

MRSA VAP – Is vancomycin obsolete?

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Conflict of Interest

❖ Pfizer

❖ Astellas

❖ Bayer

❖ Intercell AG

❖ Kalobios

❖ Johnson & Johnson

❖ American Thoracic
Society

❖ Novartis

❖ Arpida

❖ Wyeth

❖ Forrest

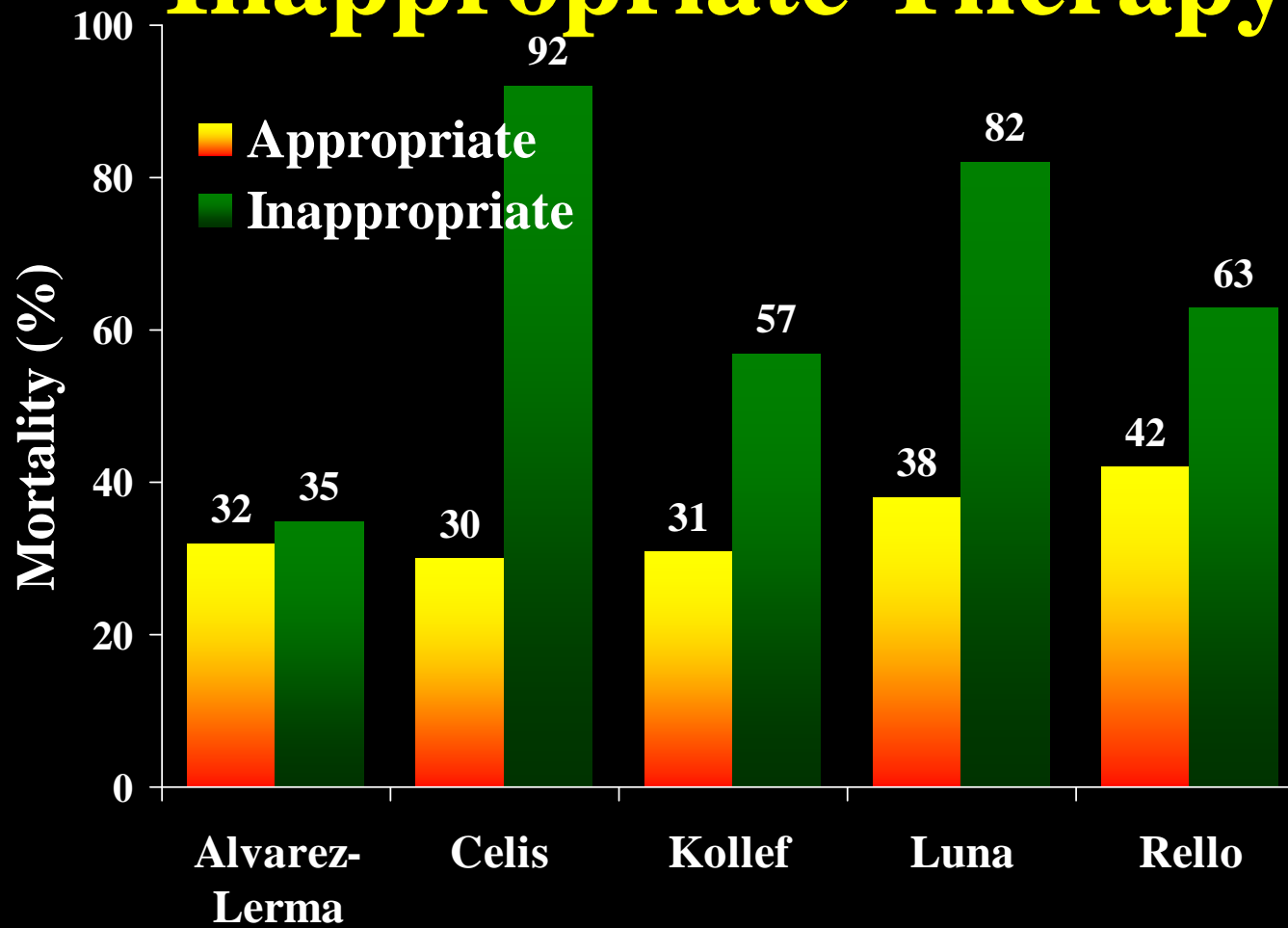
❖ Nektar

❖ Astra Zeneca

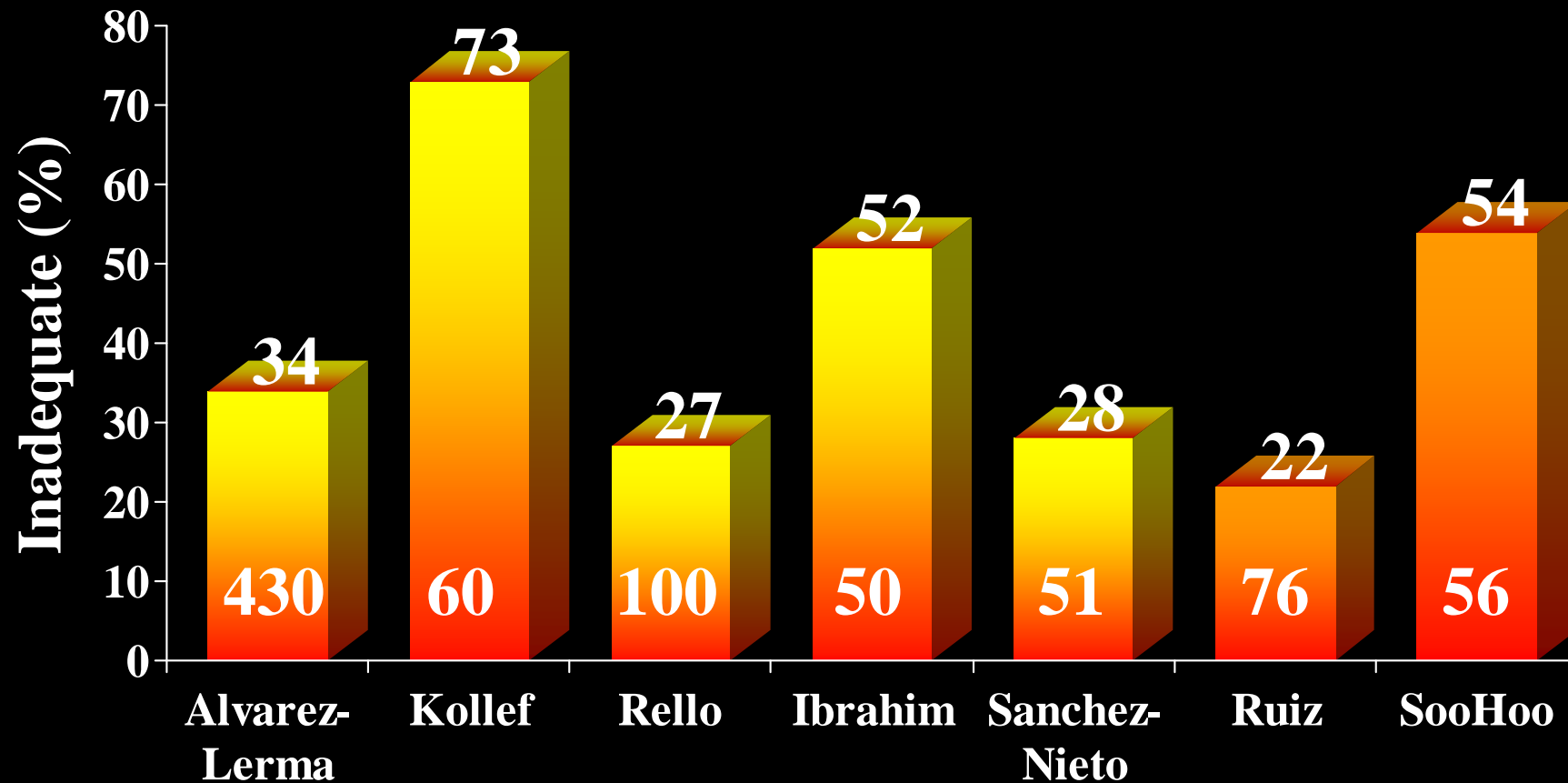
❖ Inverness Medical

❖ BioMerieux

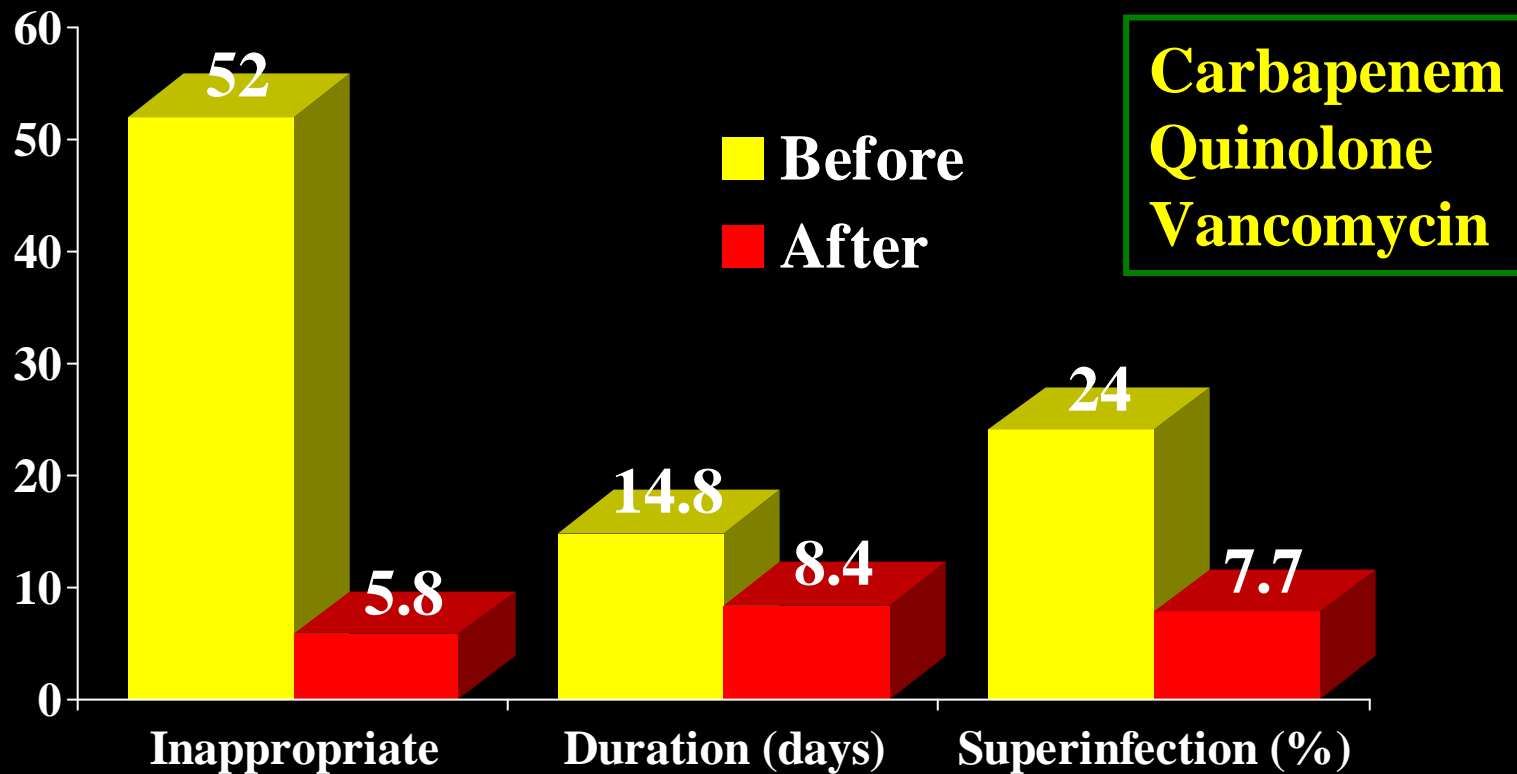
VAP Mortality and Inappropriate Therapy



Inappropriate Initial Antimicrobial Therapy

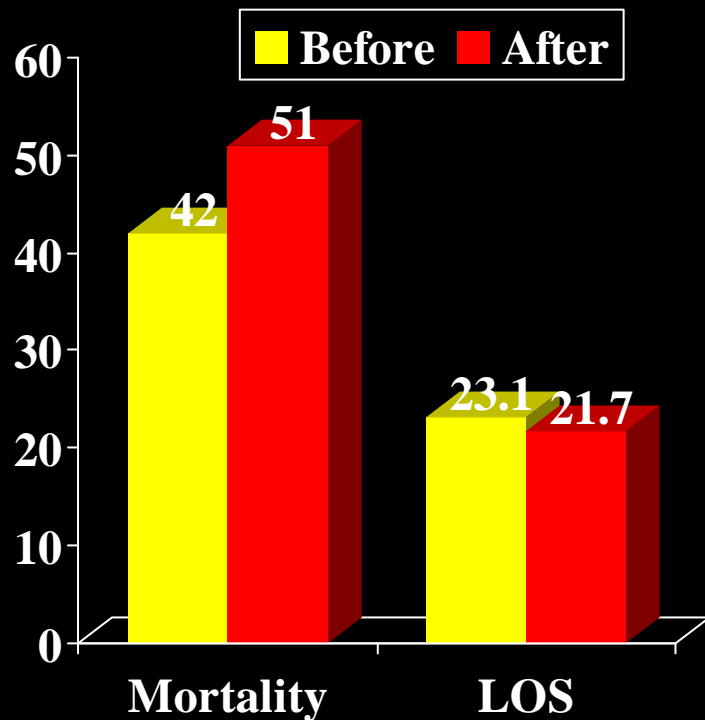


Inappropriate Antibiotics for VAP

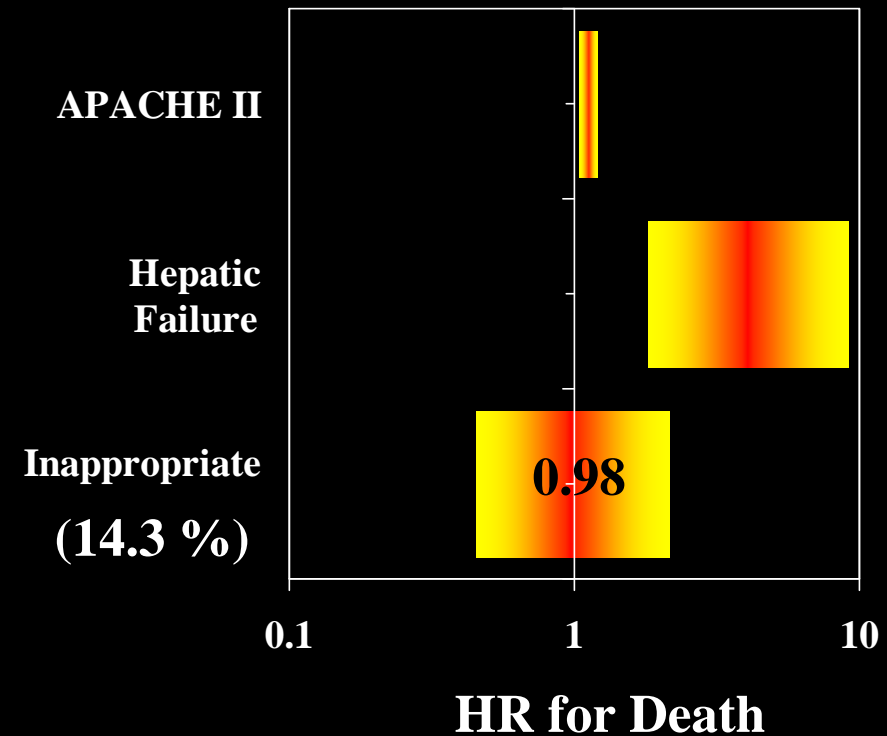


Ibrahim, Crit Care Med, 2001

Mortality with Low Inappropriate Initial Antibiotic Rates



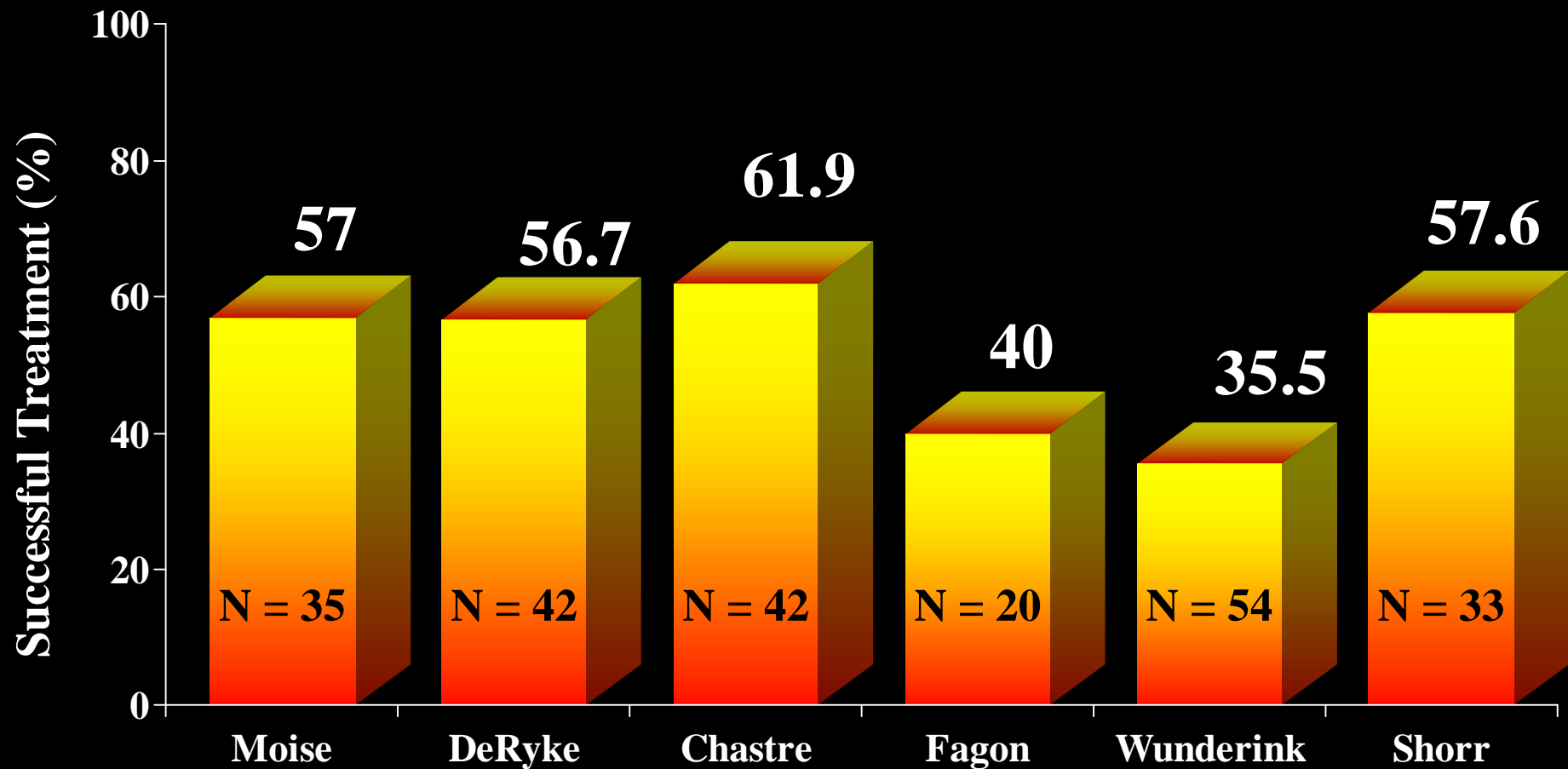
Ibrahim, Crit Care Med, 2001



Fowler, Chest, 2003

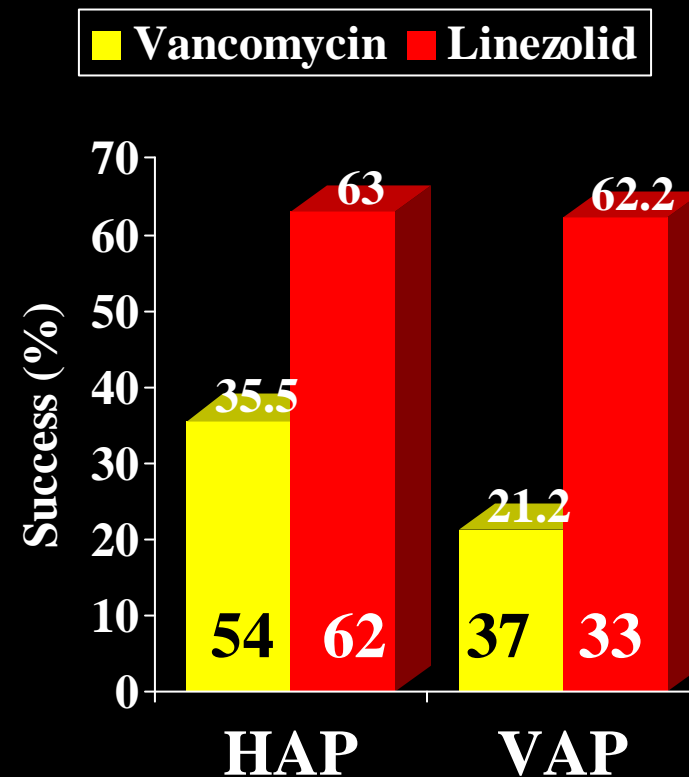
Appropriate empiric
antibiotic therapy is
necessary but may not be
sufficient to improve
mortality of VAP

MRSA Treatment with Vancomycin



MRSA Nosocomial Pneumonia: Clinical Response

- 116 patients from 2 Phase III trials
- Intention to Treat Failure Multivariate analysis
 - vancomycin (OR 3.59, $p = 0.0073$)
 - multi-lobe ventilator
 - renal comorbidity
 - oncologic comorbidity

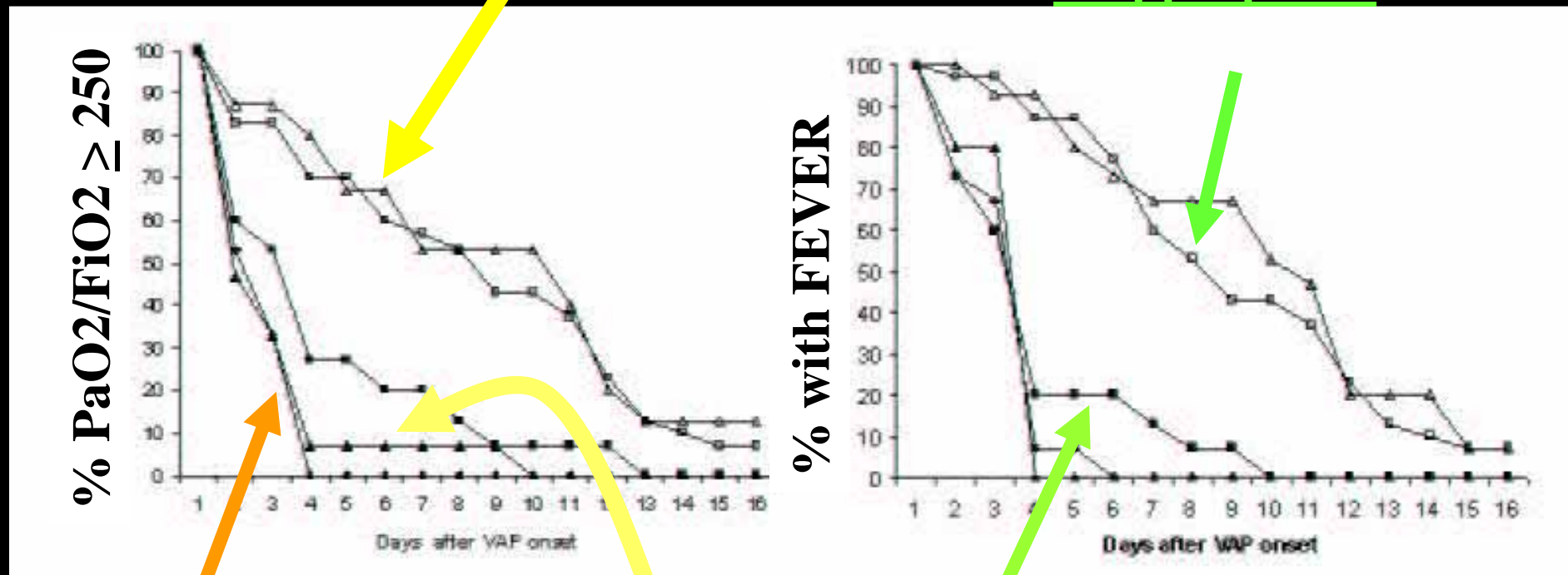


Wunderink. *Chest*. 2003.

Effect of Microorganism and Initially Appropriate Antibiotics on VAP Resolution

Vidaur, Chest, 2008

Pseudomonas with initially Inappropriate Tx



H. influenzae

MRSA

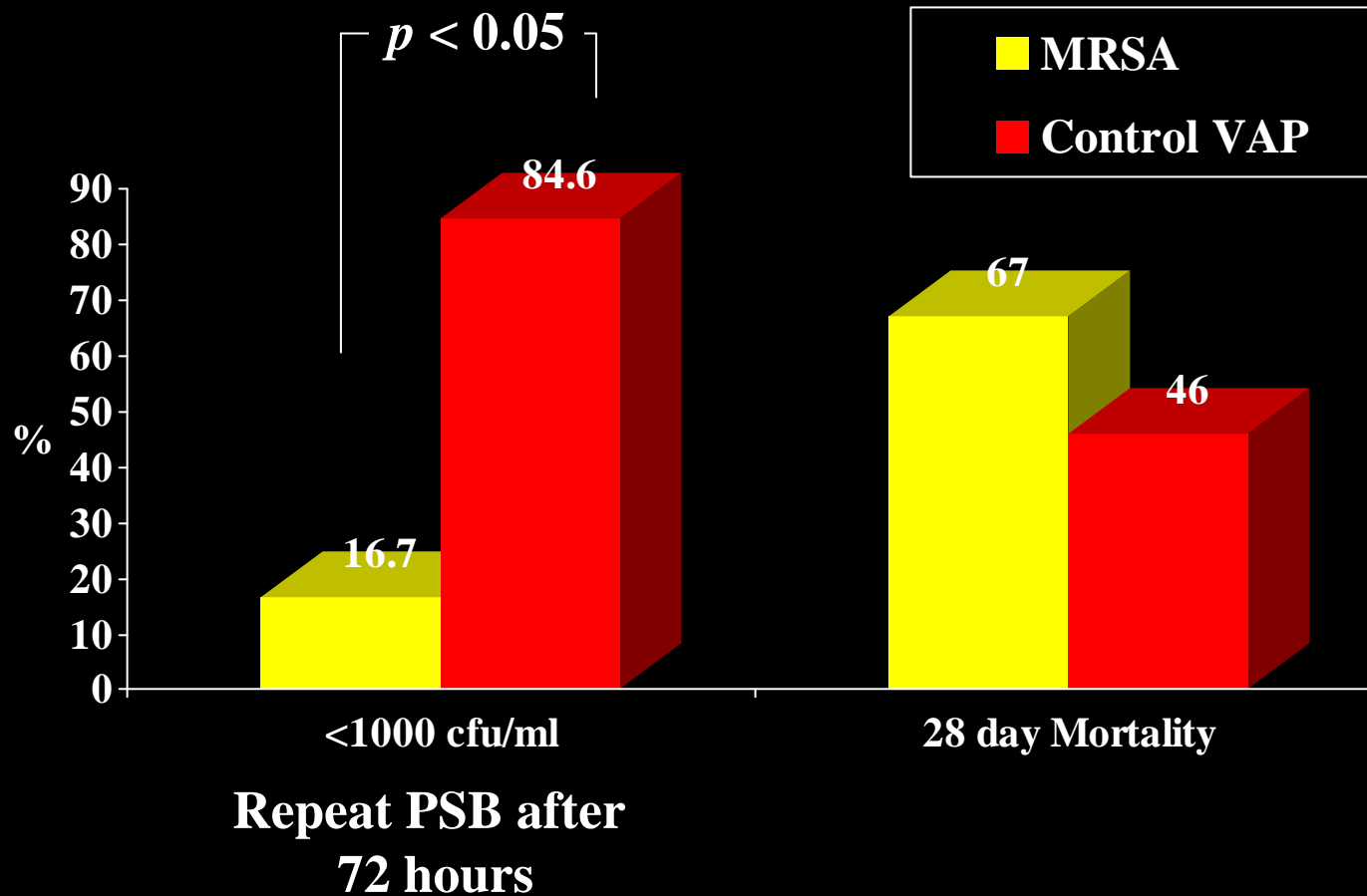
MSSA

Pseudomonas with Appropriate initial Tx

**If clinical response is
unreliable, can we follow
microbiologic response?**

MRSA VAP:

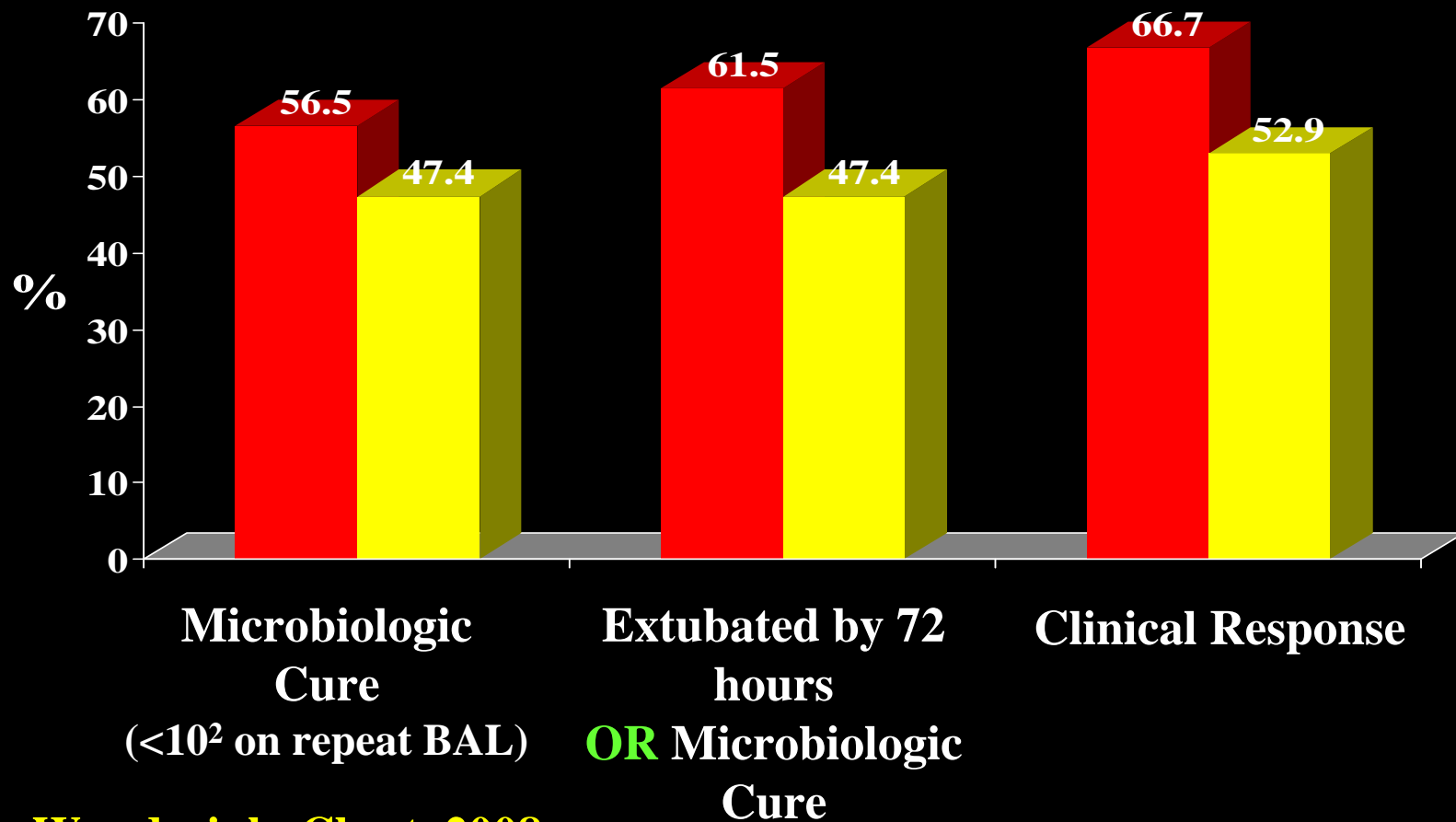
Microbiologic Response to Vancomycin



Baughman. *J Intensive Care Med.* 2003.

Microbiologic Response in Confirmed MRSA VAP

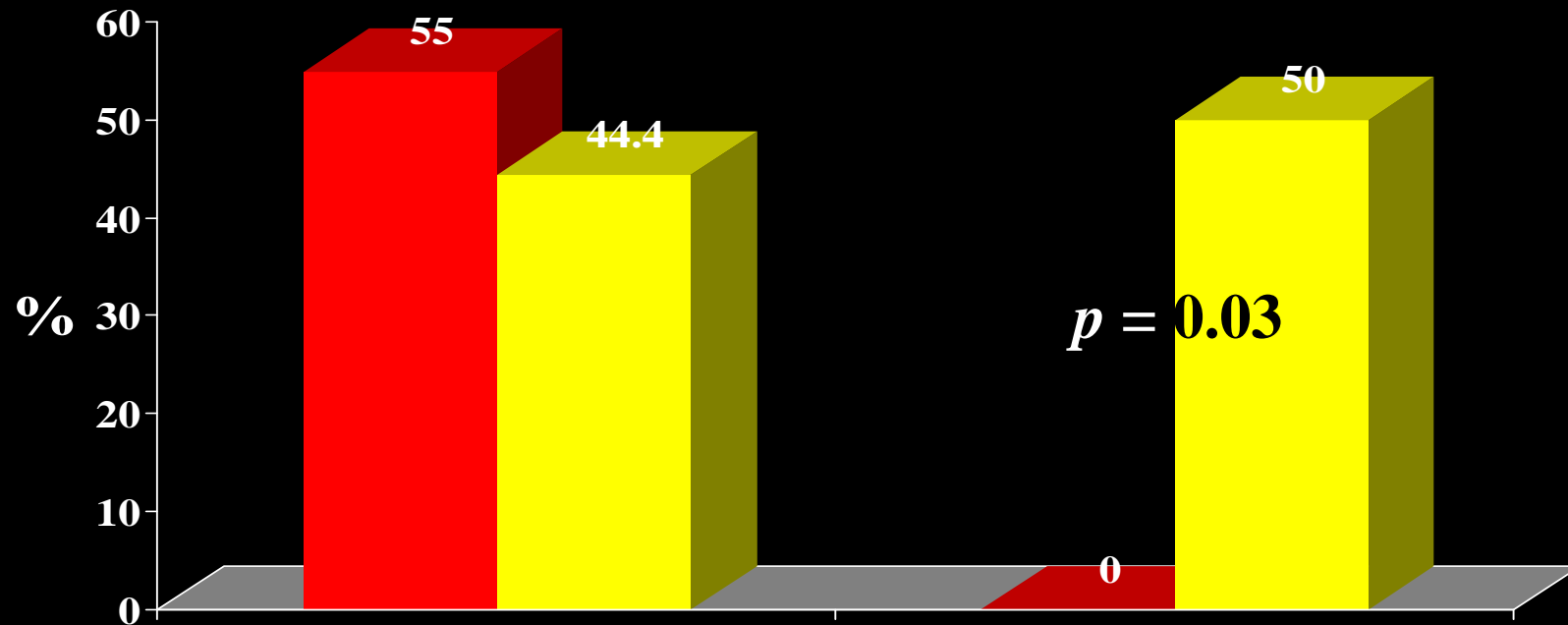
■ Linezolid ■ Vancomycin



Wunderink, Chest, 2008

Microbiologic Response in Confirmed MRSA VAP

■ Linezolid ■ Vancomycin



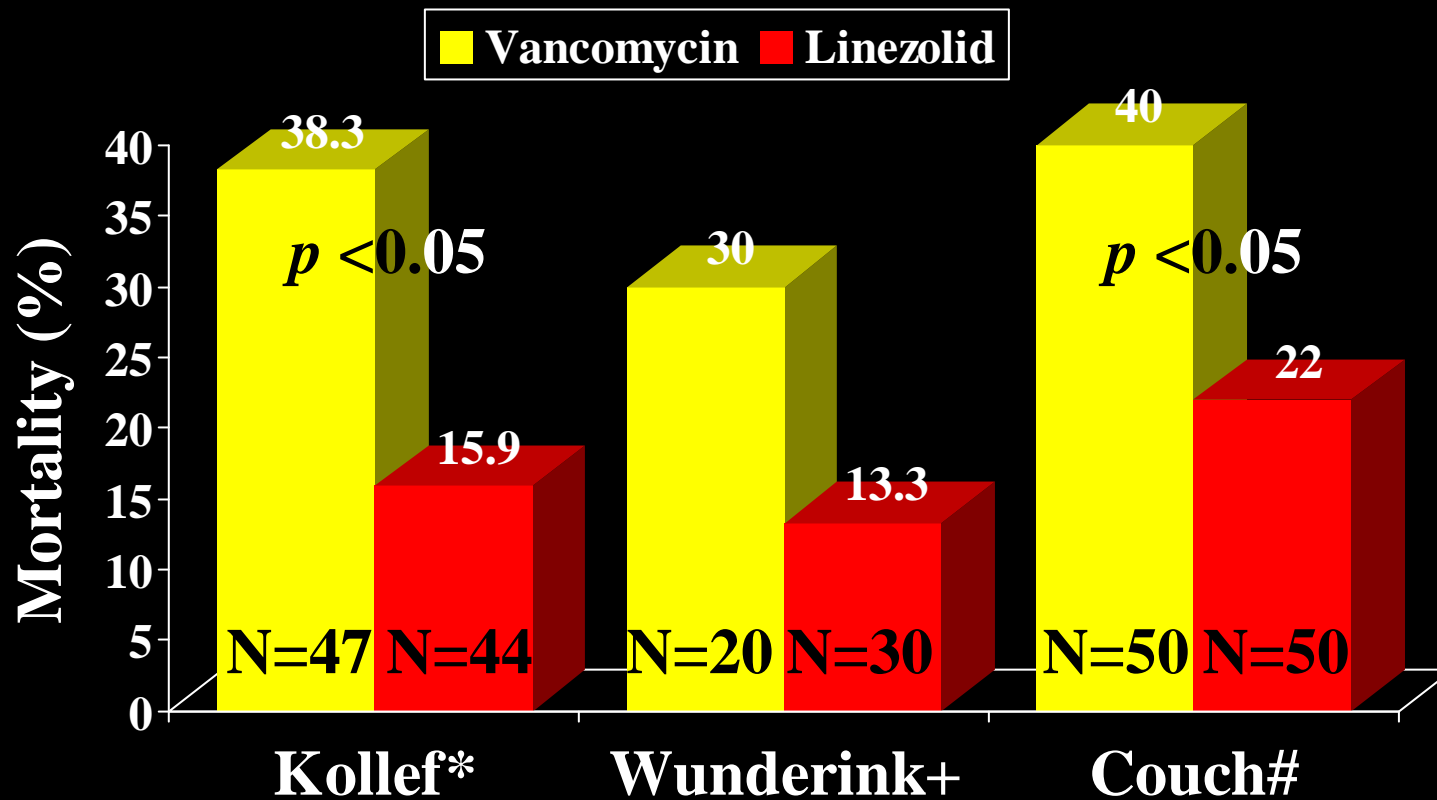
Microbiologic Cure
($<10^2$ on repeat BAL)

Mortality in
Microbiologic Failures

Wunderink, Chest, 2008

(N = 10 patients each)

Mortality of MRSA VAP



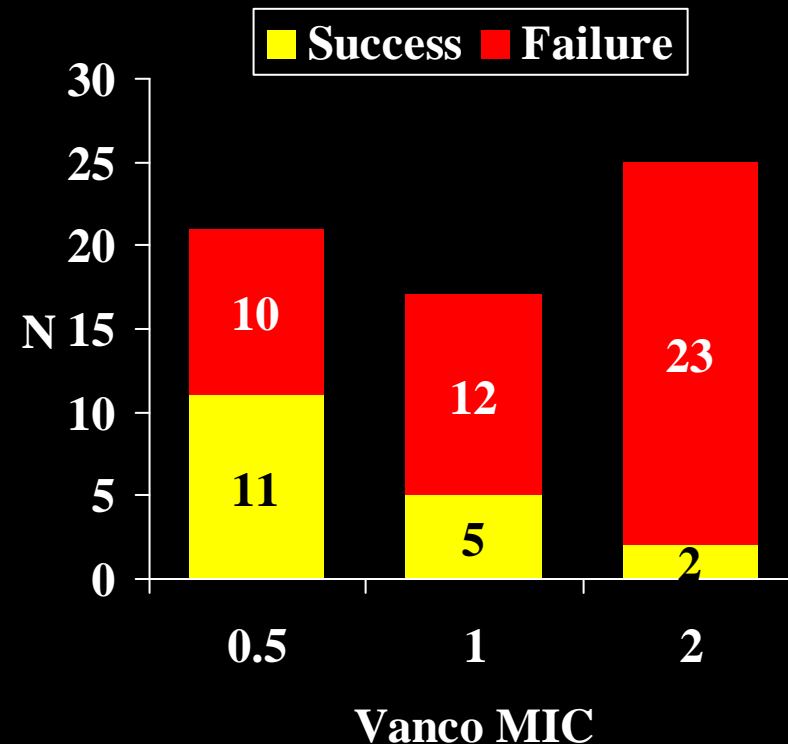
* Intensive Care Medicine, 2004

+ Chest, 2008 # abstract, IDSA, 2007

Why does vancomycin fail so frequently in VAP?

Vancomycin MIC and Clinical Cure of MRSA Infections

- ❖ Renal insufficiency also significant risk for clinical failure
- ❖ Success decreased approx 20% for every 10 ml/min decrease in CrCl



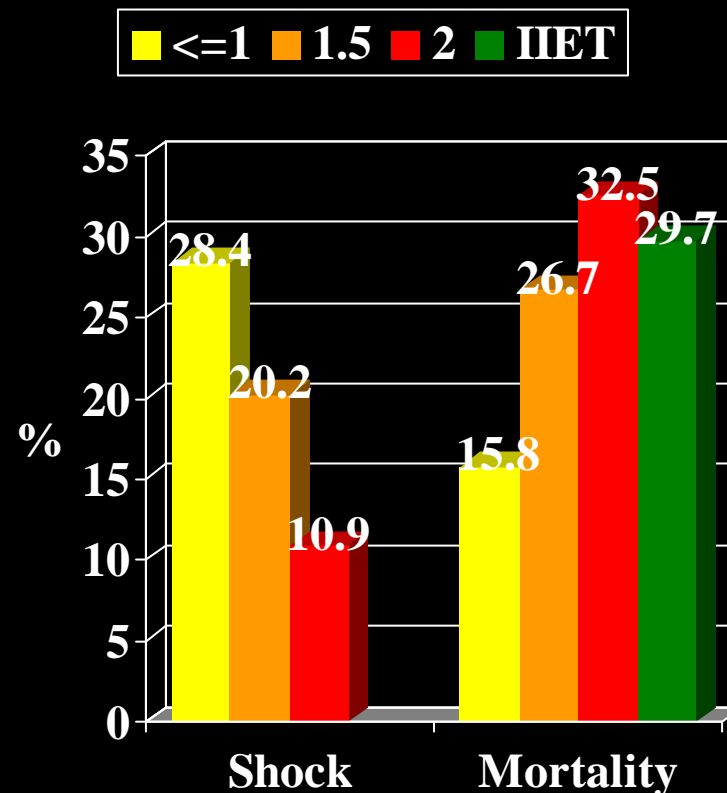
Moise-Broder. *CID*. 2004.

Vancomycin MICs and MRSA Bacteremia

- 414 cases bacteremia

Mortality

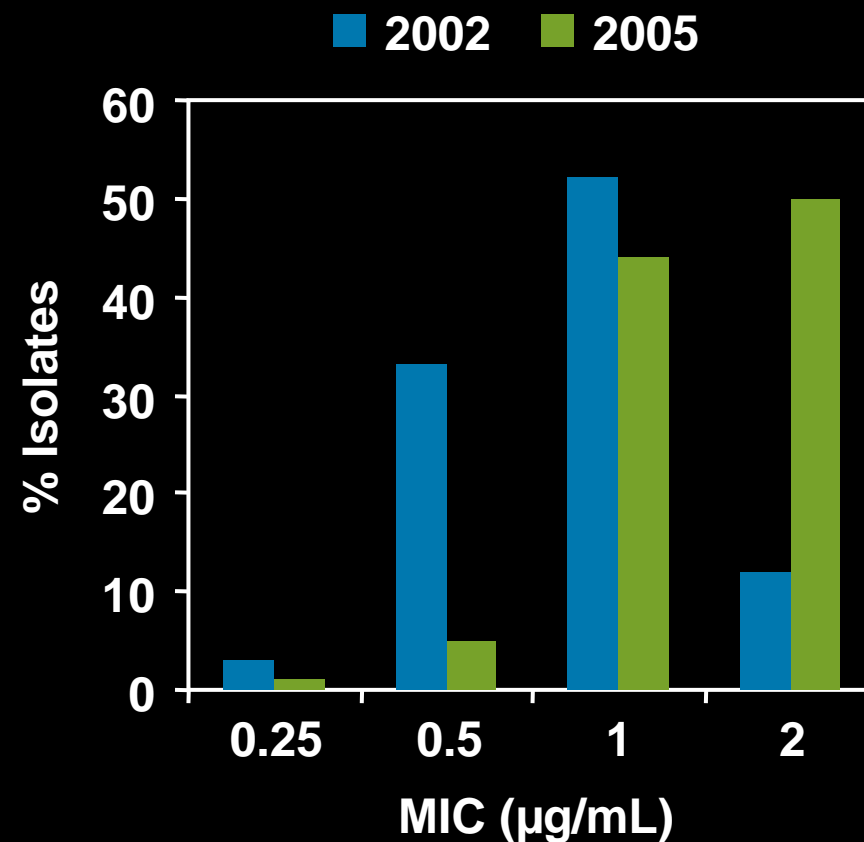
- Vanco Tx with MIC₂=6.39
- Inaprop Init Emp=3.62
- Shock=7.38
- High (incl Pneumo)=3.6 or Intermed Risk=2.18
- Steroids=1.85
- Ultim=10.2 or rapidly fatal underlying disease=1.81
- Age=1.02/year



Soriano, Clin Infect Dis, 2008

'MIC Creep' Among Vancomycin-sensitive Strains of MRSA

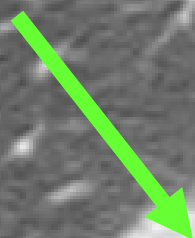
- ❖ *In vitro* comparison of vancomycin MICs between 2002 and 2005 at New England Medical Center
- ❖ A dramatic increase in MICs for MRSA bloodstream isolates



Se:5
Im:85

[A]

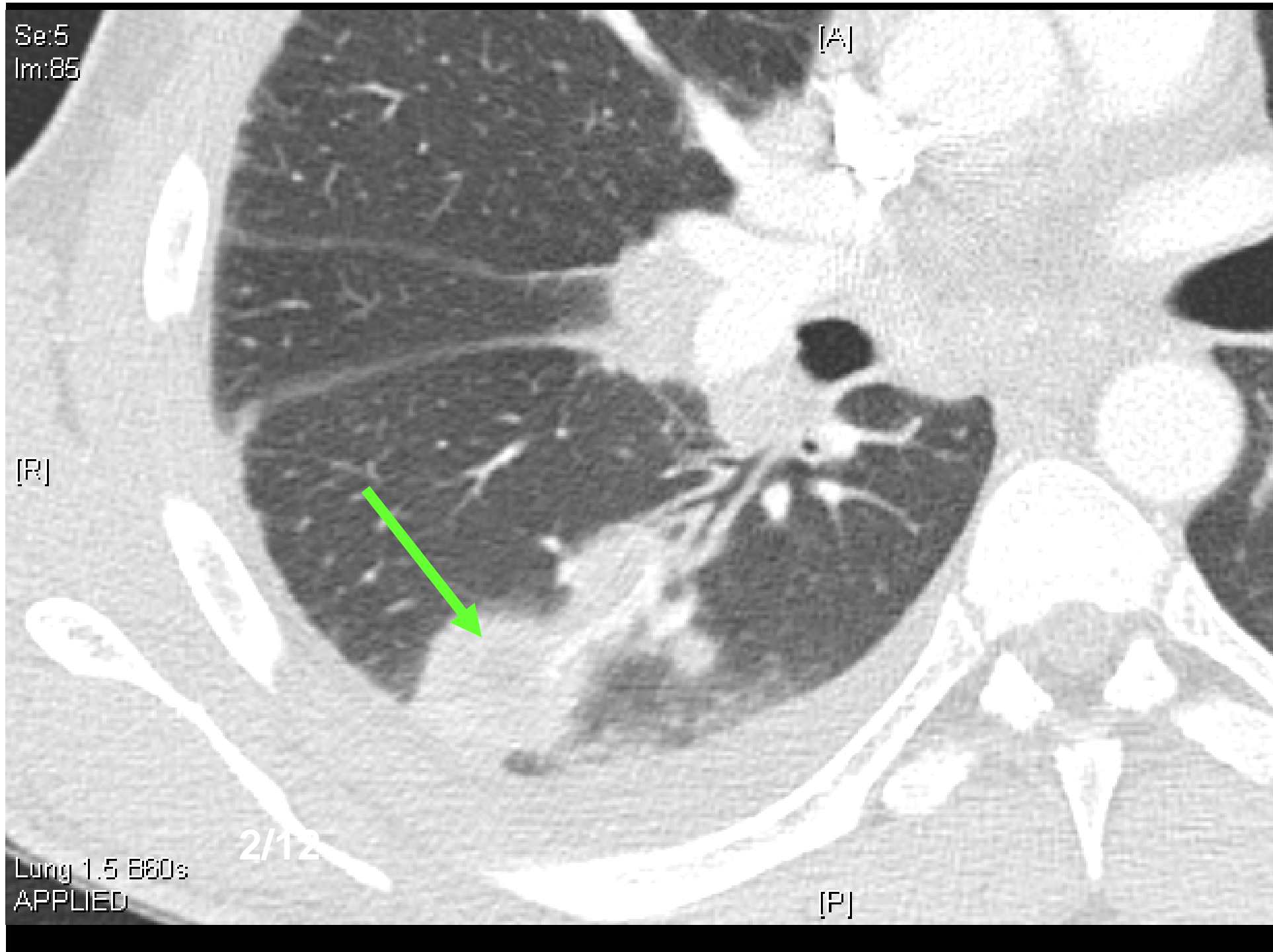
[R]



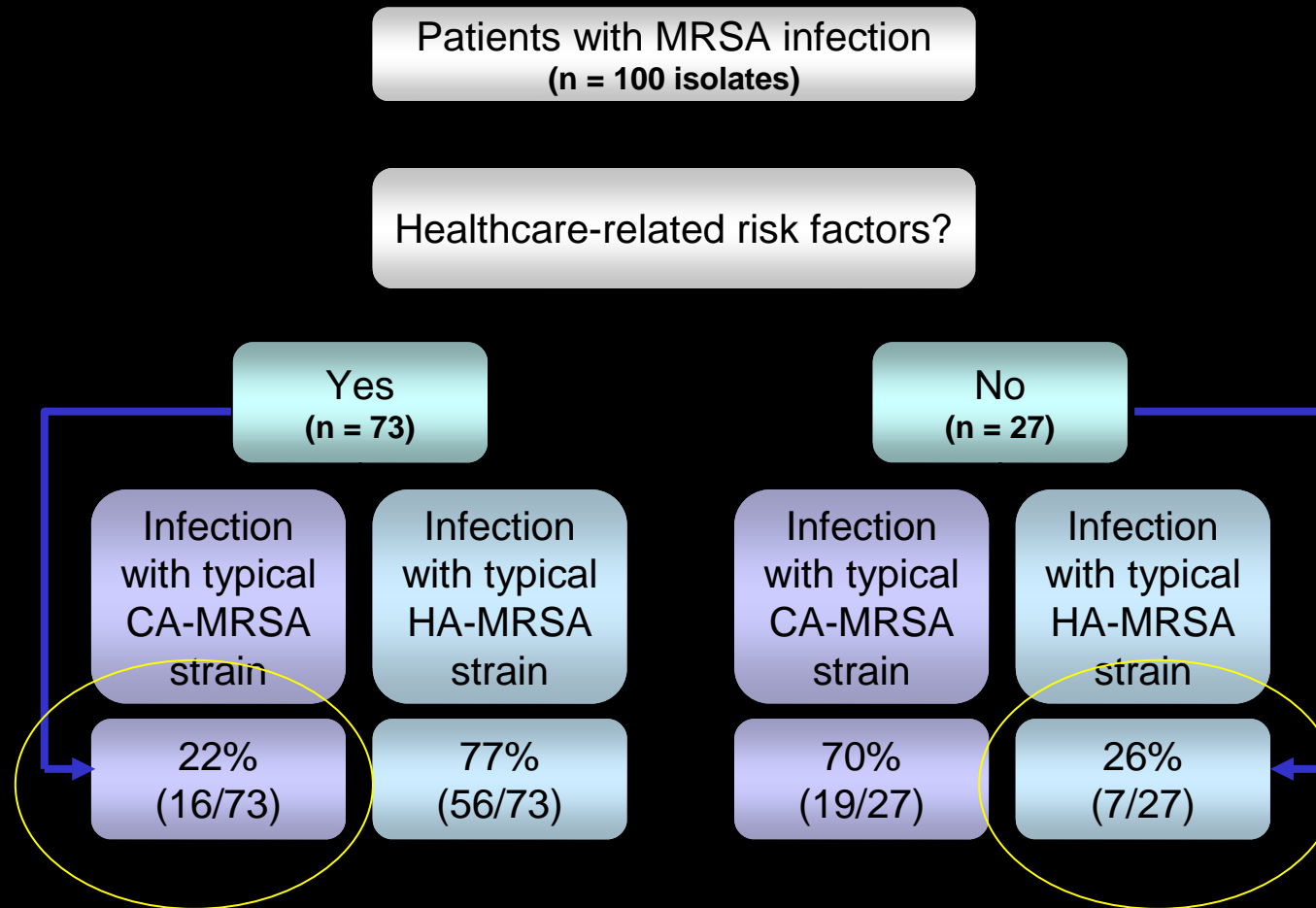
2/12

Lung 1.5 B60s
APPLIED

[P]



Distinction Between CA-MRSA and HA-MRSA Is Blurring



Klevens RM, et al. *Emerg Infect Dis.* 2006;12:1991-1993.

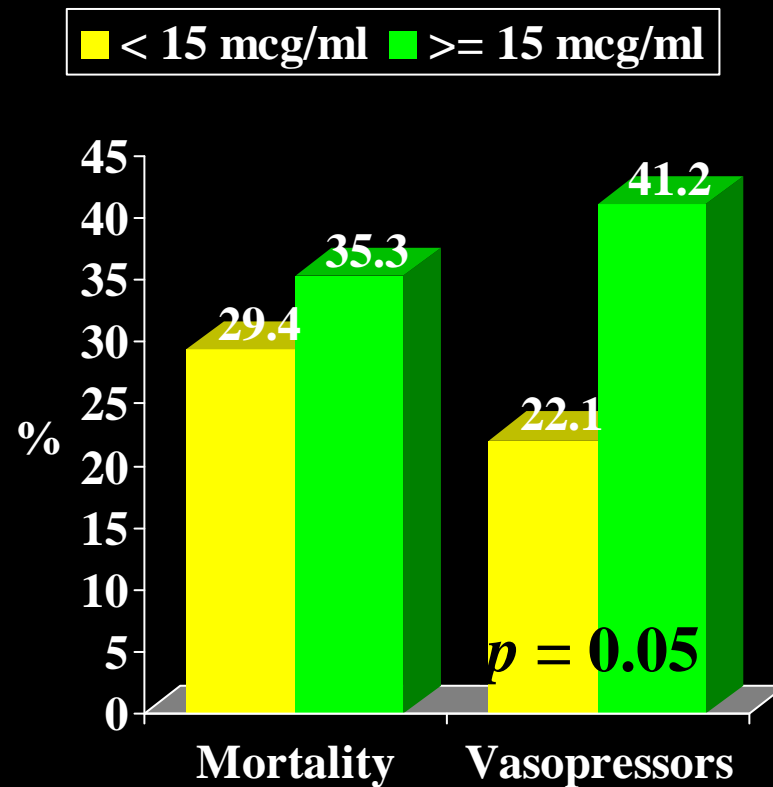
Can we make vancomycin a better drug?

-dosing

-combination therapy

High Dose Vancomycin in MRSA VAP

- ❖ All patients dosed at 15 mg/kg bid
- ❖ Actual, extrapolated, or calculated troughs
- ❖ 2/3 had troughs < 15 mcg/ml
 - Wt based dosing inadequate



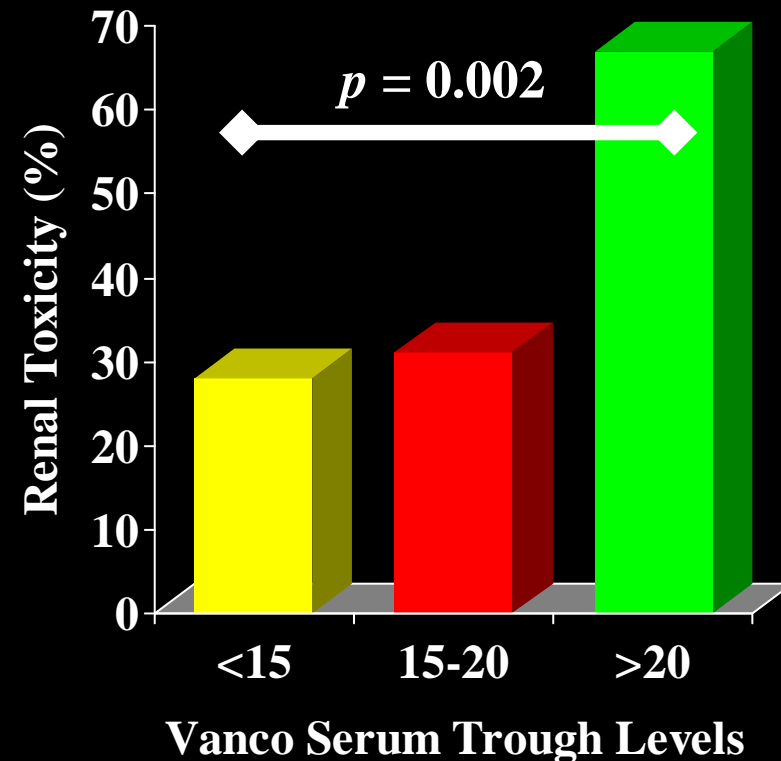
Jeffres et al. *Chest*. 2006.

Vancomycin Nephrotoxicity in HCAP/VAP

- Retrospective review

Multivariate linear regression

- ❖ Only trough $> 20 \mu\text{g/ml}$ for all (RR 2.82)
- ❖ Only duration of vanco > 14 days if vasopressor use excluded (RR 3.33)

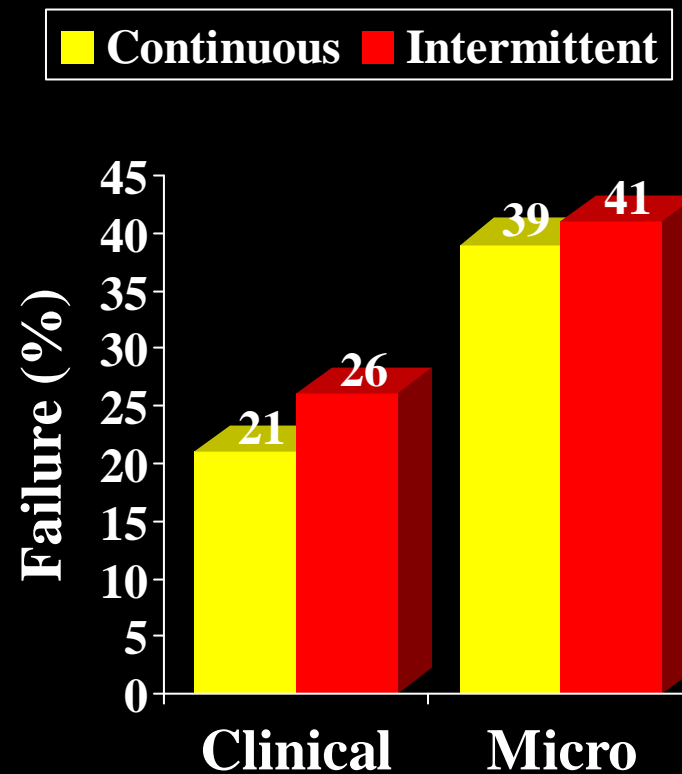


Jeffres et al. *Clin Ther.* 2007.

Continuous Infusion Vancomycin

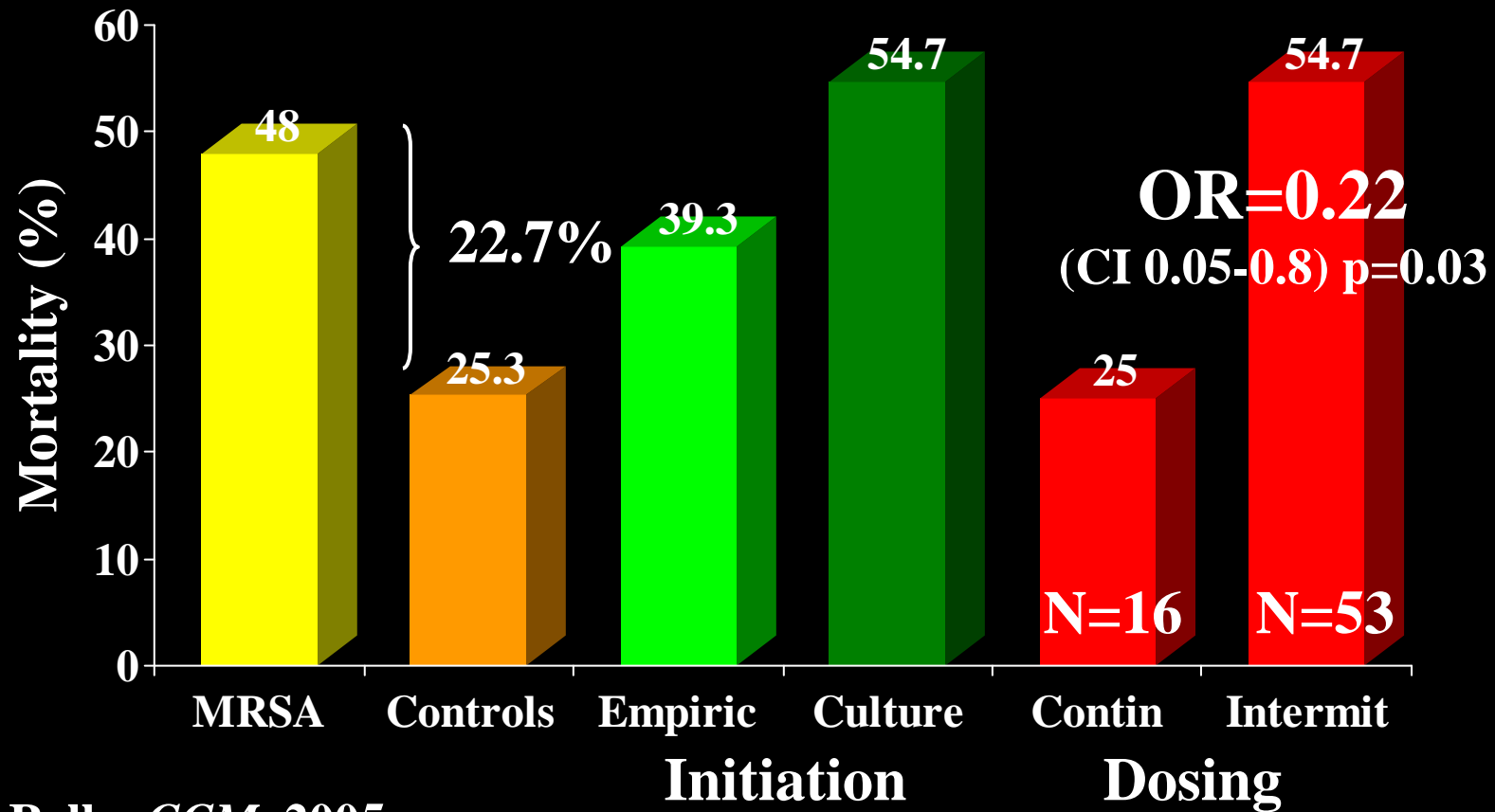
RCT 119 patients

- ❖ **48% pneumonias**
 - 10% less pneumonia in continuous group
- ❖ **20% CNS**
- ❖ **60% with MIC = 2**
 - ❖ Trough 10-15 in intermit
 - ❖ AUC_{24} 685 in failures
- ❖ **20% nephrotoxicity**
 - Only with other nephrotoxins



Wysocki. AAC. 2001.

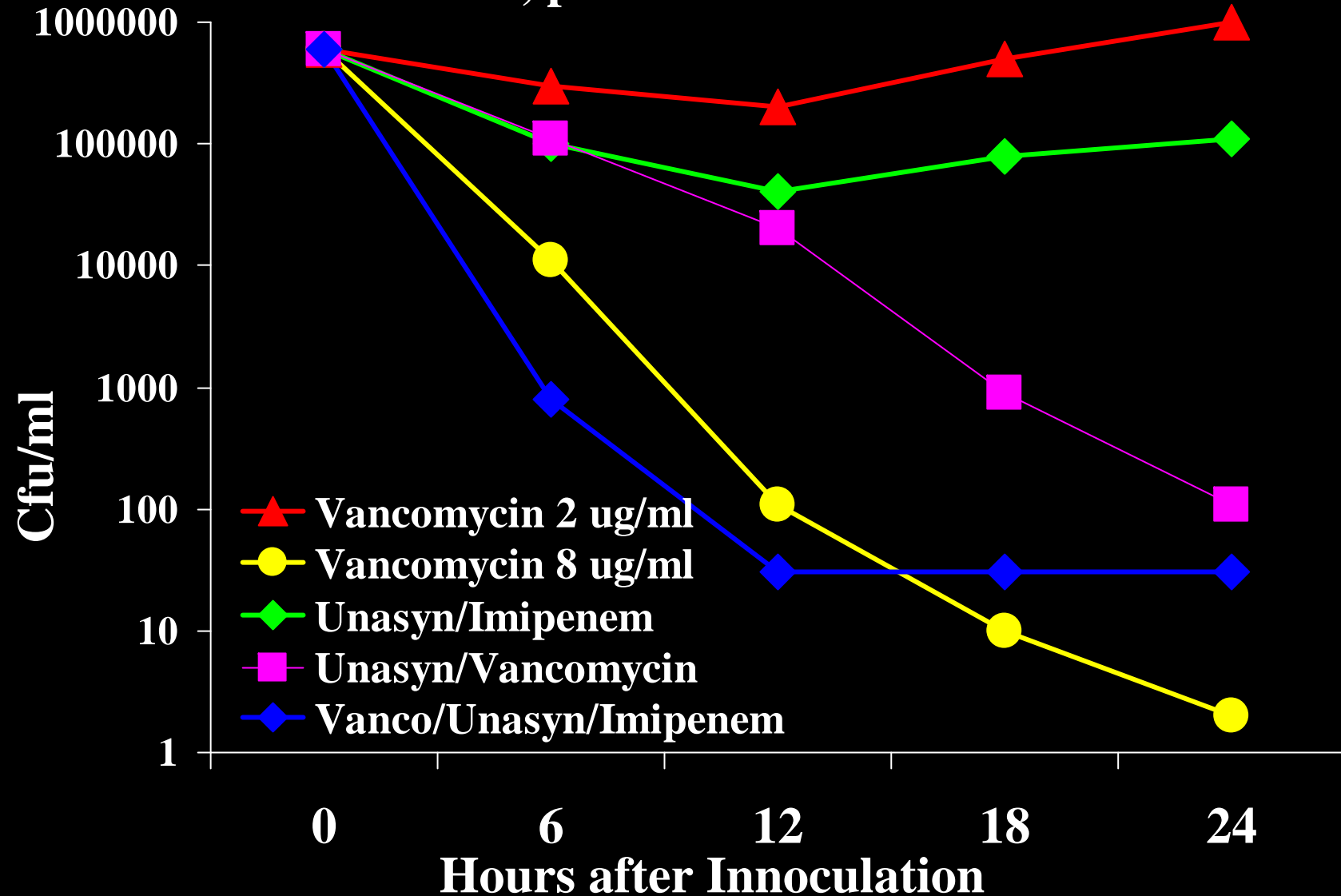
Vancomycin Treatment of MRSA VAP



Rello. CCM. 2005.

Synergistic Antibiotics

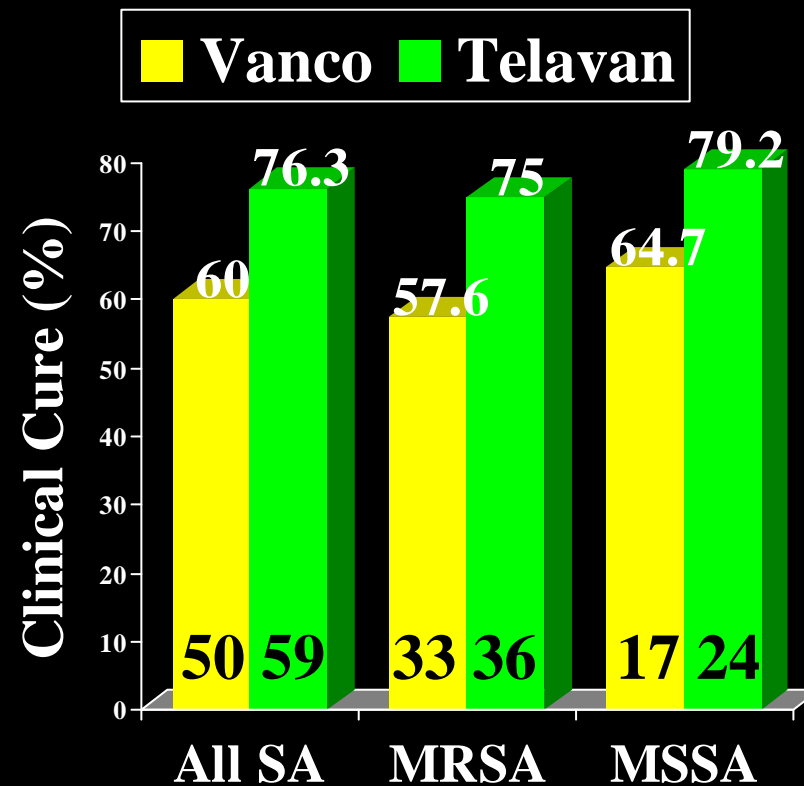
Stratton, personal communication



**Is there something new in
MRSA treatment?**

Telavancin for VAP

- Subgroup analysis of 2 Phase III trials
- Vanco 1 Gm q12 adjusted per site
- Telavancin 10 mg/kg q 24 (renal adjusted)
- *S. aureus* VAP
 - 109/1503 (7.3%) total
 - 109/421 (25.9%) VAPs



Schorr, abstract 2008 ATS

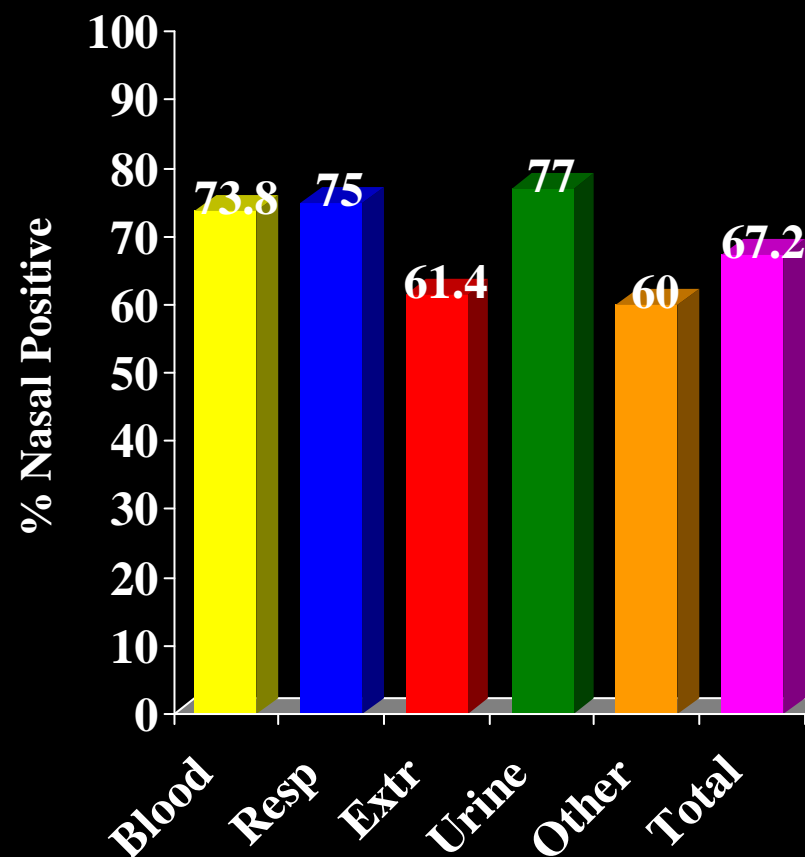
Nasal MRSA Colonisation

Respiratory

- Sensitivity - 0.75
- Specificity = 0.90
- PPV = 0.30; NPV = 0.98
- LR+ = 7.18; LR- = 0.28

Subsequent MRSA Pneumonia

- Colonised 18/60 (30%)
- Not colonised: 6/366 (1.6%)
- **RR= 18.3 (7.6-44.2)**



Robicsek. *J Clin Microbiol.* 2008.

Conclusions

- **Better alternatives exist**
- **Vancomycin probably is obsolete for VAP**
- **Pushing doses to improve outcomes likely to result in increased nephrotoxicity**
- **Combination therapy will increase risk of MDR pathogens**
- **Screening nasal PCR likely to decrease need for such extensive use for empirical treatment**