30 (23%)	..	10 (33%)	40 (23%)	..	7 (18%)

Kett et al, Lancet ID, 2011

Lethal Bacterial HAP/VAP

- *Pseudomonas aeruginosa*
- **Methicillin-resistant *S. aureus***
- ***Acinetobacter* sp.**
- **MDR Enterbacteriaceae**
  - **ESBL**
  - **KPC**
- ***Stenotrophomonas maltophilia***

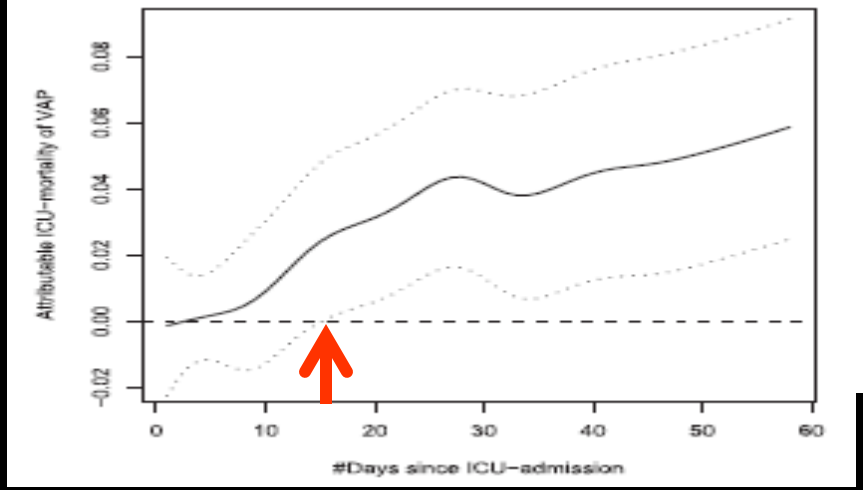
Attributable Mortality of Ventilator-Associated Pneumonia

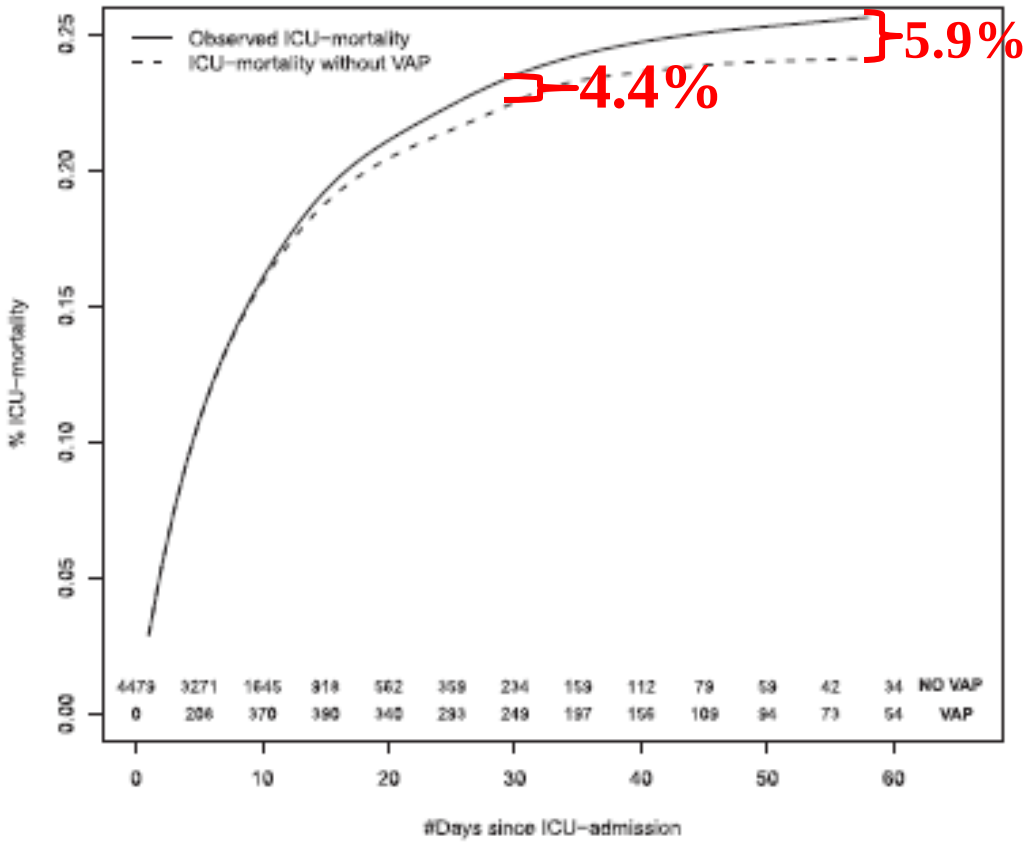
A Reappraisal Using Causal Analysis

Maarten Bekaert[1], Jean-Francois Timsit[2,3], Stijn Vansteelandt[1,4], Pieter Depuydt[5,6], Aurélien Vésin[3], Maité Garrouste-Orgeas[7], Johan Decruyenaere[5], Christophe Clec'h[8], Elie Azoulay[9], and Dominique Benoit[5] on behalf of the Outcomerea Study Group*

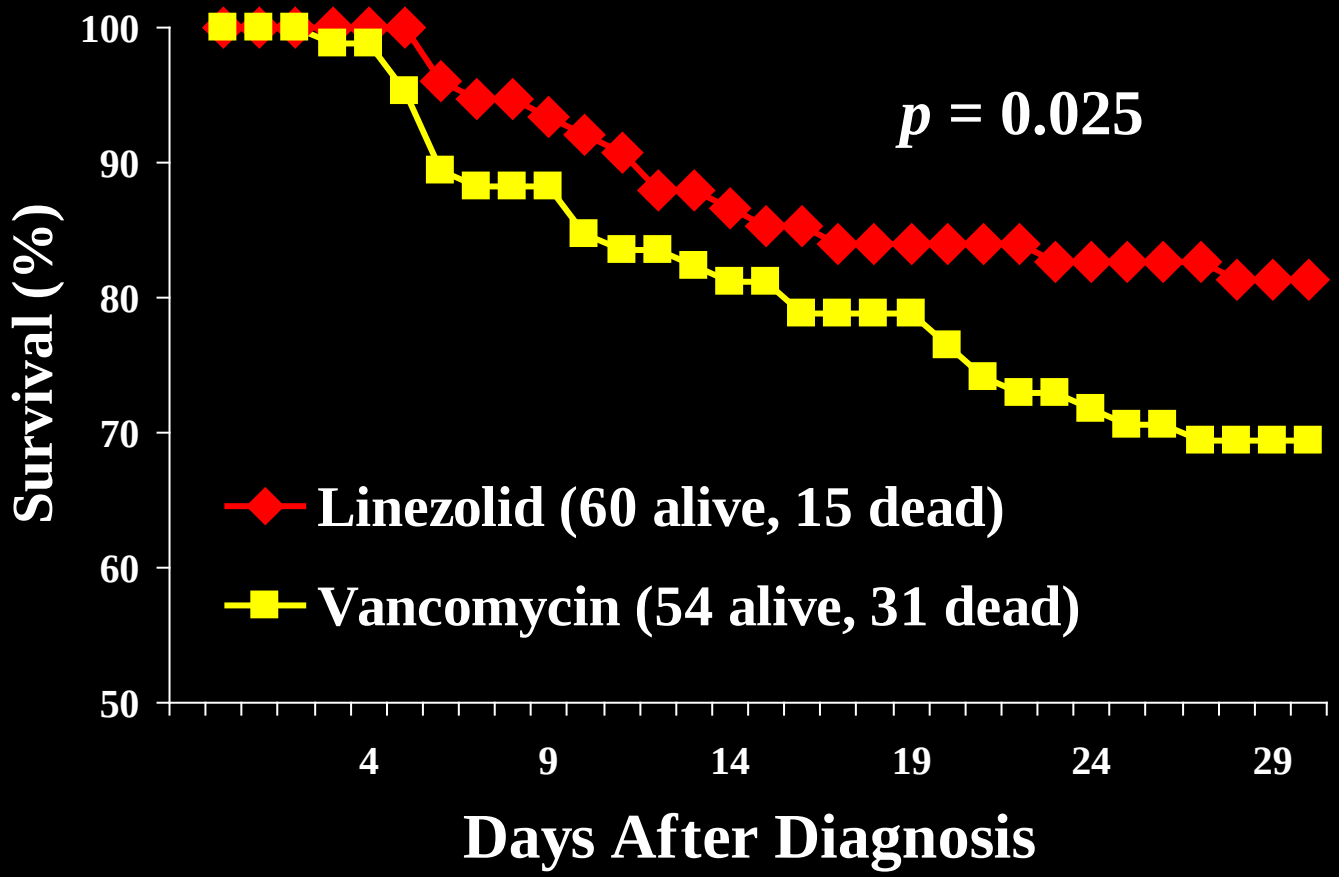
TABLE 3. HAZARD RATIOS OF INTENSIVE CARE UNIT DEATH PER ADDITIONAL DAY SINCE INFECTION CALCULATED FOR PATIENTS WITH DIFFERENT SAPS II SCORES ON ADMISSION (DIFFERENT PERCENTILES)

SAPS II on Admission	Hazard Ratio of ICU Death per Additional Day Since Infection (95% CI)	*P* Value
15 (5%)	1.023 (0.980–1.068)	0.31
28 (25%)	1.037 (1.018–1.056)	<0.001
40 (50%)	1.038 (1.025–1.052)	<0.001
53 (75%)	1.027 (1.013–1.041)	<0.001
73 (95%)	0.990 (0.960–1.010)	0.28
Overall	1.023 (1.011–1.034)	<0.001



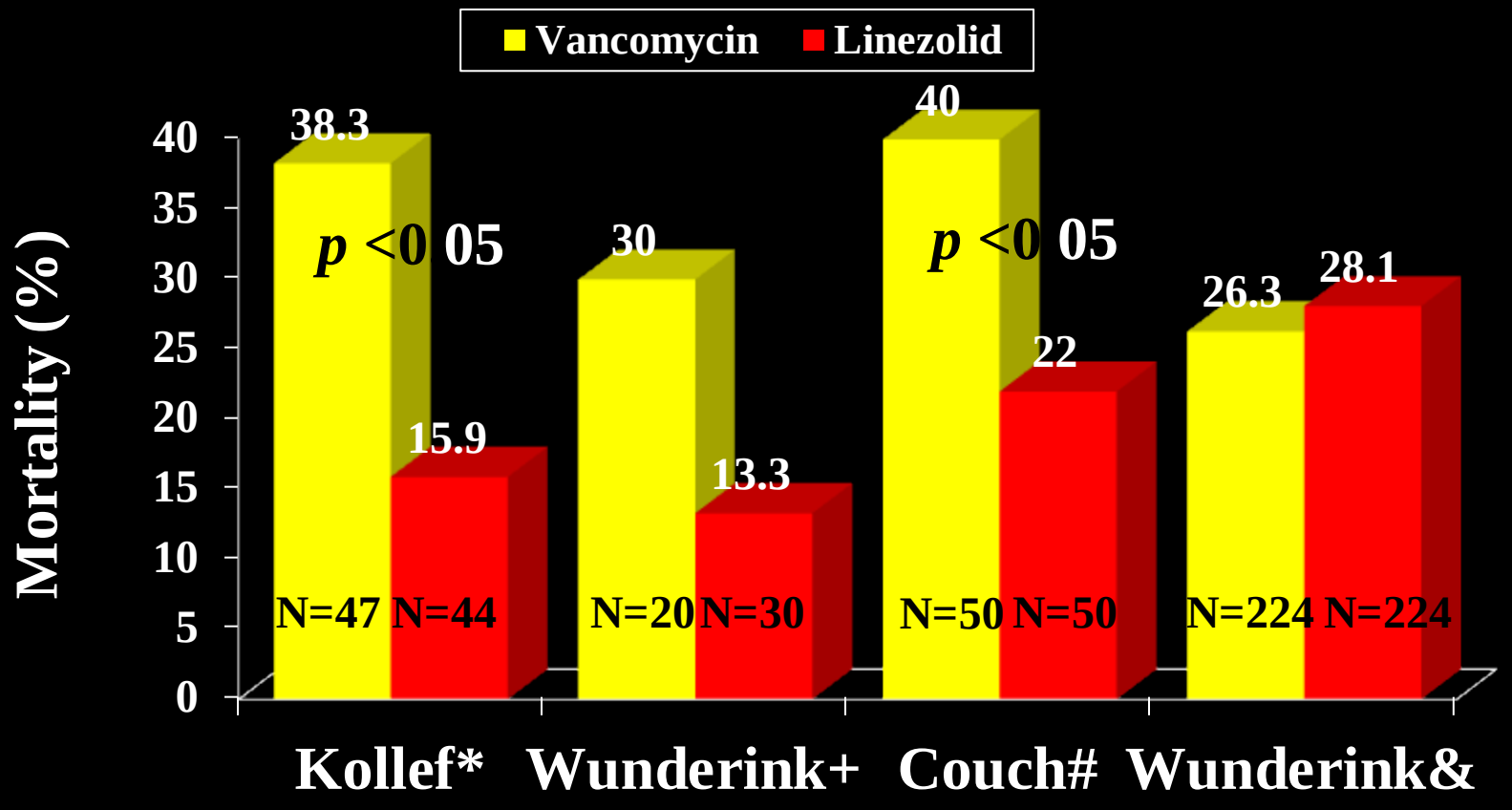


Hospital-acquired MRSA Pneumonia



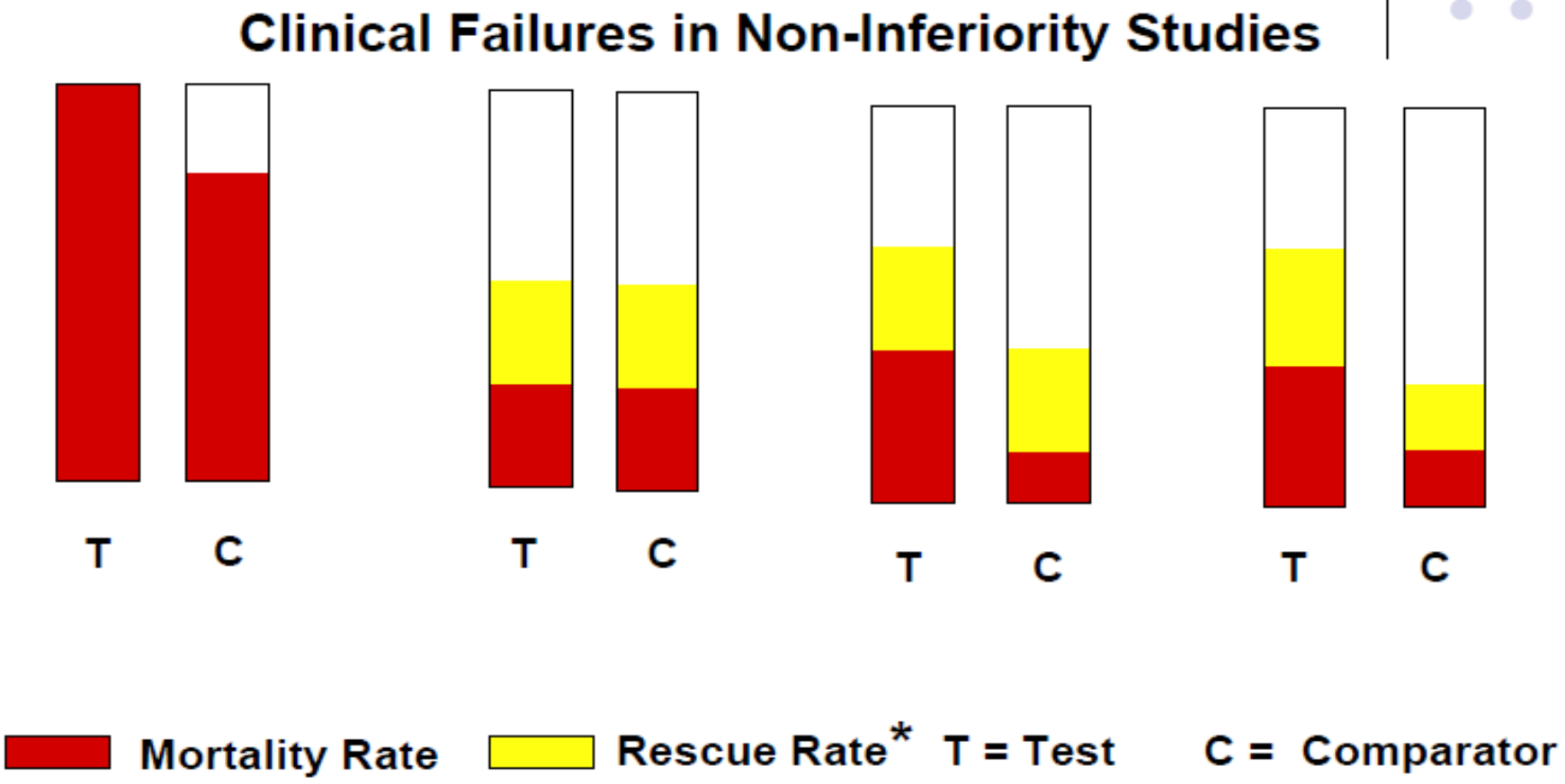
Wunderink, Chest, 2003

Mortality of MRSA HAP/VAP



*Intens Care Med 2004, + Chest 2008,
abstract, IDSA, 2007, & Clin Infect Dis, 2012

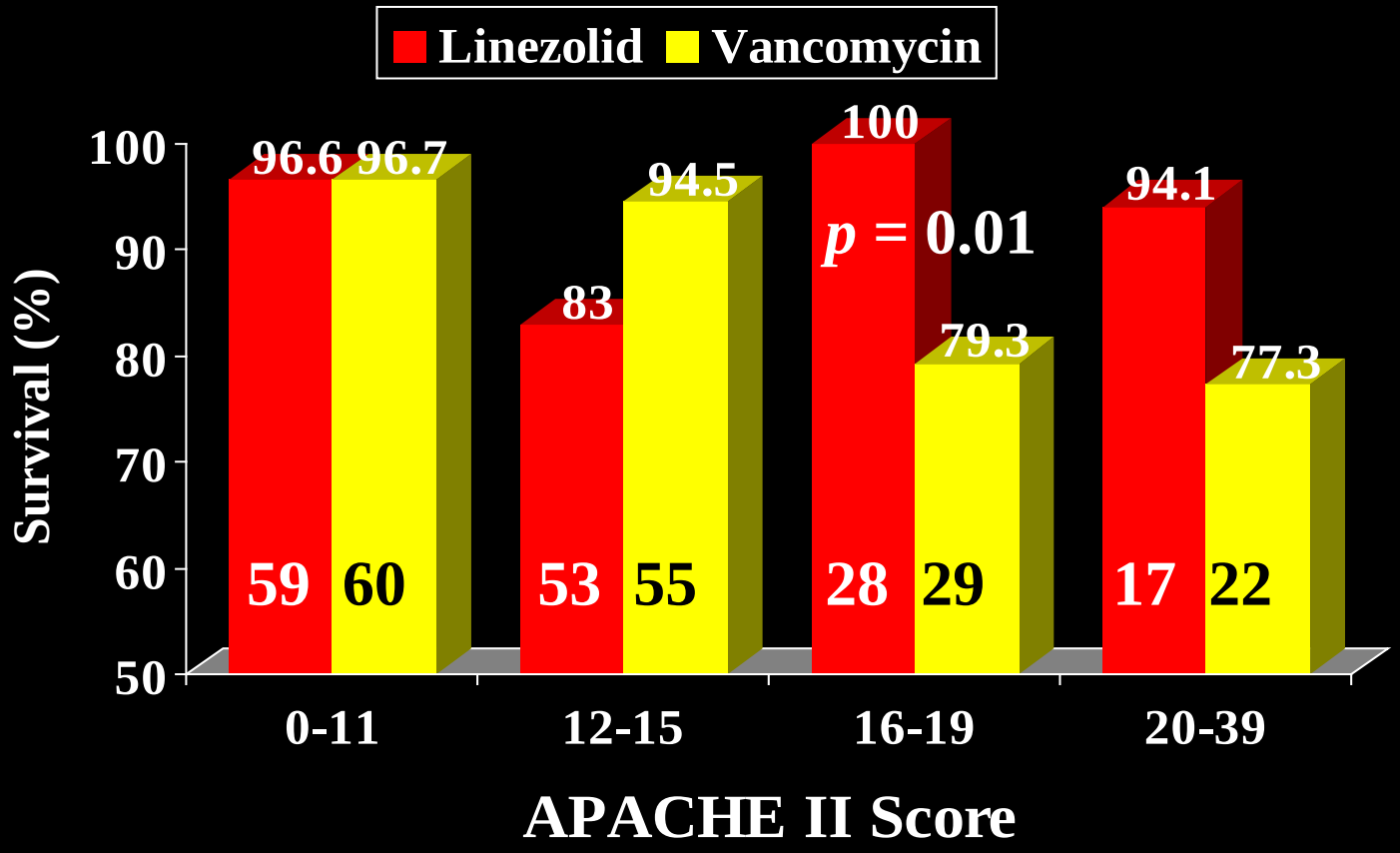
Clinical Failures (~15%) and Mortality Rates Differential Effects



Laessig, FDA, 2009

Effect of Linezolid by Baseline APACHE II Score

ITT Population



Wunderink, Clin Therap, 2003

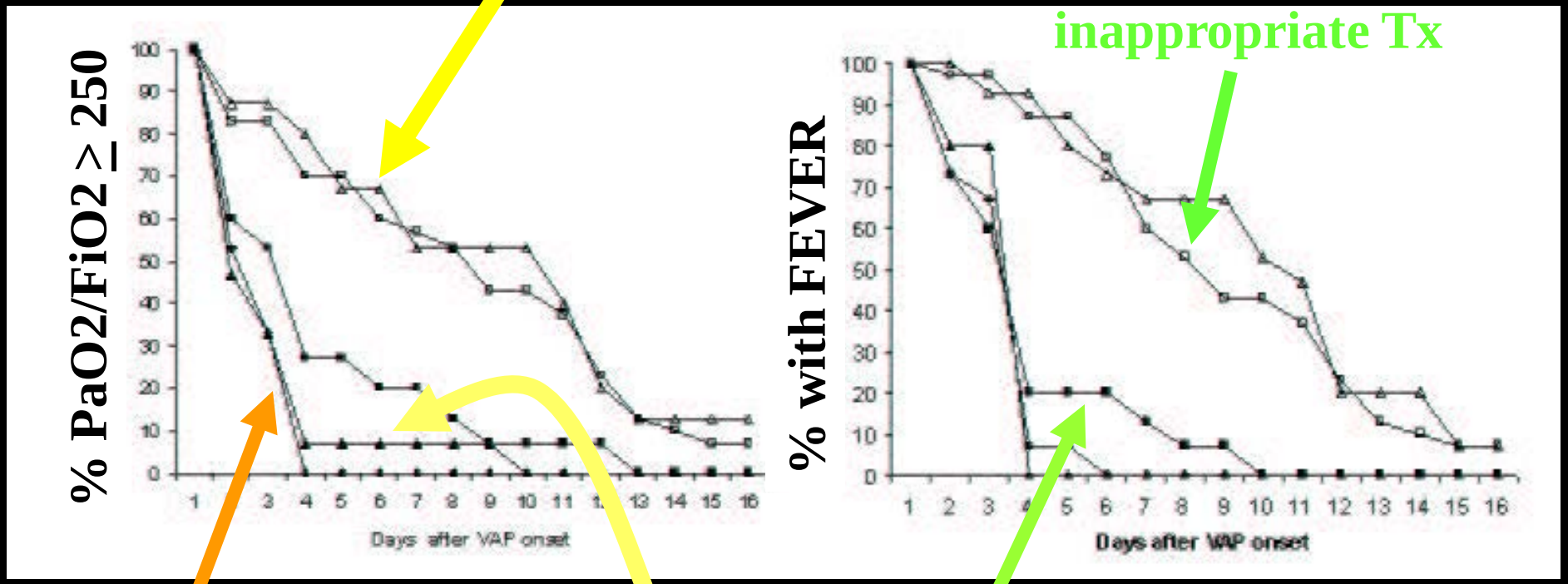
Mortality as an endpoint for HAP/VAP Studies

- Probably is an attributable mortality
  - Significantly less in sophisticated, high-tech North American/Western European systems
  - Requires focus on recruiting populations at risk

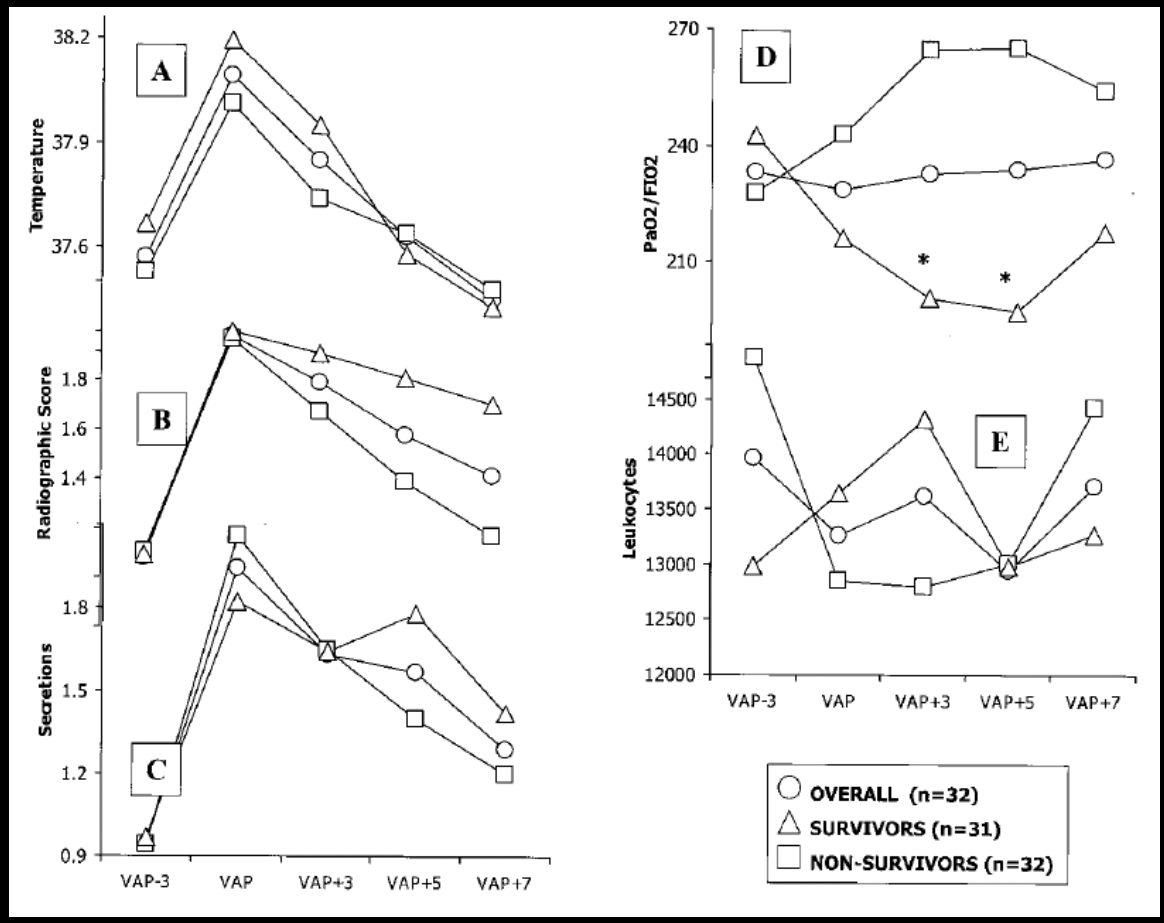
Clinical and Biomarker Endpoints

Effect of Microorganism and Initially Appropriate Antibiotics on VAP Resolution

Vidaur, Chest, 2008

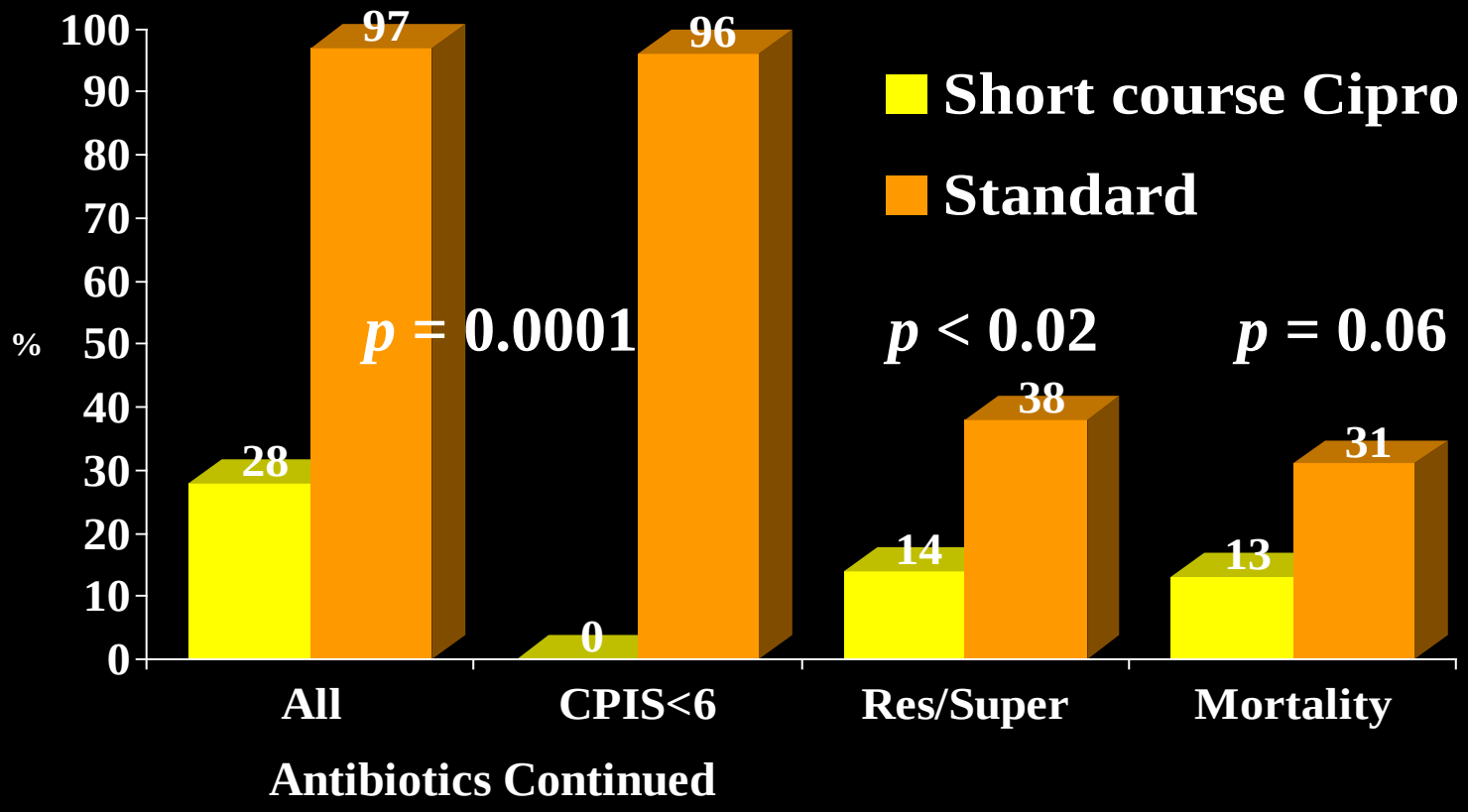


CPIS Score in Response to VAP Treatment



Luna, Crit Care Med, 2003

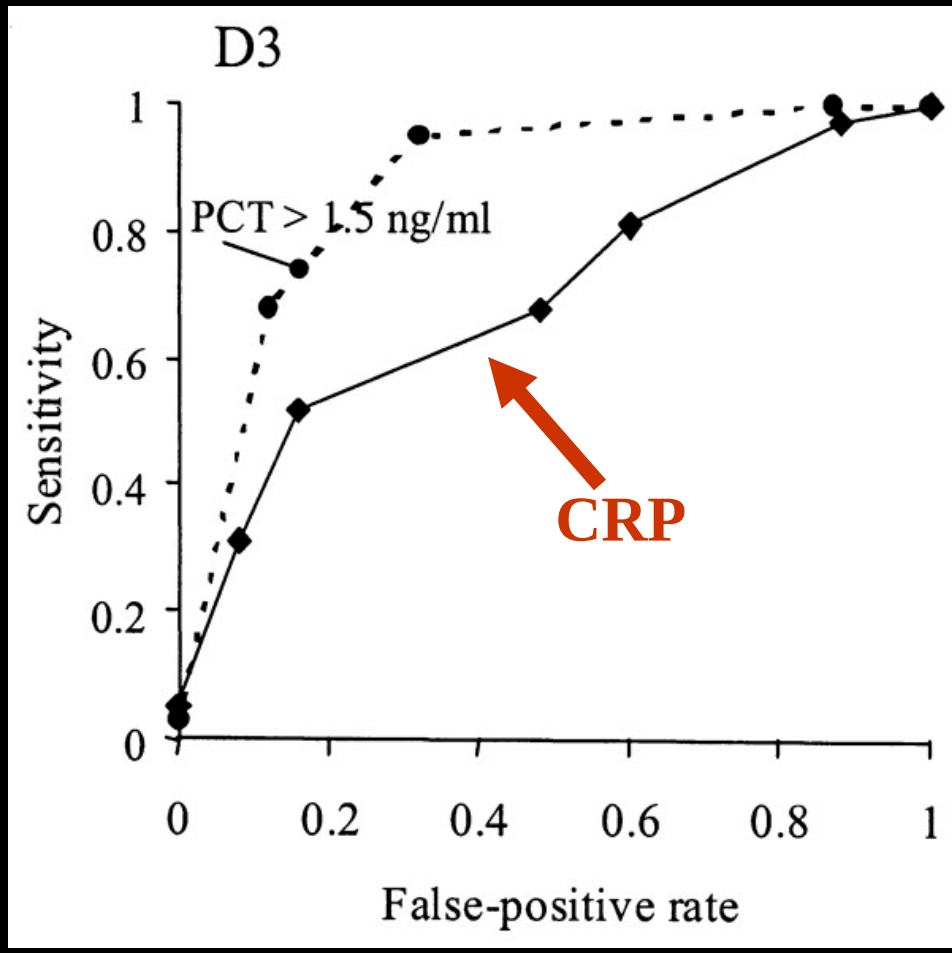
Short Course Empiric Strategy

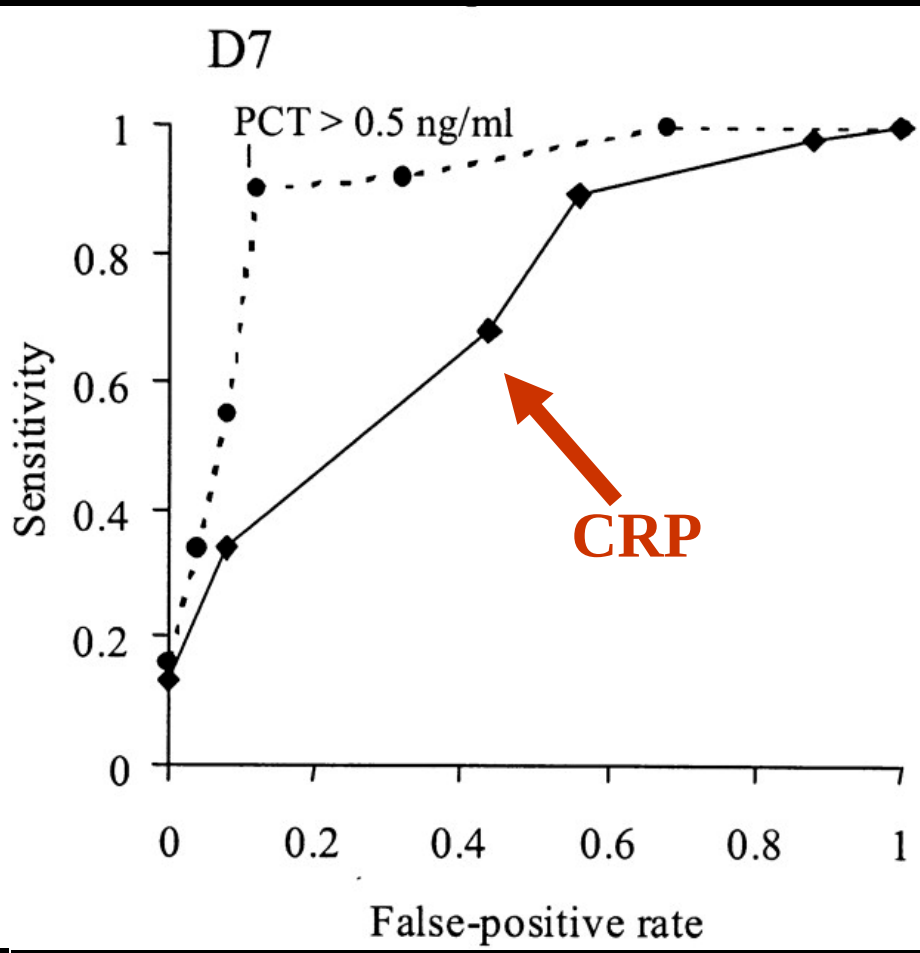


Singh, Am J Respir Crit Care Med, 2000

Procalcitonin Response in VAP

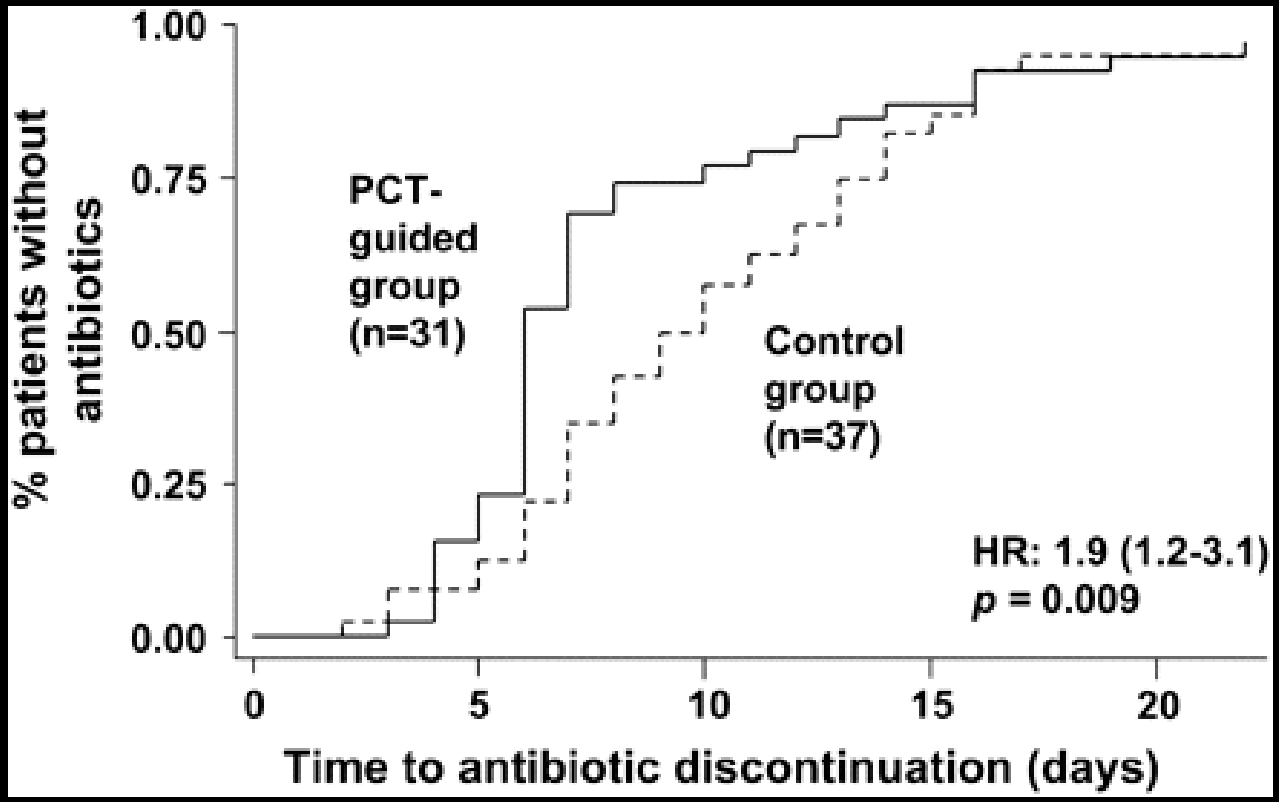
Luyt, AJRCCM, 2005





Procalcitonin to Guide Duration of Antibiotic Therapy in Sepsis

Nobre, AJRCCM, 2008

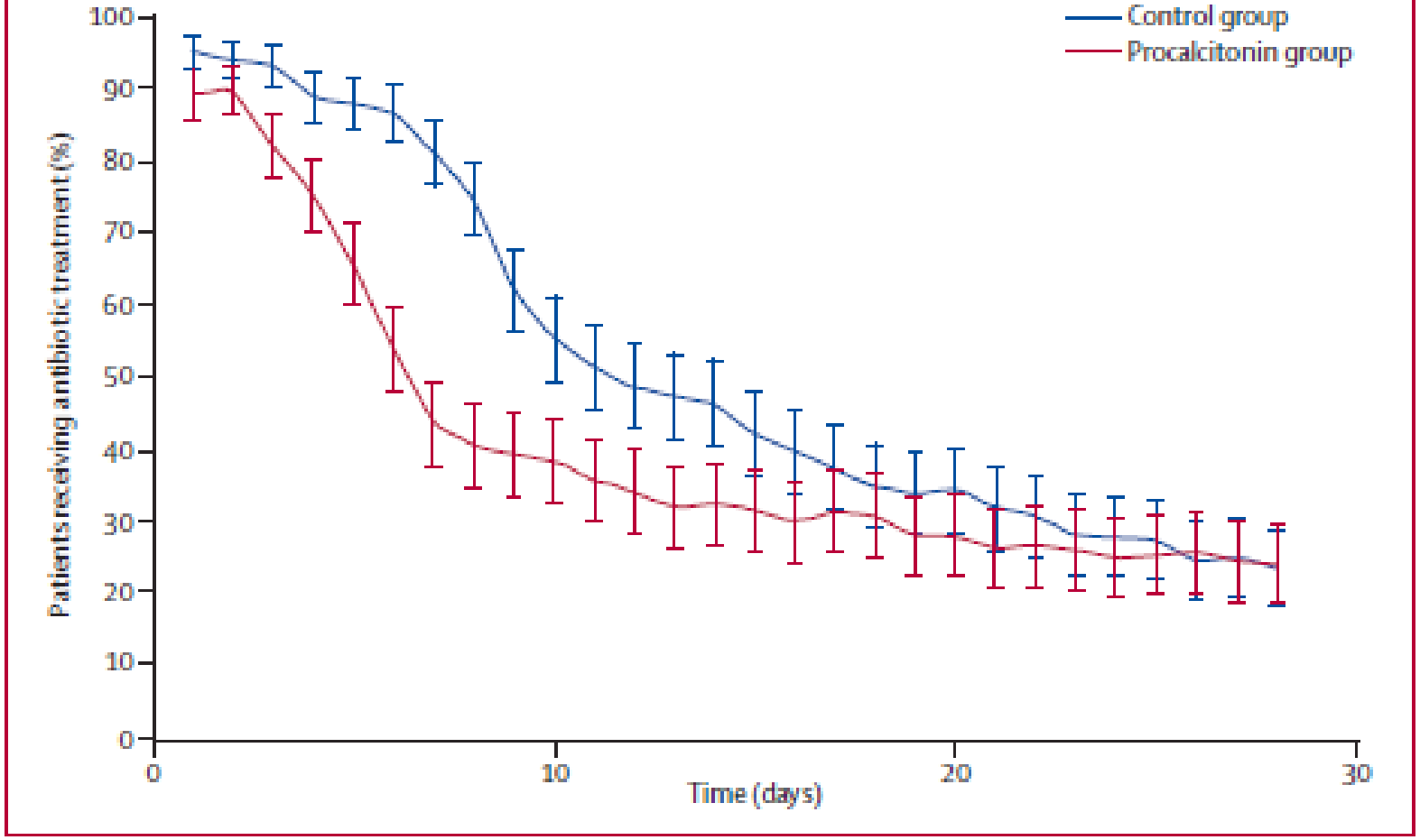


Majority were pulmonary infections, both CAP and HAP

***Pseudomonas, Acinetobacter, Legionella* were *a priori* excluded because of perceived need for prolonged antibiotics**

PRORATA Study

Bouadama, Lancet, 2010



Biomarkers: Procalcitonin

- " a better WBC"
- Value in clinical trials
  - More objectively define success
  - Trigger for further evaluations
- At some point, reverts to marker of uncontrolled inflammatory state

Why do patients with HAP/VAP Die?

Why do patients with HAP/VAP Die?

- Septic shock
  - More of an issue with CAP
  - Marker for inadequate antibiotics
- Respiratory failure
- Multiple organ dysfunction
- Recurrent Infections

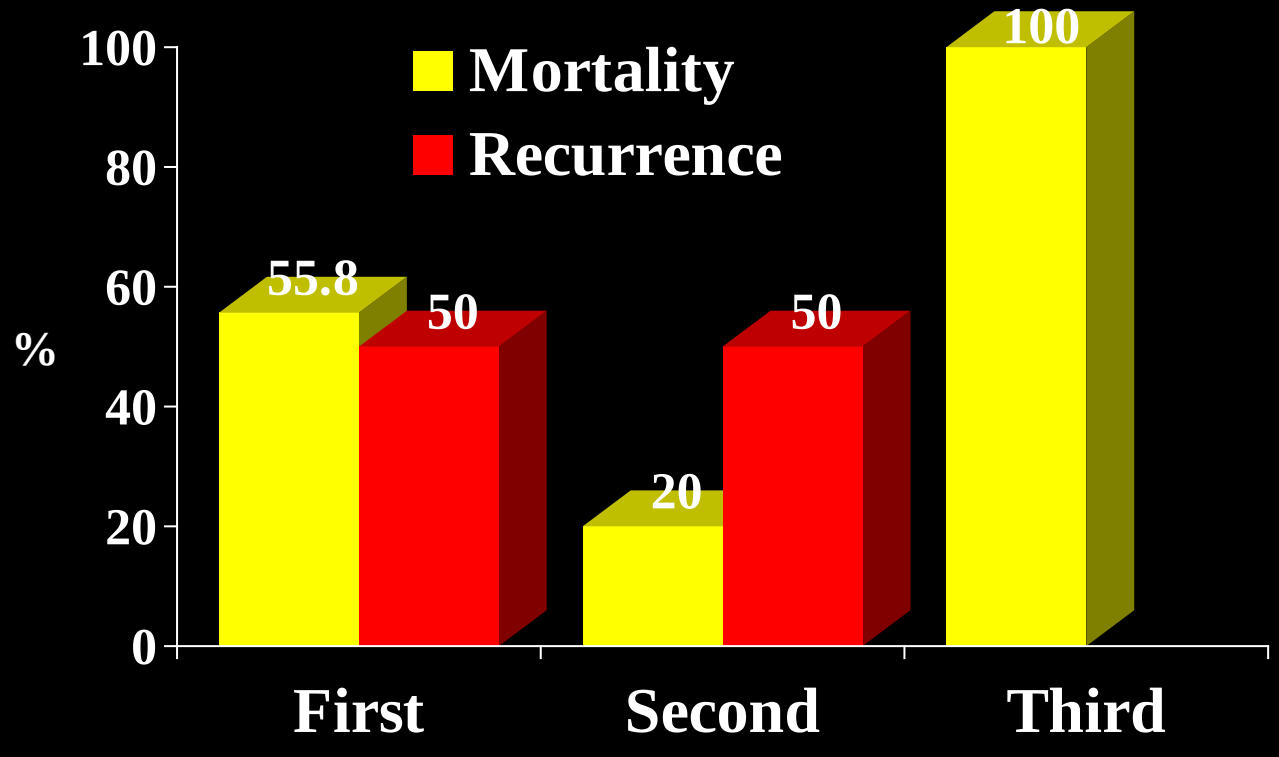
Withdrawal of Care

Mortality as an endpoint for HAP/VAP Studies

- Probably is an attributable mortality
  - Significantly less in sophisticated, high-tech North American/Western European systems
  - Requires focus on recruiting populations at risk
- Unsophisticated understand of the role of antibiotic treatment in mortality
  - "Treatment as prevention"


Juan Gris - The Complete Works

Recurrent *Pseudomonas* VAP



Silver, Chest, 1992

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

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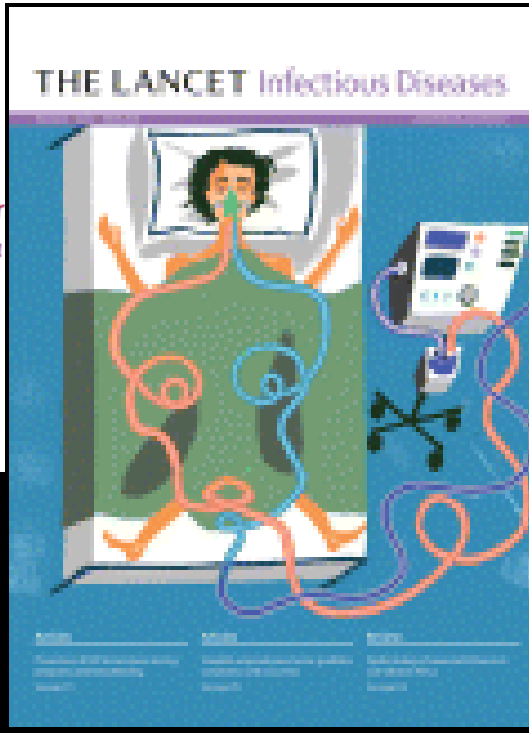

Lancet ID, 2011

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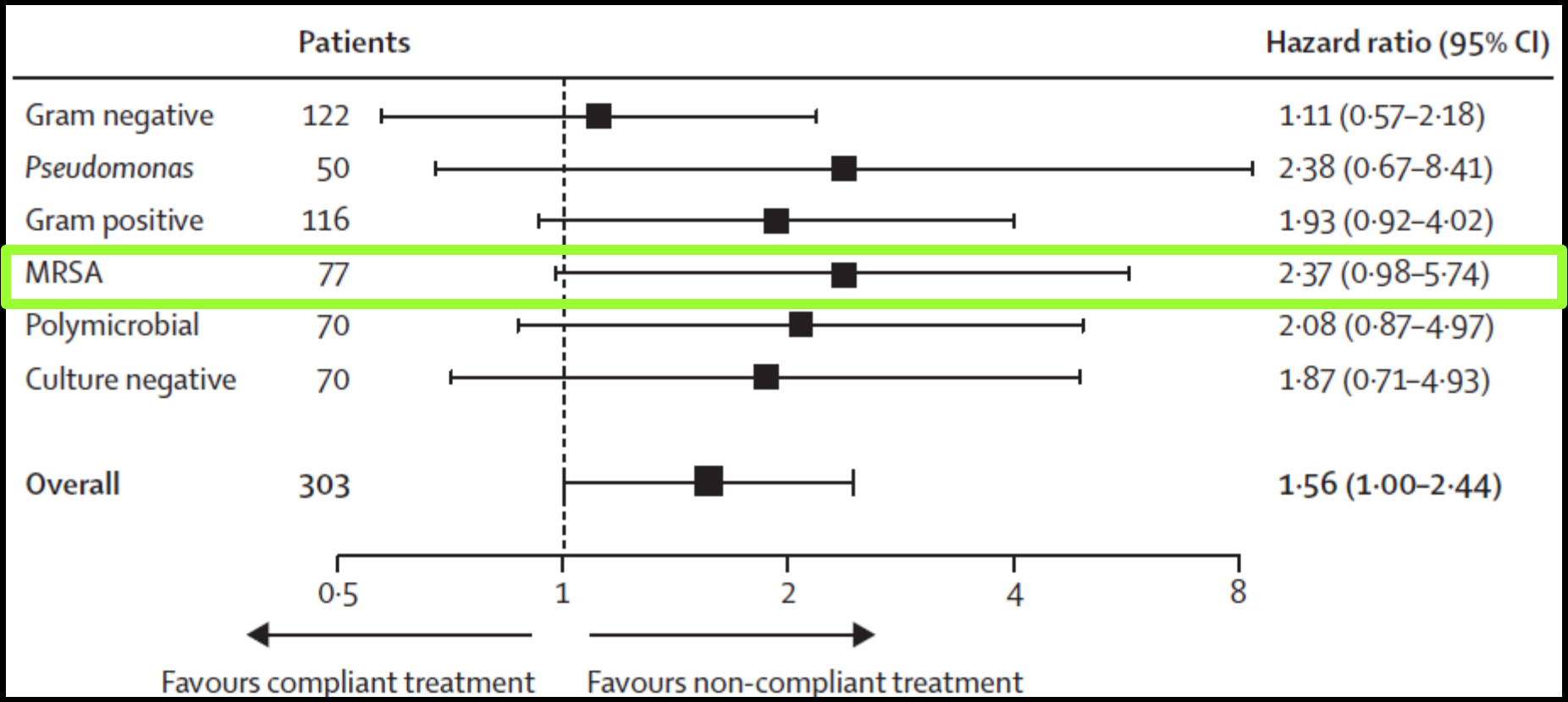
ATS/IDSA Guideline-based Therapy



Kett et al, Lancet ID, 2011

Inadequacies of Study

- Lacks face validity
  - empirical coverage for MRSA is associated 2.4 OR excess mortality in culture-positive MRSA patients?
- Inadequacy of propensity score adjustment
  - Higher shock, higher # Pseudomonas in "compliant"
- Non-compliance with de-escalation
  - 52% of vanco/LZD in MRSA negative
  - <50% of second GN agent in Pseudo/Acineto negative
  - ? Culture negative (OR 1.8 for "compliant')
  - More nephrotoxicity in "compliant" group

If compliant with de-escalation (not analyzed), study may actually validate ATS/IDSA guidelines

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Comparison of Two Fluid-Management Strategies in Acute Lung Injury

The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network*

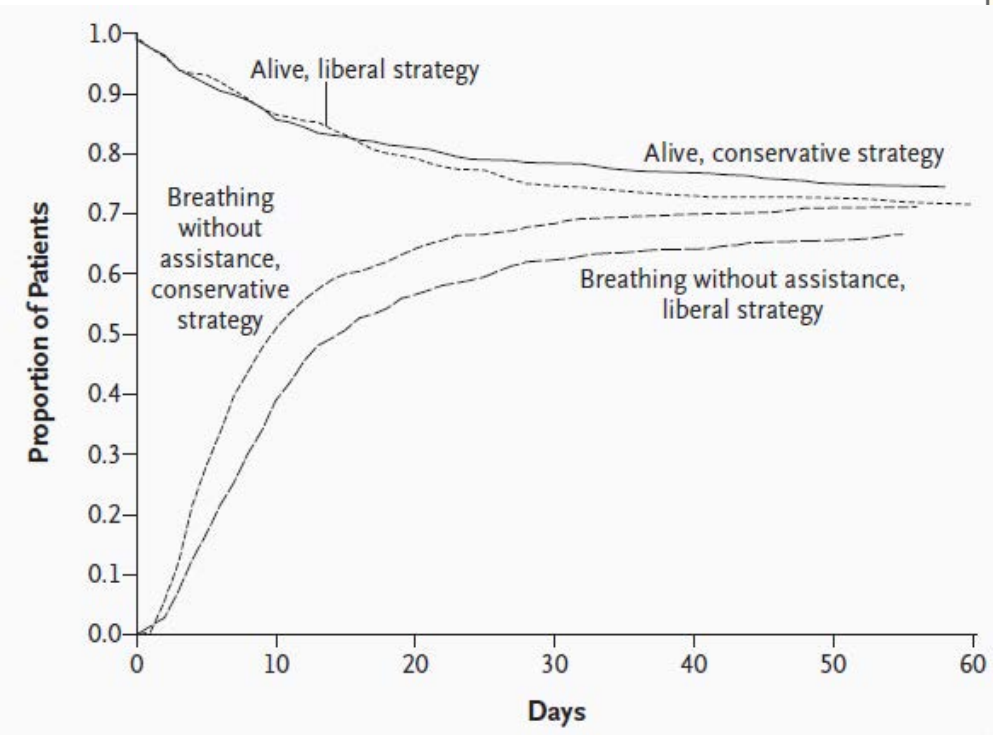


Table 3. Main Outcome Variables.*

Outcome	Conservative Strategy	Liberal Strategy	P Value
Death at 60 days (%)	25.5	28.4	0.30
Ventilator-free days from day 1 to day 28†	14.6±0.5	12.1±0.5	<0.001
ICU-free days†			
Days 1 to 7	0.9±0.1	0.6±0.1	<0.001
Days 1 to 28	13.4±0.4	11.2±0.4	<0.001
Organ-failure–free days†‡			
Days 1 to 7			
Cardiovascular failure	3.9±0.1	4.2±0.1	0.04
CNS failure	3.4±0.2	2.9±0.2	0.02
Renal failure	5.5±0.1	5.6±0.1	0.45
Hepatic failure	5.7±0.1	5.5±0.1	0.12
Coagulation abnormalities	5.6±0.1	5.4±0.1	0.23
Days 1 to 28			
Cardiovascular failure	19.0±0.5	19.1±0.4	0.85
CNS failure	18.8±0.5	17.2±0.5	0.03
Renal failure	21.5±0.5	21.2±0.5	0.59
Hepatic failure	22.0±0.4	21.2±0.5	0.18
Coagulation abnormalities	22.0±0.4	21.5±0.4	0.37
Dialysis to day 60			
Patients (%)	10	14	0.06
Days	11.0±1.7	10.9±1.4	0.96

Conclusions

- Mortality is an appropriate endpoint but a blunt instrument to measure outcome in HAP/VAP trials
- Clinical scores and biomarkers objectify clinical outcomes but regress to the mean
- More sophisticated endpoints paralleling ARDS/ALI may need to be developed
  - "Days alive and infection/organ failure free"