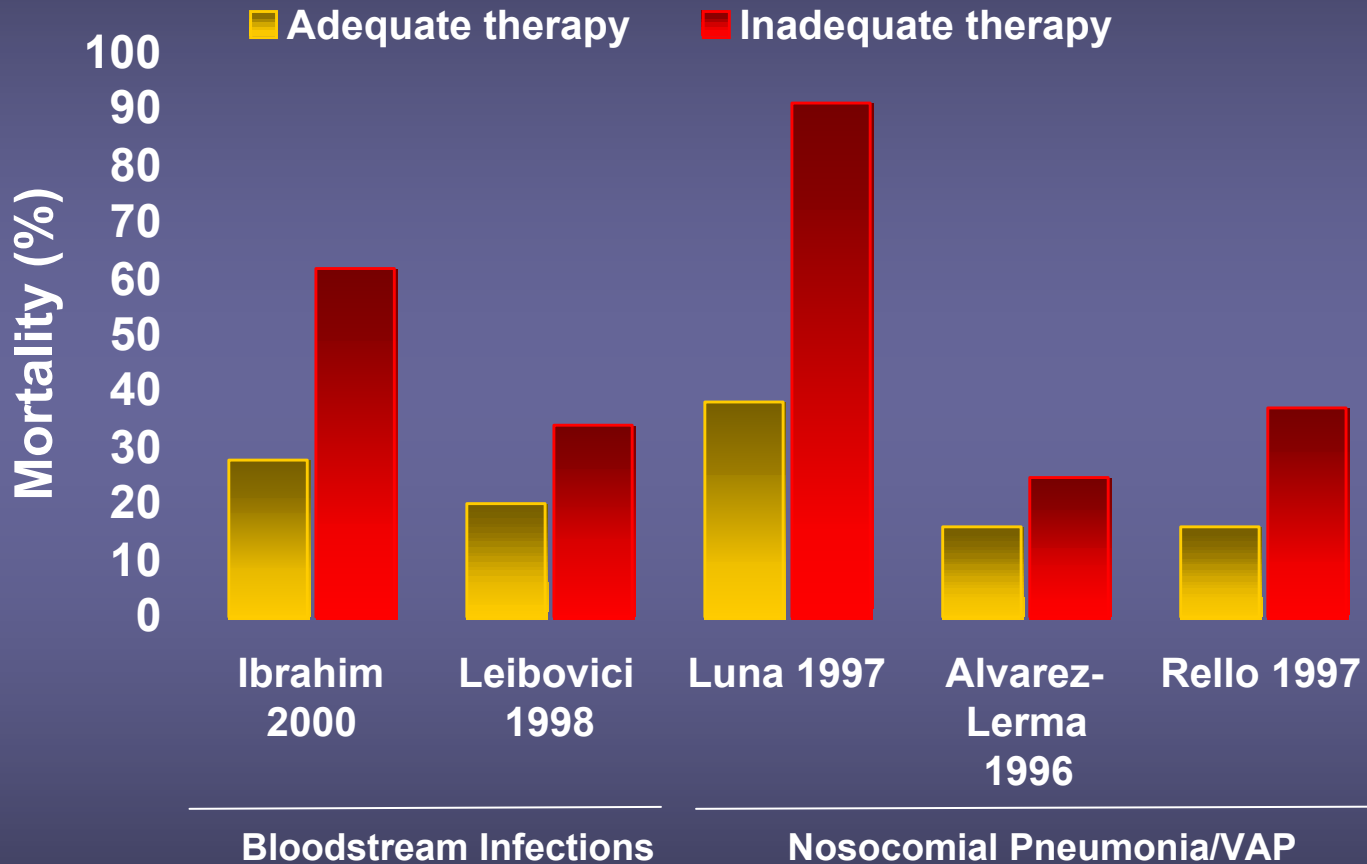


Thresholds for Empiric Antimicrobial Therapy: a Key Driver of Resistance in the ICU

Most antimicrobial therapy is provided because of:

- Concern for “attributable mortality” of untreated infection based on case controlled retrospective studies
- Lack of application of rapid or strict diagnostic testing

Studies that suggest that inadequate antibiotic therapy increases mortality



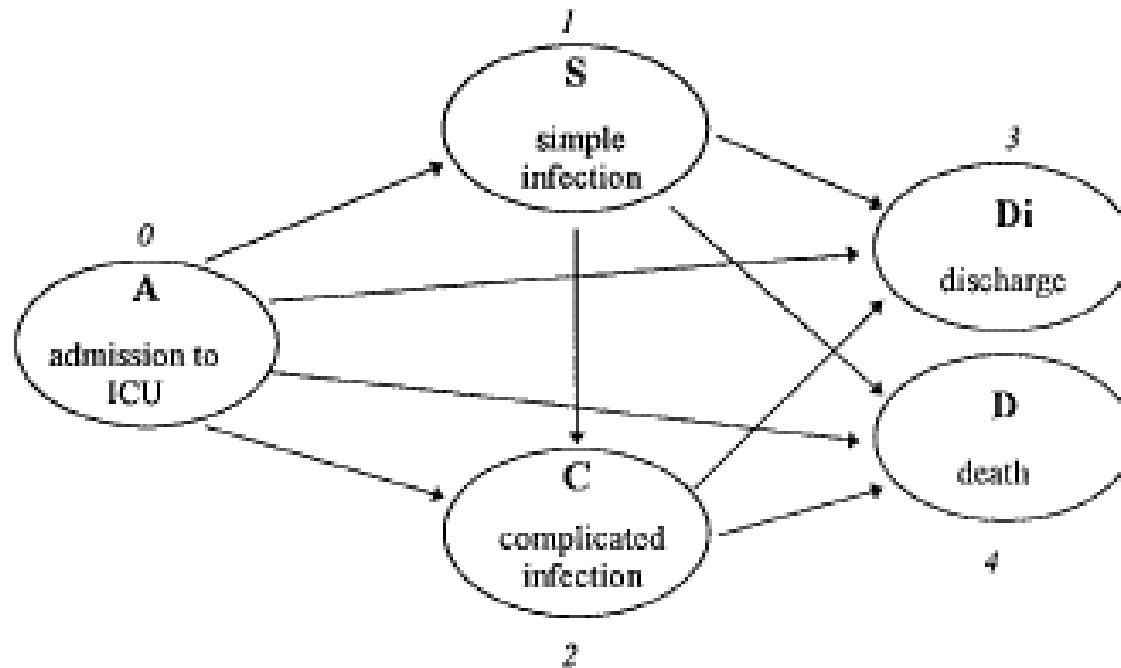
Ibrahim, et al. *Chest*. 2000;118:146-155. Leibovici, et al. *J Intern Med*. 1998;244:379-386.
Luna, et al. *Chest*. 1997;111:676-685. Alvarez-Lerma, et al. *Intensive Care Med*. 1996;22:387-394

Effect of Restricted Duration of Rx on Acquisition of Resistant Organisms

	Limited Rx	Standard Rx	P Value
Antimicrobial resistance and/or superinfections	5/37 (14%)	14/37 (38%)	P=0.01
Pseudomonas aeruginosa	3/37 (8%)	6/37 (16%)	
MRSA	2/37 (5%)	5/37 (14%)	
Other GNR	1/37 (3%)	4/37 (14%)	
Enterococcus species	1/37 (3%)	4/37 (11%)	
Candida species	3/37 (8%)	5/37 (14%)	

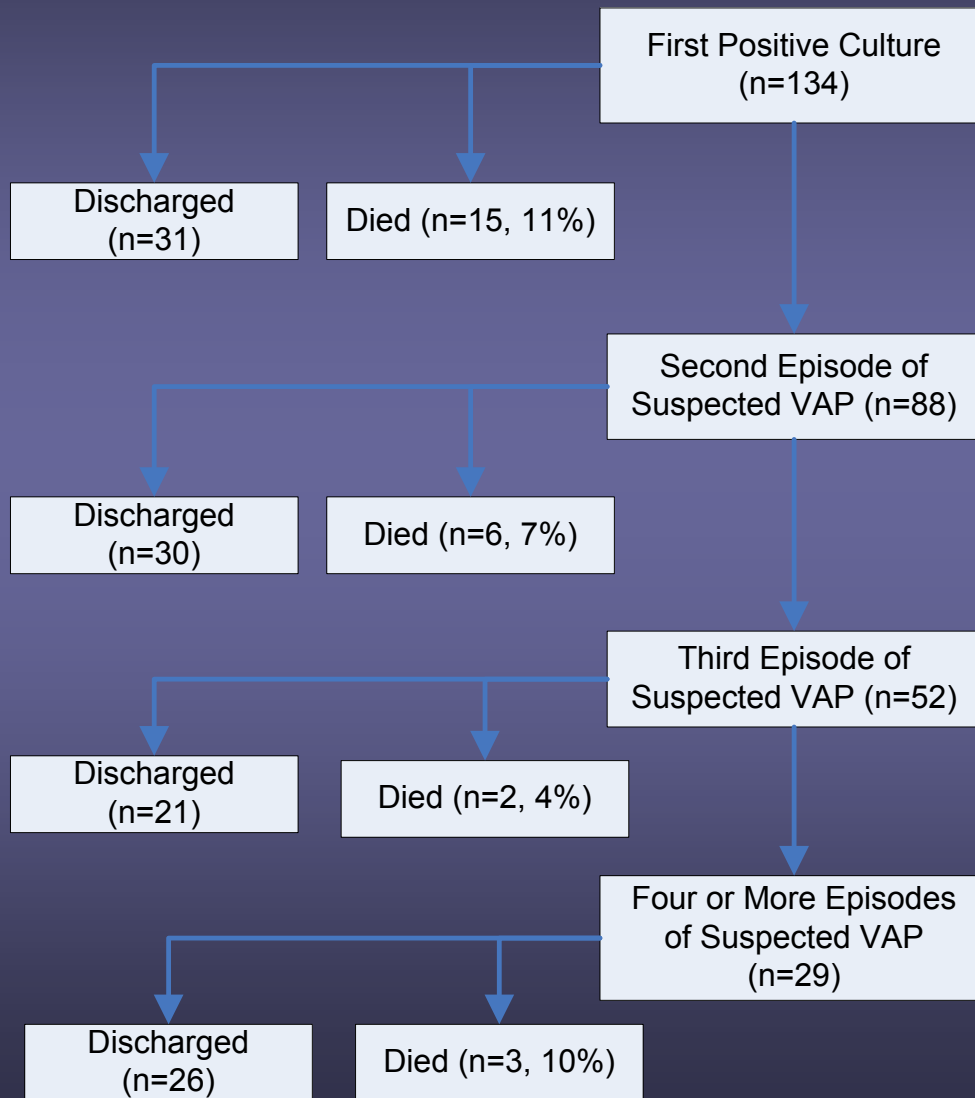
ICUs are Poor Settings for Outcomes Assessments

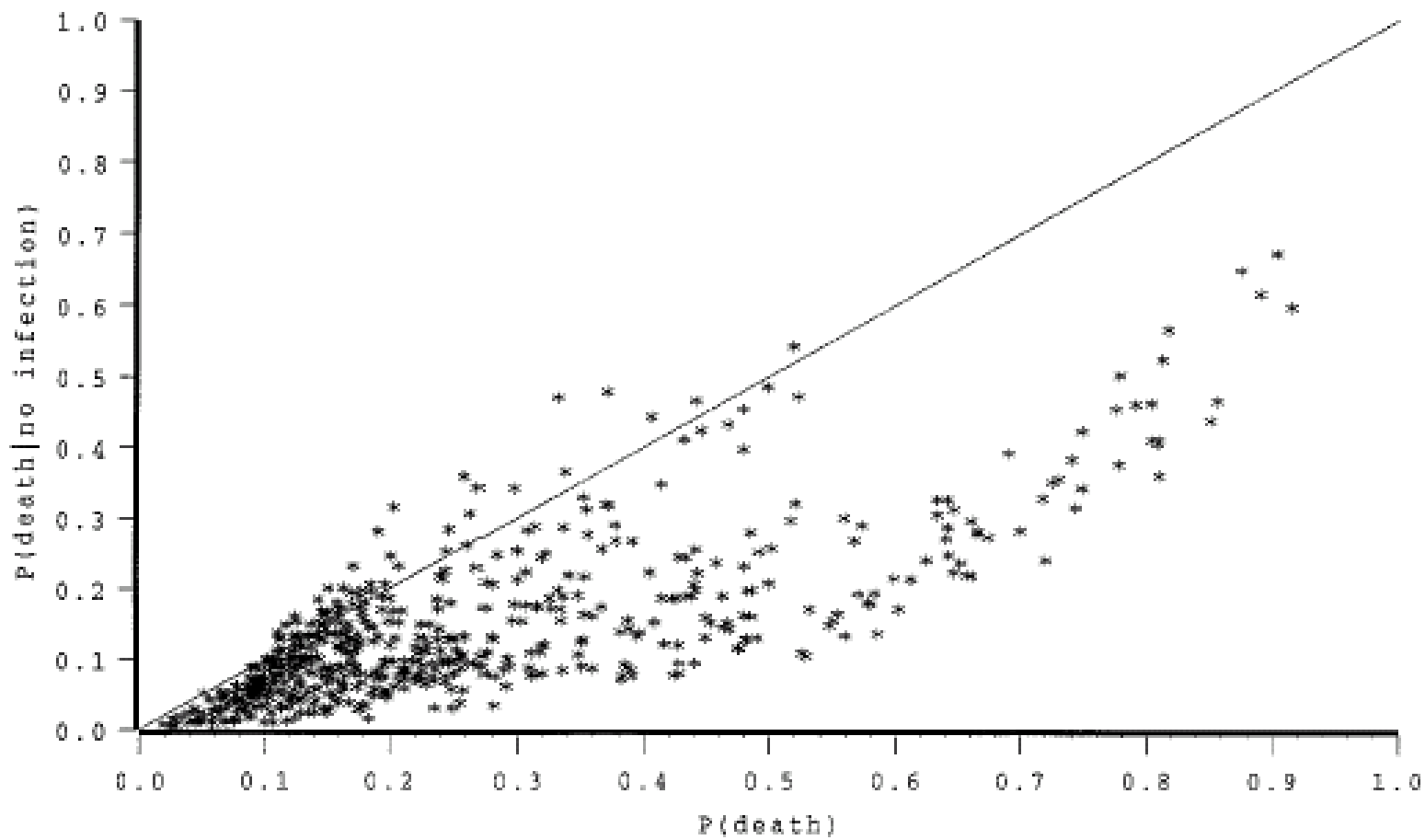
- ICU patients are complex, with multiple concurrent and interacting problems and interventions
- most ICU therapies are only supportive, and therefore may not individually result in improved outcome



Escolano S, Golmard JL, Korinek AM, Mallet A.:
A multi-state model for evolution of intensive care unit patients:
prediction of nosocomial infections and deaths. Stat Med. 2000; 19:3465-82

Multiple VAP Episodes in an SICU Population





Does VAP Cause Death?

Variable	With VAP	Without VAP	Significance
Mortality	30.4	30.6	N.S.
Duration of mechanical ventilation	14.3±15.5	4.7±7.0	P<0.001
ICU LOS	11.7±11.0	5.6±6.1	P<0.001
Hospital LOS	25.5±22.8	14.0±14.6	P<0.001
Hospital charges	104,983±91,080	63,698±75,030	P<0.001

Rello J, Ollendorf DA, Oster G, et al.

Epidemiology and outcomes of ventilator-associated pneumonia in a large US database.

Chest 2002; 122: 2115-2121

Consequences of VAP

Excess Length of Stay (days)

Medical (n=108)	6.5	3.1-9.8
Surgical (n=69)	0.7	-3.8-5.1
Trauma (n=35)	3.8	0.6-7.5

Attributable Mortality (relative risk index)

Medical (n=33/108)	65	-10.3-140.3
Surgical (n=8/69)	-27.3	-91.1-36.6
Trauma (n=35)	50	-228-329

Case Matching Technique Determines Findings

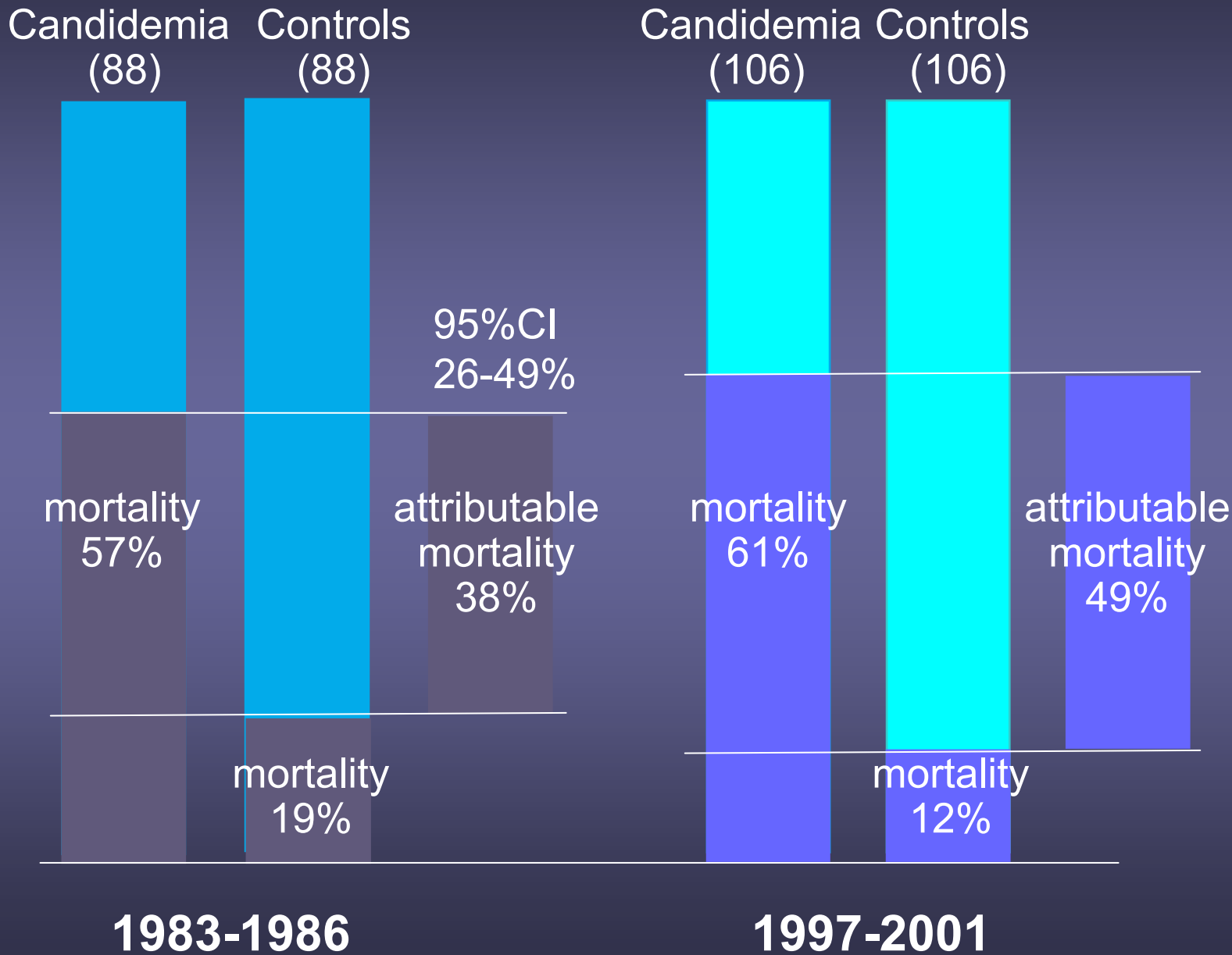
	Common	Tight
Age	+	+
Sex	+	+
Admitting Diagnosis	+	+
ICU Admission (Y/N)	+	+
Duration of Hospital Stay at Diagnosis	+	+
Prior Therapeutic Antibiotics		+
Severity Score at Time of Diagnosis		+

Matching Criteria in Two Studies of Attributable Mortality in Candidemia

- age within 10 years
- sex
- primary diagnosis at admission
- surgical procedure(s)
- length of time at risk: the time from hospital admission to onset of candidemia

Wey SB, Mori M, Pfaller MA et al: Hospital-acquired candidemia. The attributable mortality and excess length of stay. *Arch Intern Med* 1988;148: 2642-5.

Gudlaugsson O, Gillespie S, Lee K, et al: Attributable mortality of nosocomial candidemia, revisited *Clin Infect Dis* 2003;37:1172-1177



Effect of Adding APACHE II Score and Length of ICU Stay Before Onset of Candidemia

- 73 patients, two matched controls per patient
- Candidemia associated with:
 - More respiratory failure: 97% vs 88%;
 - Longer ICU/hospital stay: 29/77 vs 19/64 days
- Mortality: 48% vs 43%
- Age (1.13/10 y), ARF (1.4), APACHE II (1.14/5 points) risk factors for death

Lack of Mortality in Smaller Studies

Matching for Severity

- observational study of nosocomial pneumonia acquired in medical and surgical ICUs.
- comparison of all patients empirically treated (ET) with those not treated until culture results (NET) became available.
- well matched (APACHE II at diagnosis 17 ± 6 ET vs. 18 ± 7 days NET).
- mechanical ventilation (9 ± 9 days ET vs. 14 ± 15 days NET).
- Mortality was no different ($92/490$, 19% ET vs. $21/75$, 28% NET, $p=NS$).

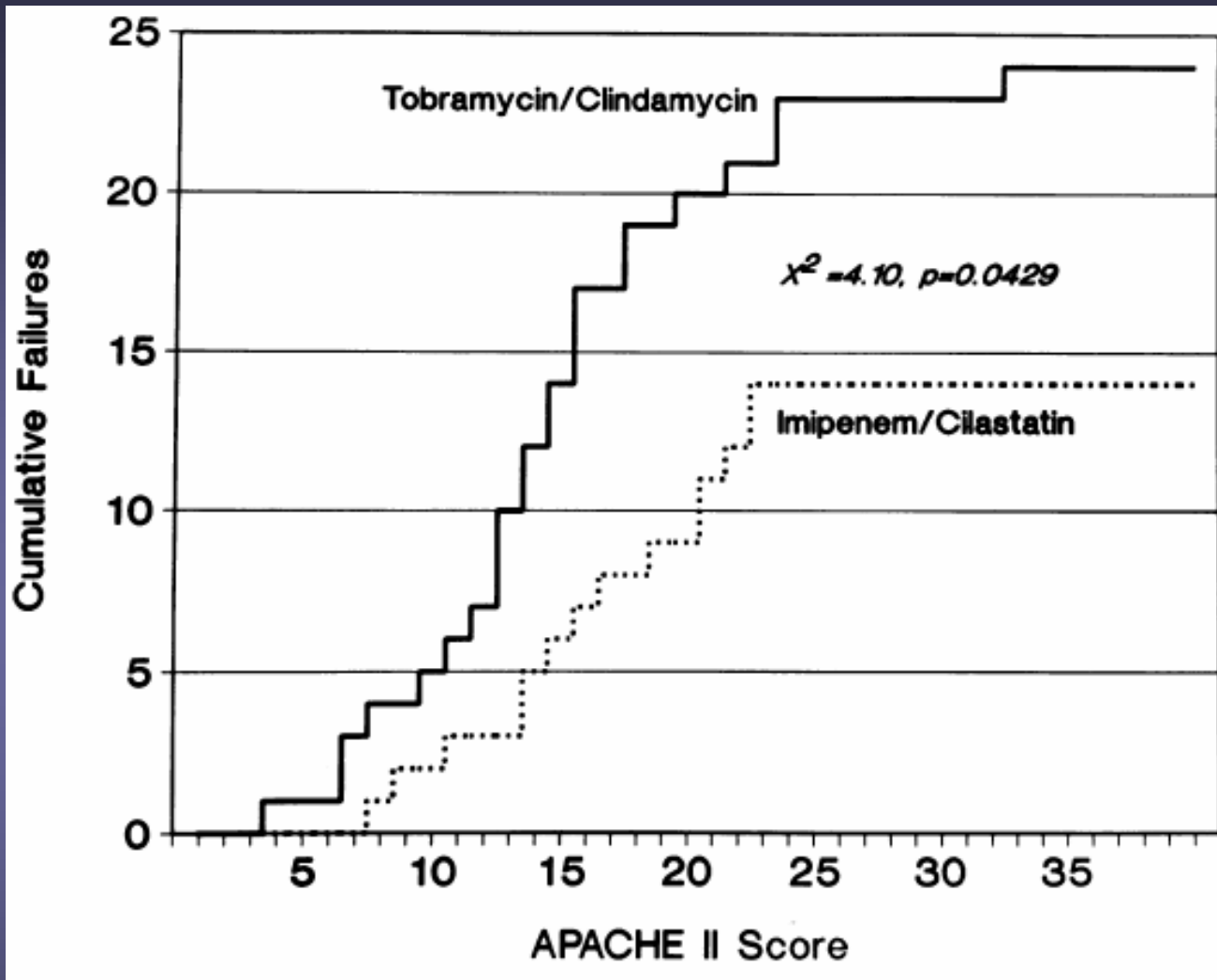
Alvarez-Lerma F. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-Acquired Pneumonia Study Group. Intensive Care Med 1996; 22(5):387-394.

Retrospective trials do not compare like groups of patients

- Treatment decisions are not random
- Patients with resistant flora (“inadequately treated”) typically are much different than those with susceptible (“adequately treated”) organisms
 - Often have suffered prior infection
 - Often have advanced organ failure
 - May be less fit in ways currently difficult to measure

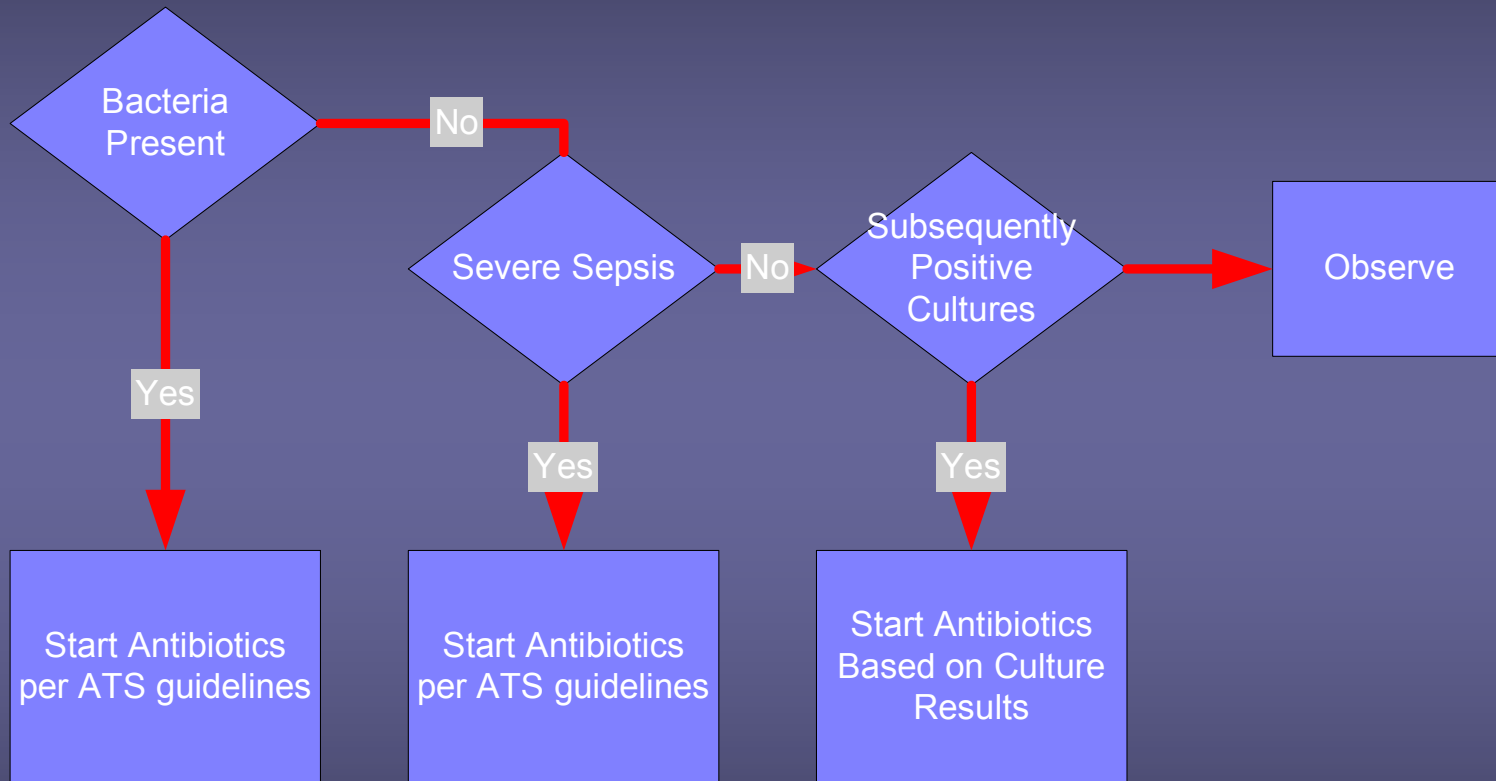
Early vs. Late: Adequate vs. Inadequate

	Inadquate Rx (n=44)	Adequate Rx (n=16)
MSSA	0	9
MRSA	12	0
P aeruginosa	19	1
S maltophilia	5	0
resistant GNR	10	1
E coli	0	1
H influenzae	0	1



APACHE II was a significant predictor of failure ($X^2 = 10.11, p = 0.0015$). There was a residual benefit of imipenem/cilastatin therapy for the entire study population with $X^2 = 4.10, p = 0.0429$. The model X^2 was 14.46, $p = 0.0007$.

Management Plan for Suspected VAP



Fagon JY, Chastre J, Wolff M, et al: Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Ann Intern Med.* 2000; 132: 621-30.

Reasons for Antibiotics

	Invasive (n=204)	Non-invasive (n=209)
positive microscopic examination	87 (43%)	180 (87%)
Severe sepsis	11	10
Late positive cultures	7	3
Observation	90	15

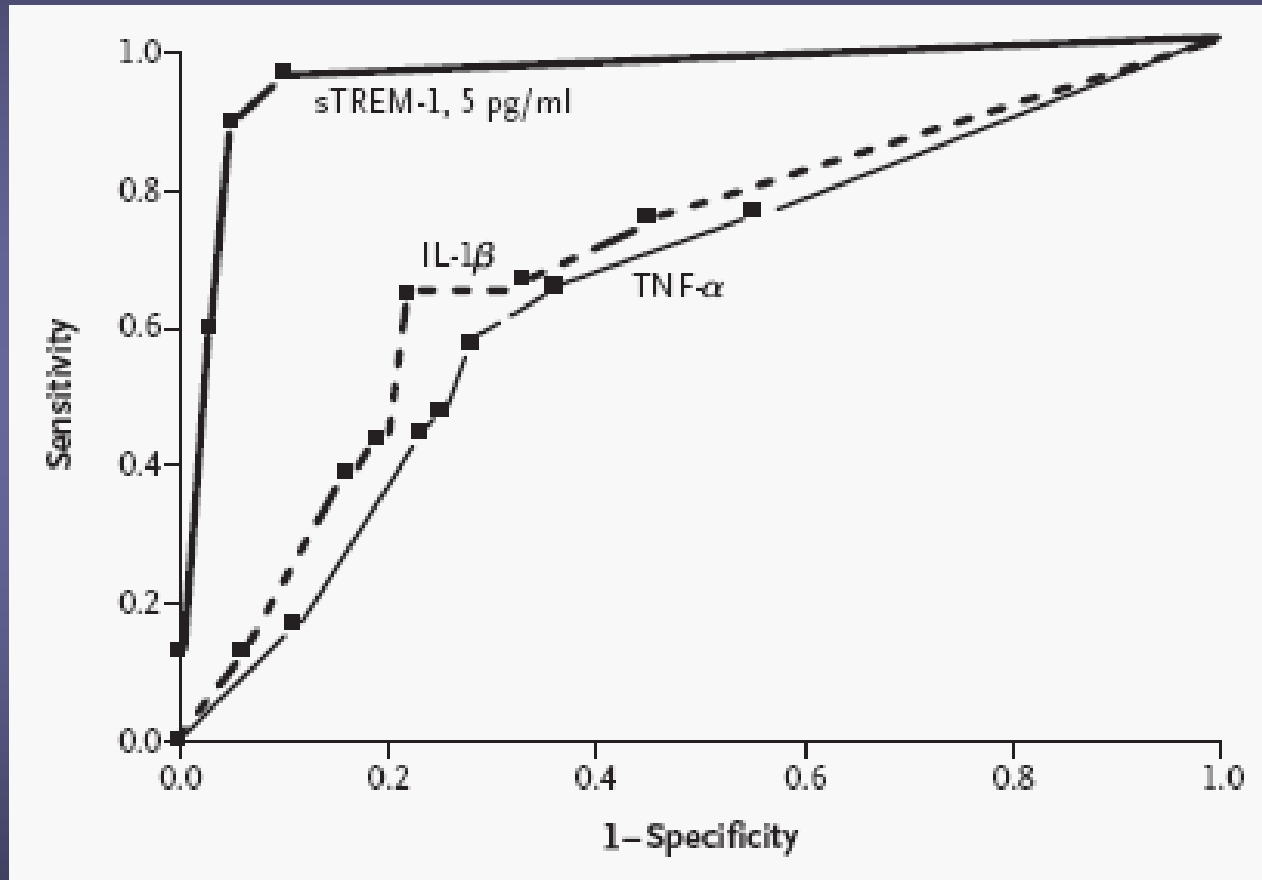
Results of a Comparison of BAL/PSB vs Clinical Judgement

	BAL/PSB	Clinical	Significance
Day 14 mortality	16% (33/204)	26% (54/209)	P=0.0022
Day 3 Organ Failure Score	6.1	7.0	P=0.033
Antibiotic Free Days at Day 28	11.5	7.5	P<0.001

Effect of Organism and Density on Mortality

Organism	n	10-50,000	50-100,000	>100,000
All	646	17.5%	15.9%	26.0%
Hemophilus influenzae	68	0%	23%	9%
Pseudomonas aeruginosa	59	3.2%	11.1%	30.8%
Acinetobacter BC	47	3.2%	0.0%	33.3%
S. maltophilia	97	7.6%	0.0%	0.0%
MRSA	38	12.0%	9.1%	18.8%
MSSA	63	7.5%	0.0%	21.4%

Receiver-Operating-Characteristic Curves for sTREM-1: Soluble Triggering Receptor Expressed on Myeloid Cells



Gibot S, Cravoisy A, Levy B, et al: Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia.

N Engl J Med. 2004 Jan 29;350(5):451-8

Comparison of Markers for VAP Diagnosis

Predictor	P Value	Odds Ratio (95% CI)
Clinical pulmonary infection score >6	0.002	3.0 (1.5-5.9)
TNF α > 150 pg/ml	0.004	2.4 (1.8-5.8)
IL-1 β >75 pg/ml	0.003	3.7 (2.0-13.2)
sTREM-1 > 5 pg/ml	<0.001	41.5 (20.9-77.6)

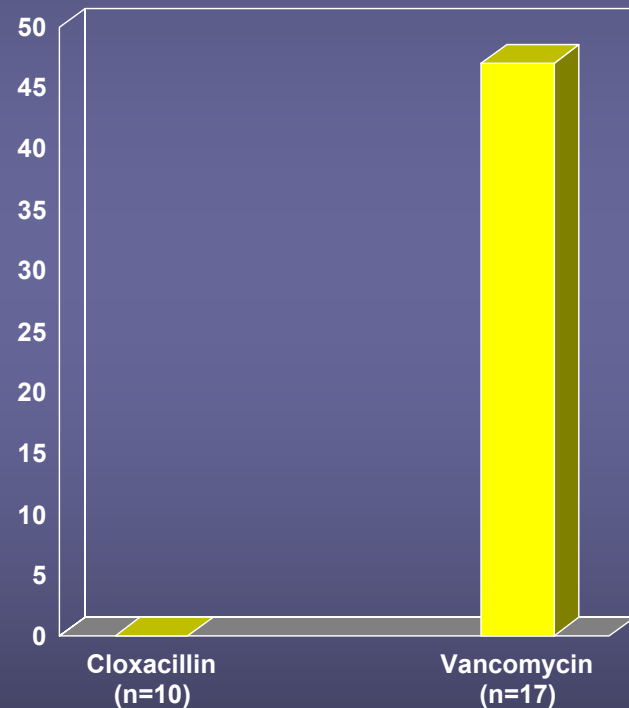
Conclusions

- Outcomes analyses for VAP may not be productive
- The problem is compounded by use of non-random study designs without appropriate statistical treatment of subgroups
- Therapeutic approaches to individual patients should prioritize minimizing appearance of resistance rather than consequences of delayed therapy for patients not in shock
- More specific and sensitive diagnostic tools for empiric and definitive therapy need to be used

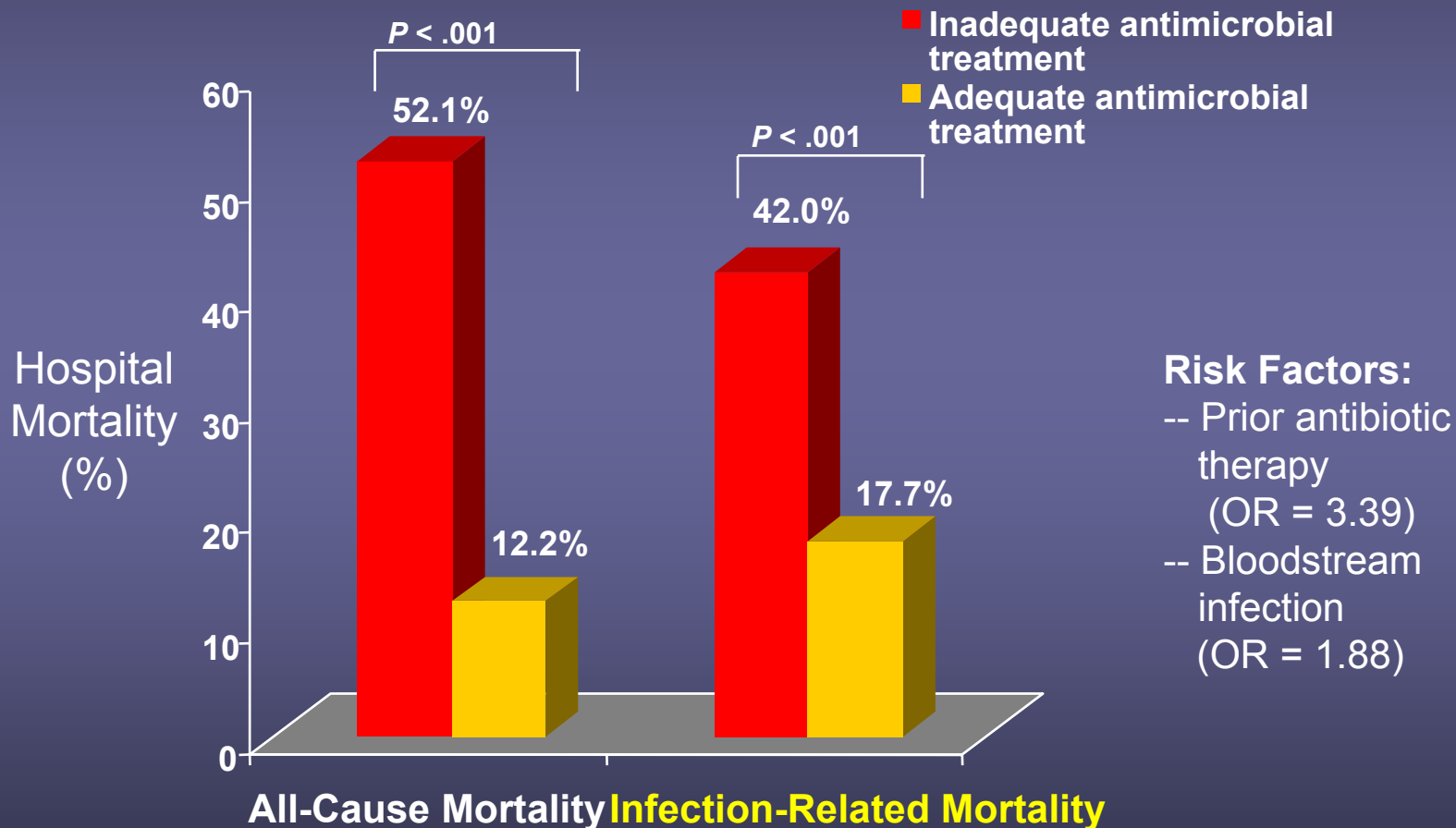


Bacteremic Pneumonia Due to *S aureus*: Comparison of Vancomycin and Cloxacillin

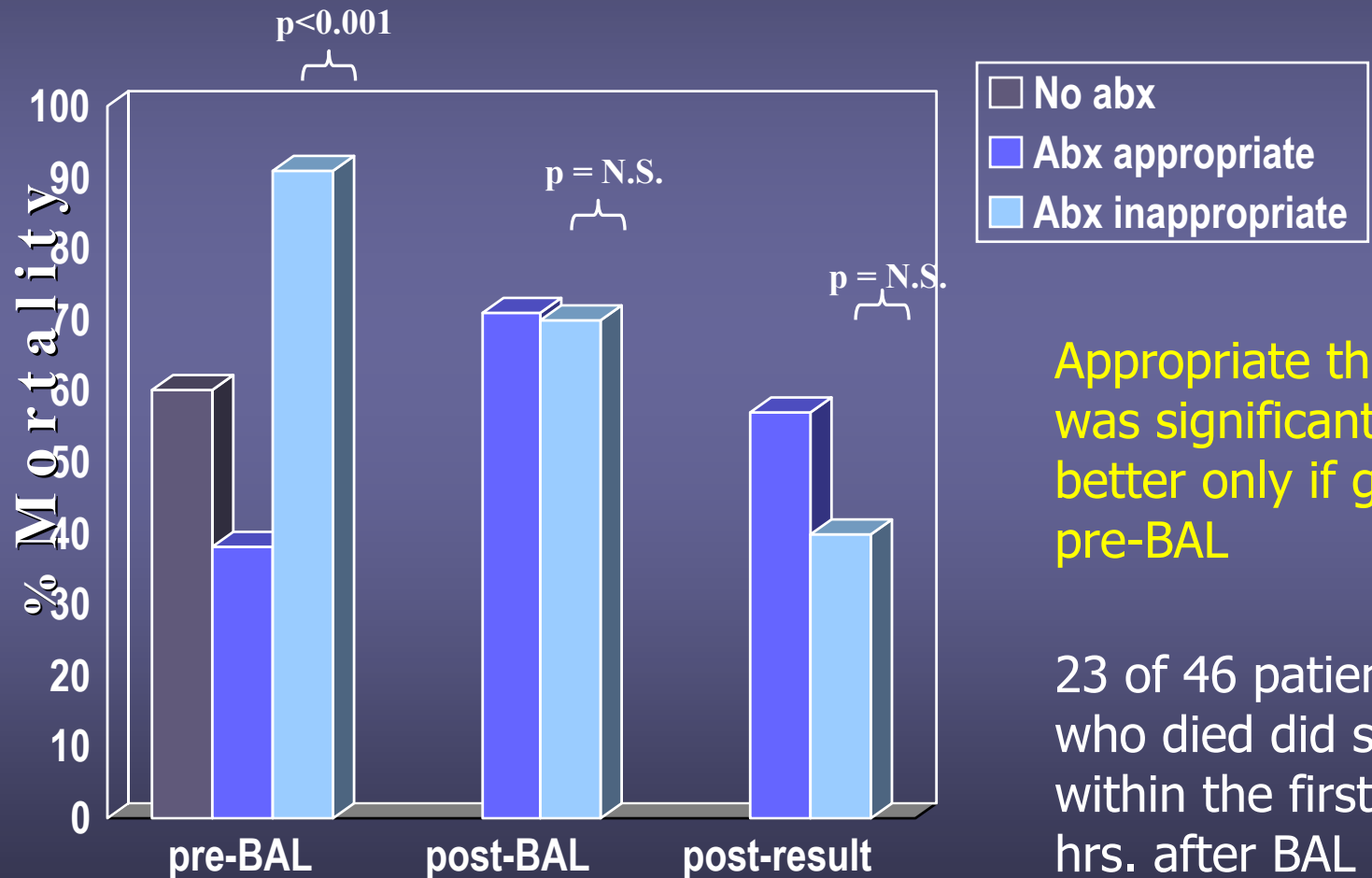
- Prospective observational study - 6 years
- Mortality significantly higher among MSSA-infected patients treated with vancomycin vs cloxacillin (8/17=47% vs 0/10=none, $P < .01$)



Inadequate Antimicrobial Therapy Associated With Higher Mortality



Antibiotic-Associated Mortality in Patients with BAL-Positive Nosocomial Pneumonia



Appropriate therapy was significantly better only if given pre-BAL

23 of 46 patients who died did so within the first 48 hrs. after BAL

Subgroups in VAP Studies

After hospitalization	% of patients	After onset of mechanical ventilation	% of patients
2 days	45.2	<48 hours MV	63.2%
3-6	29.1	48-96 hours	16%
>day 6	25.7	>96 hours	20.8%

Rello J, Ollendorf DA, Oster G, et al.

Epidemiology and outcomes of ventilator-associated pneumonia in a large US database.

Chest 2002; 122: 2115-2121

Risk Factors for VAP With High-Risk Pathogens

- Recovery of high-risk microorganisms from patients with late-onset VAP was related to the duration of mechanical ventilation and the length of hospital stay prior to ICU admission
 - Chest 1995; 108(6):1655-1662.
- Previous antibiotic therapy, particularly third-generation cephalosporin agents, increased the likelihood of VAP due to oxacillin-resistant staphylococci and highly resistant Gram-negative bacilli
 - Am Rev Respir Dis 1990; 142(6 Pt 1):1320-1324.
 - Am J Respir Crit Care Med 1994; 150(6 Pt 1):1545-1549.

Further Evidence

- by logistic regression, risk factors for the presence of potentially drug-resistant bacteria (such as methicillin-resistant *S aureus* or *P aeruginosa*):
 - duration of mechanical ventilation 7 days (OR, 6.9);
 - prior antibiotic use (OR, 13.5);
 - and prior use of broad-spectrum antimicrobial agents (OR, 4.1) .
- The rate for the presence of multi-resistant microorganisms in 135 episodes of VAP increased from 0%, in the low-risk group of patients who had received mechanical ventilation for < 7 days and had no prior antibiotic exposure, to 58.6%, in the group with both risk factors present.

Trouillet JL, Chastre J, Vuagnat A, Joly-Guillou ML, Combaux D, Dombret MC et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. *Am J Respir Crit Care Med* 1998; 157:531-539.

Effect of Positive PCL on Clinical Outcome

	Culture Positive (n=32)	Culture Negative (n=32)
Hospital days	25.4±8.6	28.1±9.8
ICU days	23.6±8.2	21.4±8.7
Ventilator days	15.7±6.1	15.1±8.1
APACHE II	18.1±7.9	18.4±6.3
Death	2	5

If the Goal is Reduced Antibiotic Exposure: What's Needed

- Determine appropriate time frame for invasive diagnostics
- Determine appropriate time frame for initiation of antibiotic therapy
- Determine time frame for revision of therapy

Reasons for Antibiotics

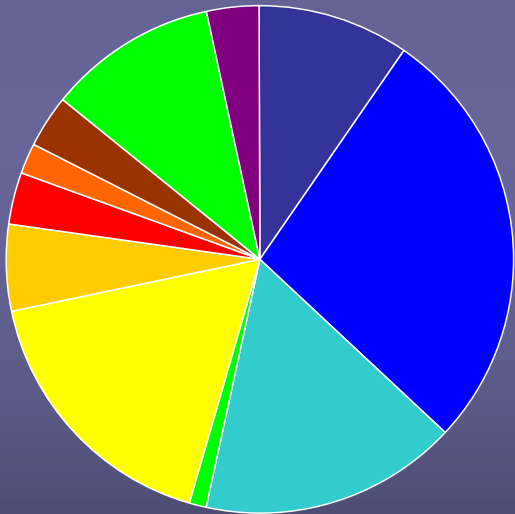
	Invasive (n=204)	Non-invasive (n=209)
positive microscopic examination	87 (43%)	180 (87%)
Severe sepsis	11	10
Late positive cultures	7	3
Observation	90	15

Microbiology Results

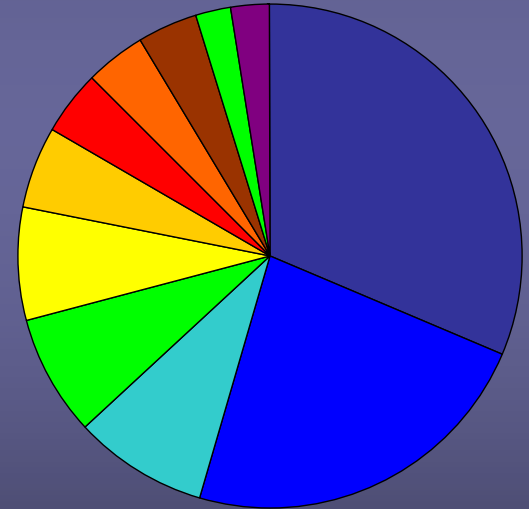
	Invasive Diagnosis	Non- invasive Diagnosis
Negative culture	56%	14%
Polymicrobial culture	12%	46%
Pseudomonas	22%	18%
H influenzae	7%	4%
S aureus	17%	13%
Fungi	4%	12%

Organisms Encountered in First Episode

> 5 Days



≤ 5 Days



- H. influenzae
- S. aureus
- Acinetobacter
- Strep. pneumo
- Stenotrophomonas
- E. coli
- Klebsiella spp
- Moraxella
- β-strep
- Pseudomonas
- Serratia

Effects on Mortality

- mortality rates between those with changes in empiric treatment (214 patients) vs. those with no change (n=242) were identical (18.4 vs. 18.1%).
- There was a significant difference in attributable mortality. For appropriate treatment was 16% (46/284) vs. 25% (36/146), an anomalous finding in that the crude mortality was not different (32%, 92/284 for appropriate Rx, 35% ,51/146, for inappropriate therapy).

Comparative Strategies

- Randomized trials
- Case-matched studies
- Cohort studies