Issues in Ventilator-Associated Pneumonia

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Disclosures

I have received consulting fees from:

- Allergan
- Merck
- Pfizer
- Tetraphase
- Shionogi

Objectives

- Upon completion of this activity, participants should be able to
  - Describe the burden of nosocomial pneumonia
  - Appreciate the evolving pathogens in this syndrome
  - Understand the importance of early appropriate therapy

The Dilemma

- Appropriate antibiotics key determinant of outcome in the ICU
- Resistance rates increasing
- Most data for use of antibiotics derive from studies in non-ICU subjects and ignores unique ICU issues (eg fluid resuscitation, MV, changing renal fxn)
- How do we optimize antibiotic administration in the ICU?

Definitions: The Old Guidelines

Hospital-acquired pneumonia (HAP)

- Pneumonia occurring ≥48 hours post-hospital admission

Ventilator-associated pneumonia (VAP)

- Pneumonia occurring >48-72 hours post-intubation

Healthcare-associated pneumonia (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

HCAP -- Microbiology

- Retrospective analysis
- Subjects:
  - Presenting to ED
  - Respiratory failure on MV
  - n=190
- All patients underwent lower airway cultures

Table 1—*Pathogens by Pneumonia Type*

Pathogen	HCAP (n = 94)	CAP (n = 96)	*P* Value
Resistant organisms			
MRSA	22.3	14.6	.193
PA	23.4	3.1	.001
ESBL-producing organisms	2.1	0.0	.001
Nonresistant organisms			
Streptococcus pneumoniae	6.4	21.9	.003
Streptococcus viridans	10.6	29.2	.002
Methicillin-susceptible *Staphylococcus aureus*	10.6	14.6	.514
Escherichia coli	12.8	4.2	.038
Klebsiella pneumoniae	10.6	4.2	.102
Legionella species	3.2	2.1	.681

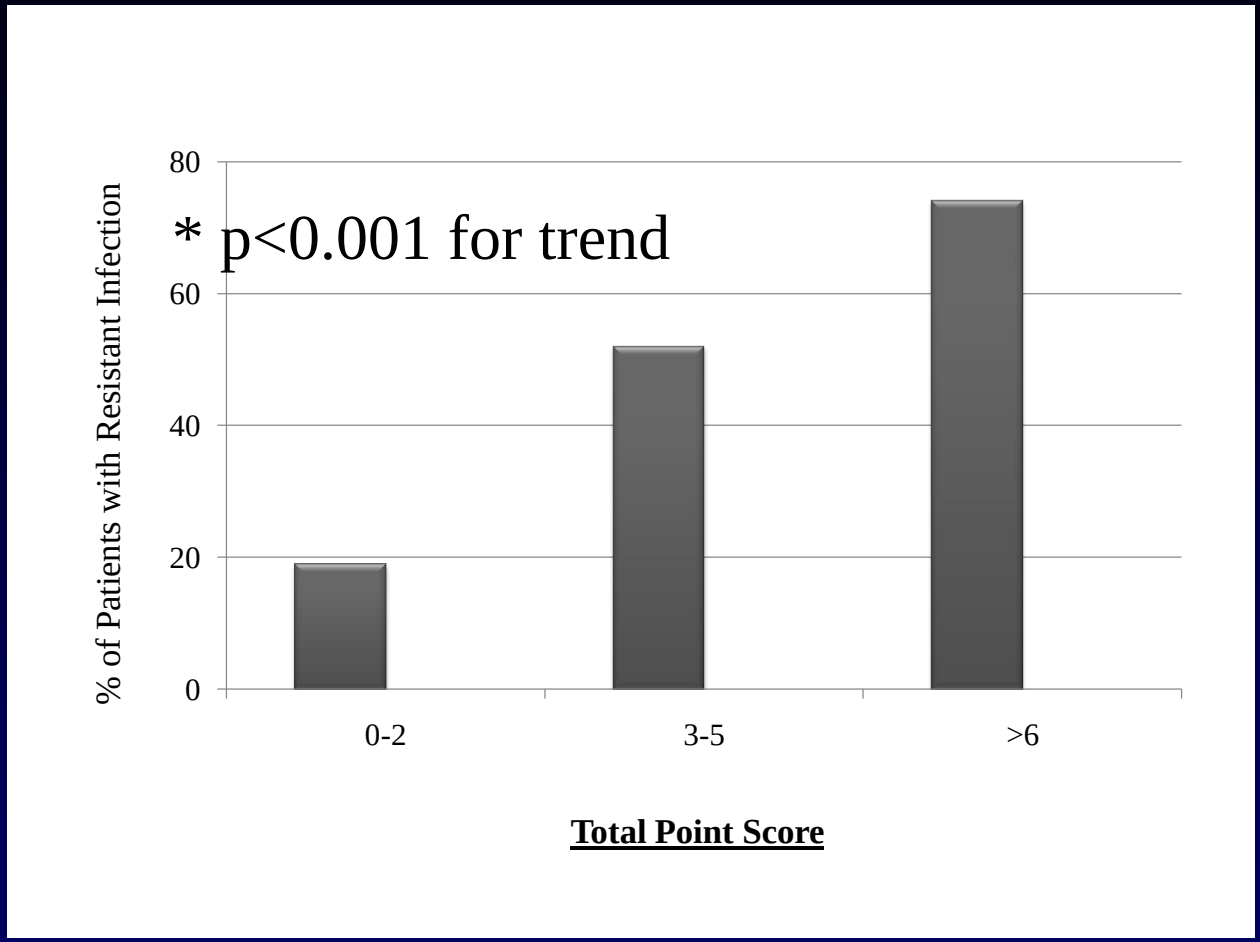
Schreiber MP, et al. Chest 2010; 137: 1283-8.

Are Clinical Predictors for Resistance in HCAP Effective?

- Secondary analysis
- Subjects:
  - Patients with HCAP/CAP
  - All severities of illness
  - n=639
- Objective: Develop risk score to identify patients with resistant pathogens

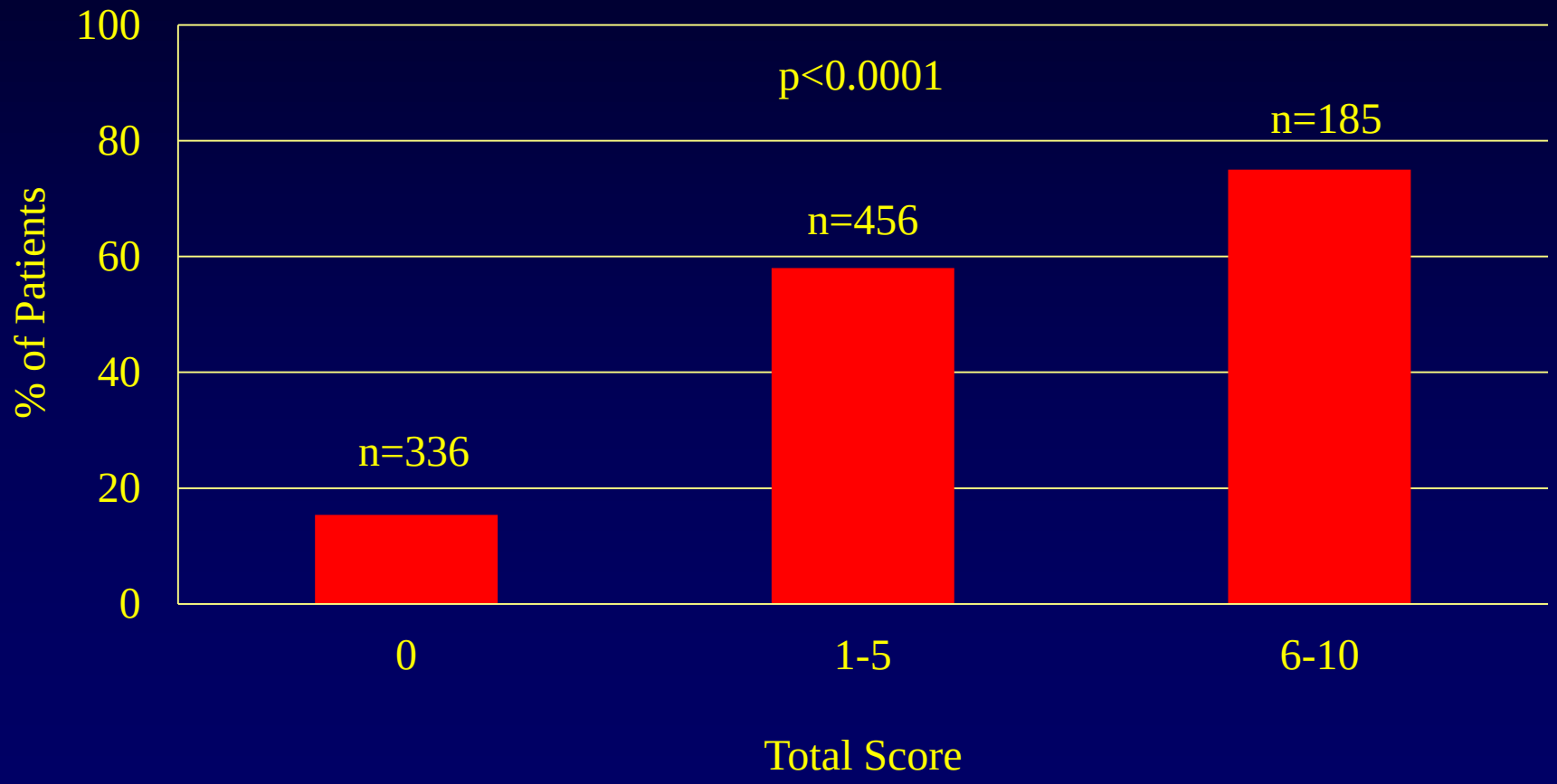
- Resistant pathogens: MRSA, PA, ESBLs
- Points assigned:
  - Nursing home: 1 point
  - Recent hospitalization: 1 point
  - Chronic hemodialysis: 1 point
  - ICU admission: 1 point

Shorr AF, et al. Arch Intern Med 2008; 168: 2205-10.



Although the score segregates patients, even in the “low risk” group the prevalence of resistance is nearly 20%

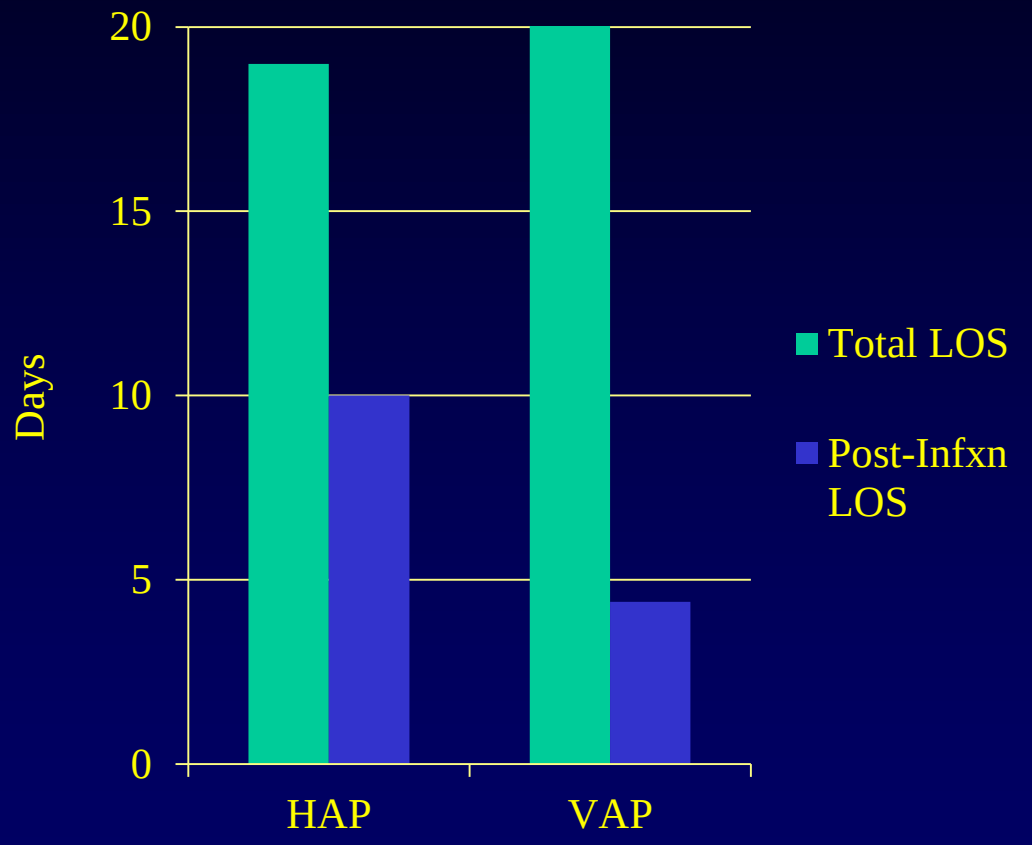
Risk Score: External Validation



Shorr AF, et al. CID 2012.

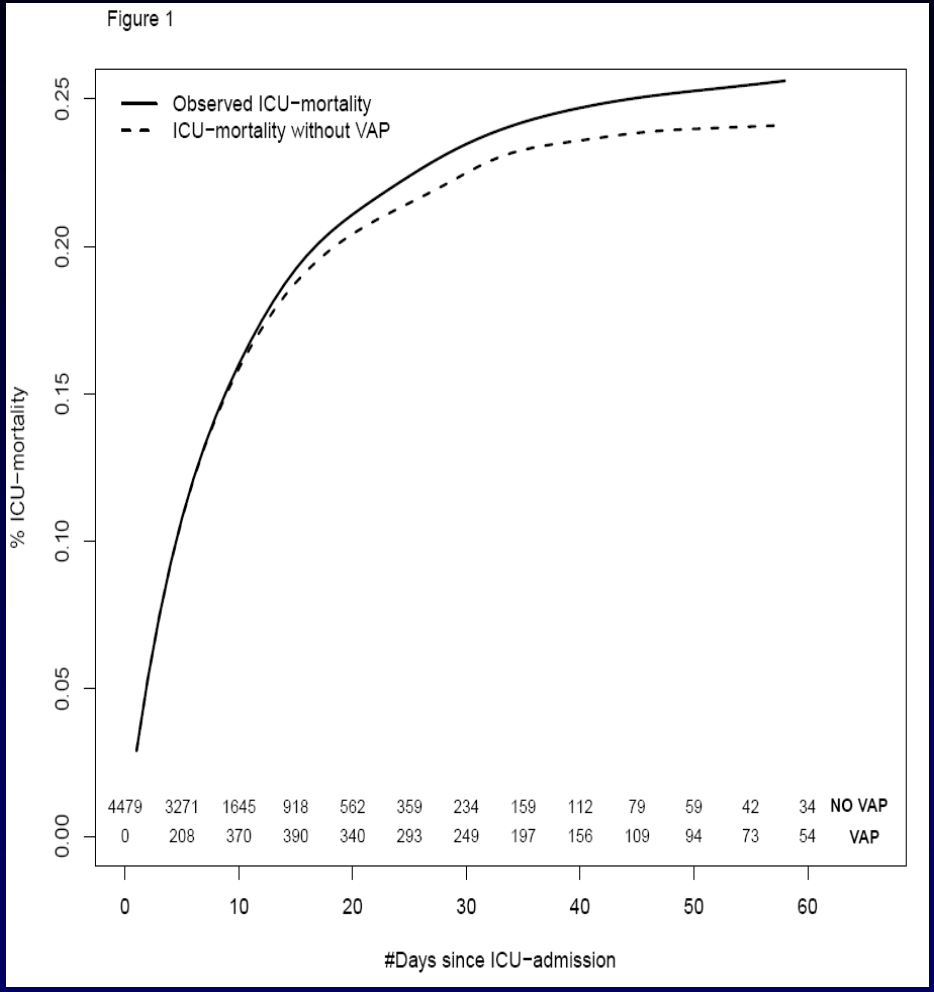
VAP: Cost

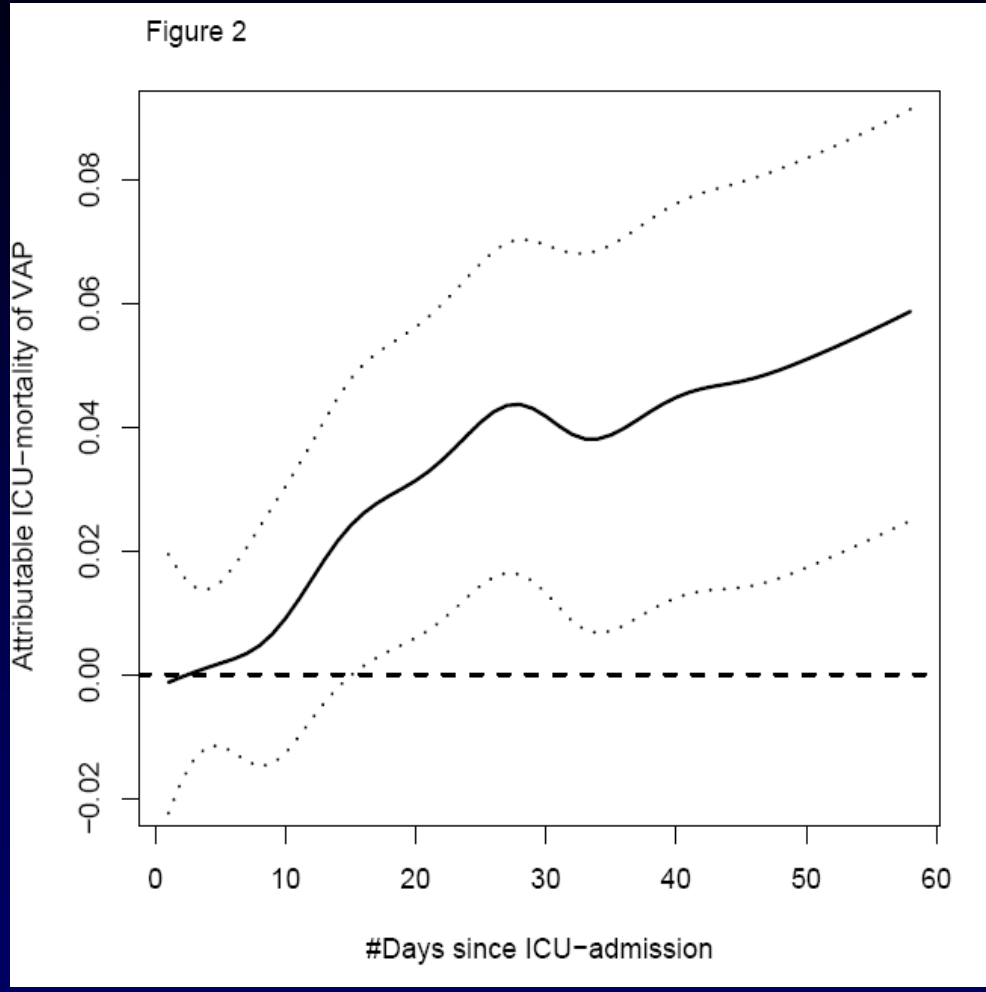
- Retrospective analysis
- Premier Database
- Patients with HAP and VAP
- Identified via novel algorithm
- n=8969
- 12% carbapenem resistant
- Resource use
  - Median cost per case: $65,000
  - Median hospital LOS: 22 days
  - VAP costs $30,000 more than HAP



Zilberberg MD, et al. Chest 2019: 4; 155: 1119-30.

Attributable Mortality by Causal Inference



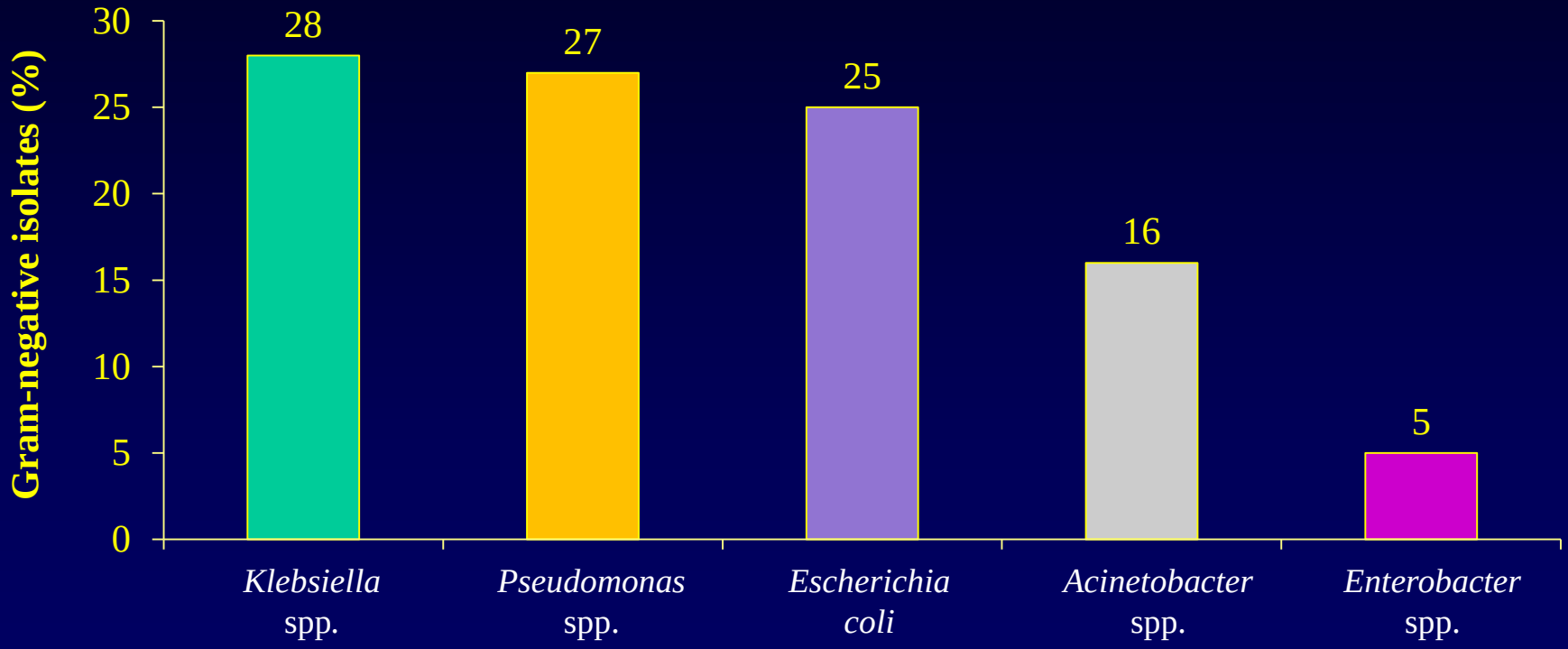


This was calculated as the difference between the observed ICU-mortality and the ICU-mortality that would have been observed for the same population if VAP were prevented for all.

Bekaert M, et al. Am J Respir Crit Care Med 2011;184:1133-1139.

Globally, Majority of ICU infections Are Due to Gram-negative Bacteria

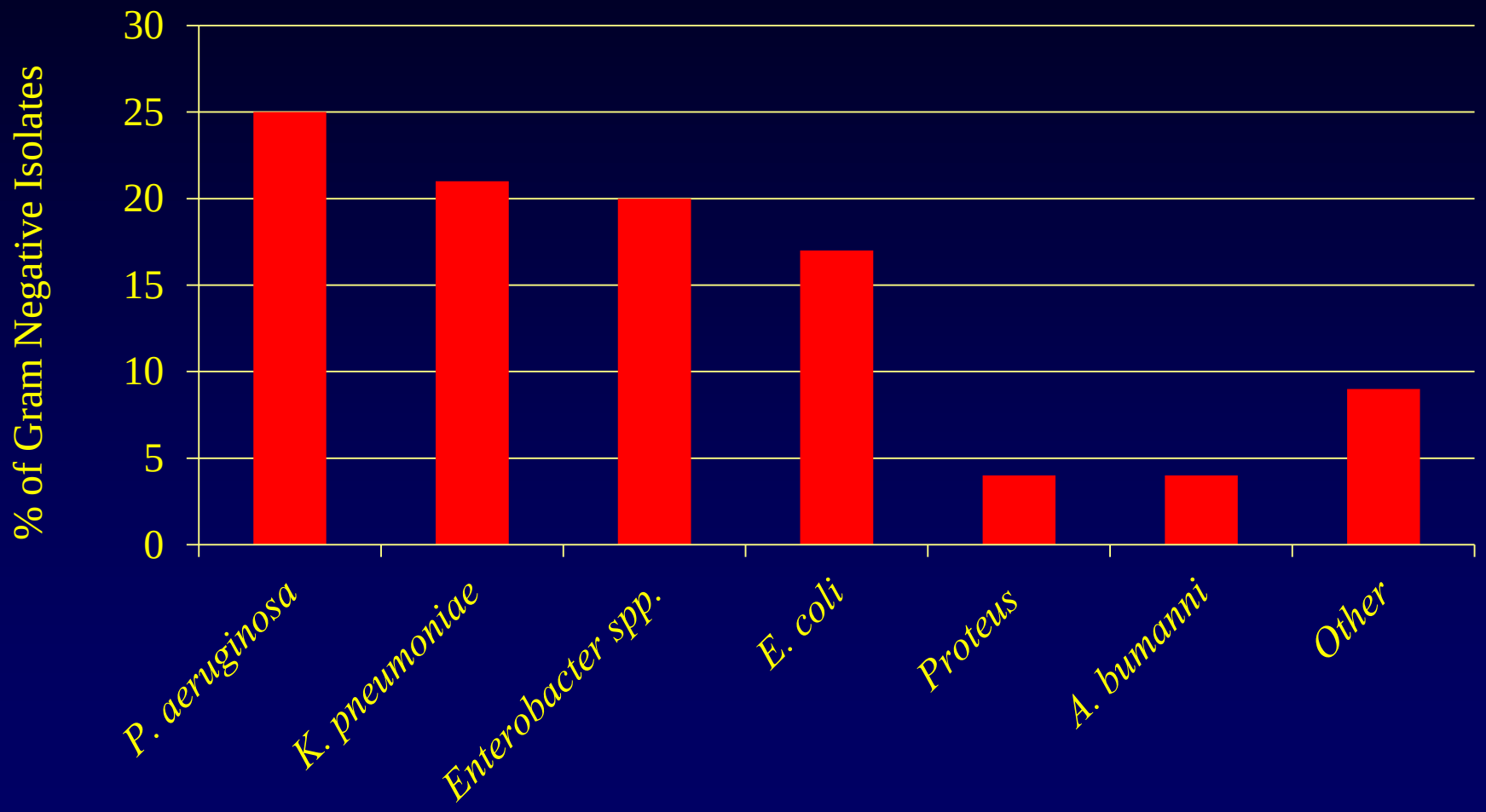
37% of GNR infections are MDR*



*50% of *Klebsiella* and 27% of *E. coli* are ESBL or CRE; 16% of *Pseudomonas* and 70% of *Acinetobacter* are Carbapenem resistant

Vincent JL, et al. JAMA 2020; 323: 1478-87.

HAP/ VAP Microbiology



Zilberberg MD, et al. Chest 20194; 155: 1119-30.

Diagnosis

- Clinical picture often confusing
- Differential diagnosis broad
- Role for invasive procedure controversial
- No diagnostic approach without problems

CPIS

TABLE 1

CPIS USED FOR THE DIAGNOSIS OF VA PNEUMONIA*

1. Temperature °C
   - ≥ 36.5 and ≤ 38.4 = 0 point
   - ≥ 38.5 and ≤ 38.9 = 1 point
   - ≥ 39 or ≤ 36.0 = 2 points
2. Blood leukocytes, mm^{-3}
   - ≥ 4,000 and ≤ 11,000 = 0 point
   - < 4,000 or > 11,000 = 1 point + band forms ≥ 500 = +1 point
3. Tracheal secretions
   - < 14+ of tracheal secretions = 0 point
   - ≥ 14+ of tracheal secretions = 1 point + purulent secretion = +1 point
4. Oxygenation: Pa_{O_2}/FI_{O_2}, mm Hg
   - > 240 or ARDS = 0 point
   - ≤ 240 and no evidence of ARDS = 2 points
5. Pulmonary radiography
   - No infiltrate = 0 point
   - Diffused (or patchy) infiltrate = 1 point
   - Localized infiltrate = 2 points
6. Culture of tracheal aspirate (semiquantitative: 0-1-2 or 3+)
   - Pathogenic bacteria cultured ≤ 1+ or no growth = 0 point
   - Pathogenic bacteria cultured > 1+ = 1 point + same pathogenic bacteria seen on the Gram stain > 1+ = +1 point

* Total points = CPIS (varies from 0 to 12 points).

CPIS

Table 7. Sensitivity and Specificity of the Clinical Pulmonary Infection Score to Diagnose Ventilator-Associated Pneumonia

Source	Clinical Pulmonary Infection Score	Gold Standard	Sensitivity, %	Specificity, %	LR (95% CI) Positive	LR (95% CI) Negative
Independent						
Papazian et al,[42] 1995	>6	Histology alone	72	85	4.8 (1.6-14)	0.33 (0.15-0.70)
Fàbregas et al,[45] 1999	>6	Histology and culture	77	42	1.3 (0.75-2.3)	0.55 (0.17-1.8)
Summary					2.1 (0.92-4.8)	0.38 (0.20-0.74)
Nonindependent						
Bregeon et al,[48] 2000	>6	Histology alone	93	85	6.0 (1.7-2.2)	0.08 (0.01-0.56)

Abbreviations: CI, confidence interval; LR, likelihood ratio.

Conclusions Routine bedside evaluation coupled with radiographic information provides suggestive but not definitive evidence that VAP is present or absent. Given the severity of VAP and the frequency of serious conditions that can mimic VAP, clinicians should be ready to consider additional tests that provide further evidence for VAP or that establish another diagnosis.

JAMA. 2007;297:1583-1593 www.jama.com

Klompas. JAMA 2007; 1583-93.

VAP: CDC Method vs. Clinical/Microbiologic

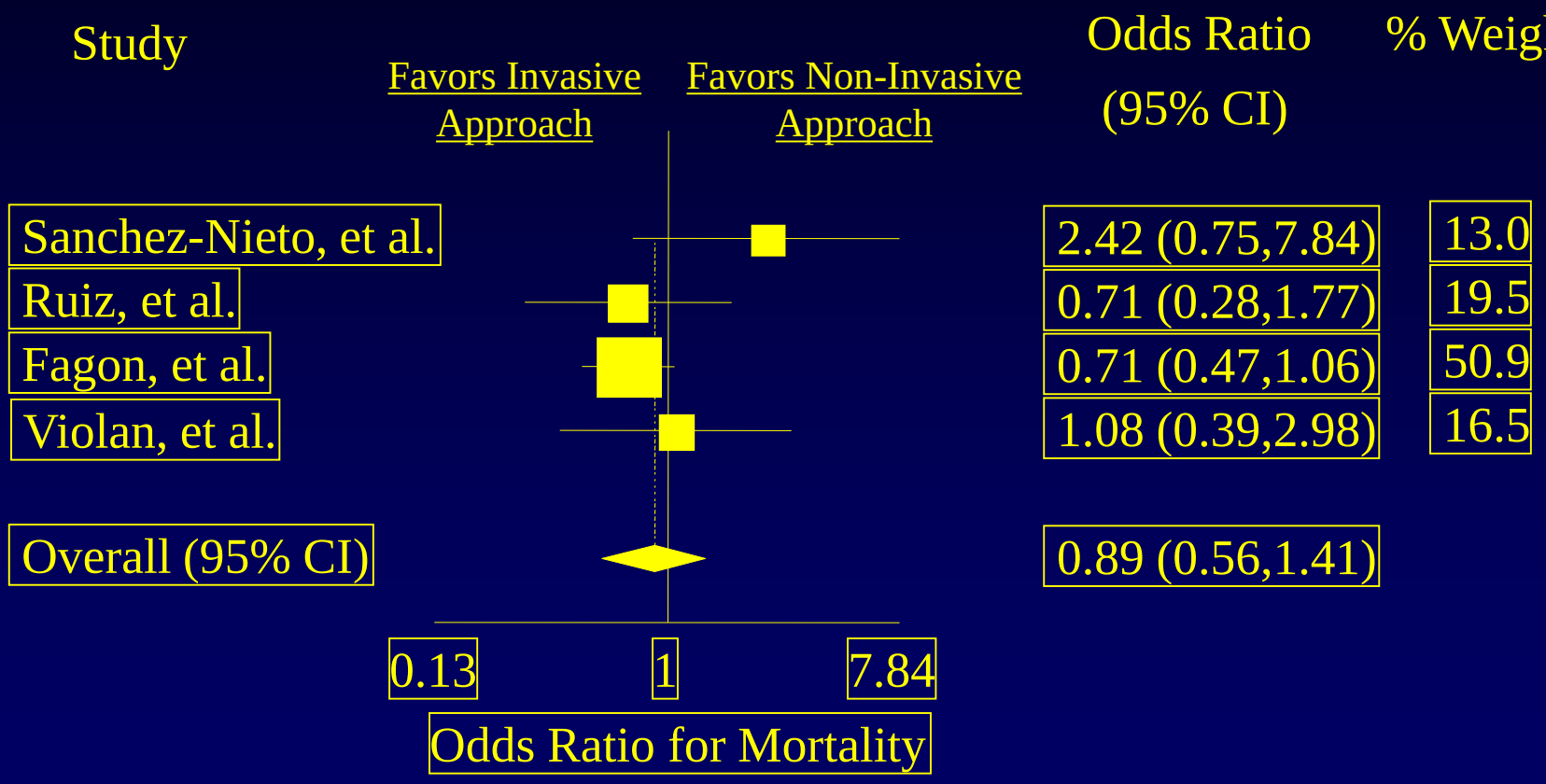
MICU & SICU 2010: n = 2060 ventilated patients

Method	VAP #	VAP Rate	Per 1000 days
Clinical	**83**	**4%**	**8.5**
CDC	**12**	**0.6%**	**1.2**

- The 12 patients meeting NHSN criteria were all identified in the clinical group.
- Agreement of the two sets of criteria was marginal (κ statistic, 0.26).

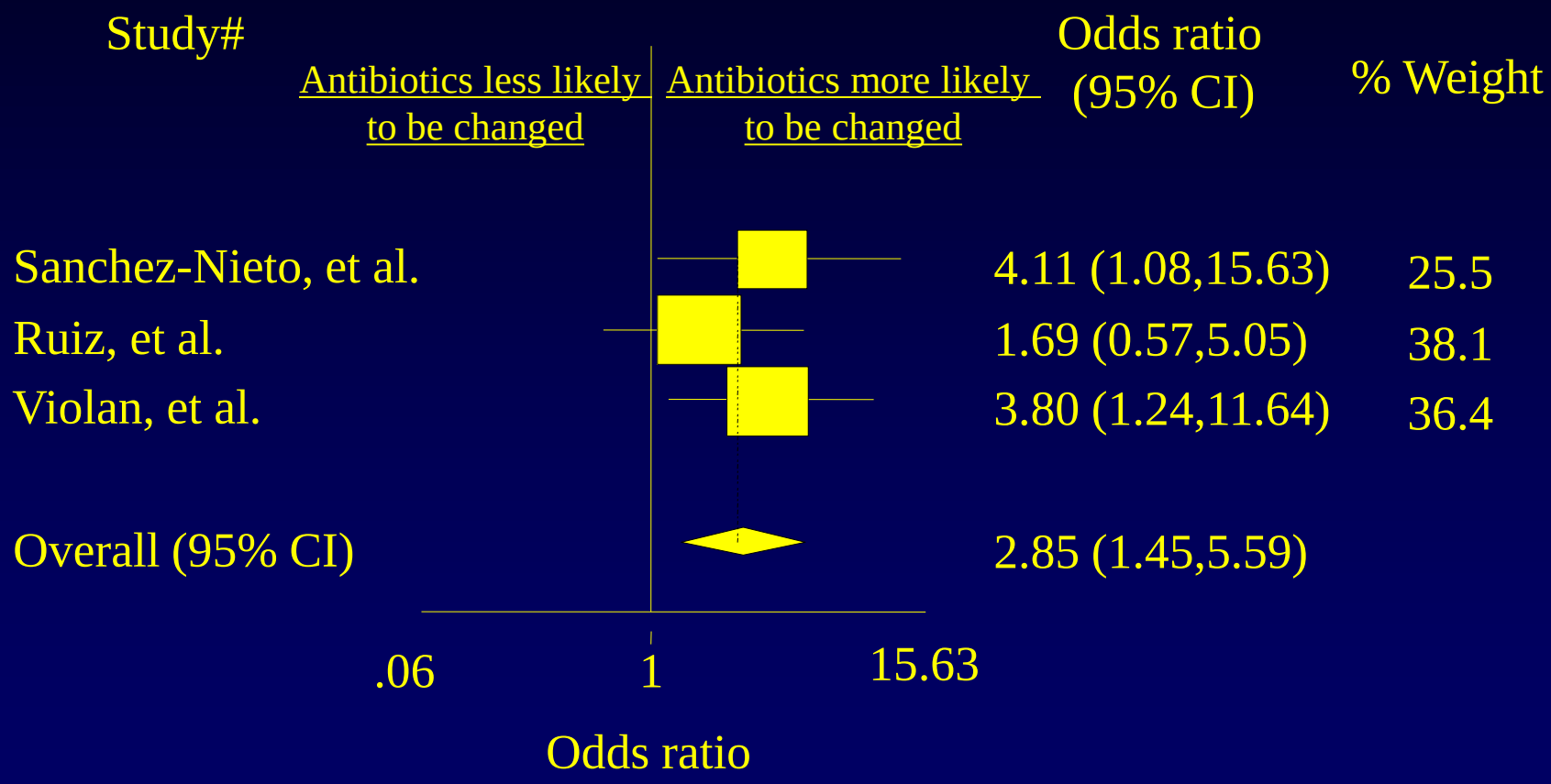
Skrupky L, et al. Crit Care Med 2011 Sep 15.

Meta-analysis of Invasive Strategies for the Diagnosis of Ventilator-Associated Pneumonia & their Impact on Mortality*



*Random effects model; Test of heterogeneity p=0.247, for Odds ratio p=0.620

Meta-analysis of the Impact of Invasive Strategies for the Diagnosis of Ventilator-Associated Pneumonia on Changes in Antibiotic Management*

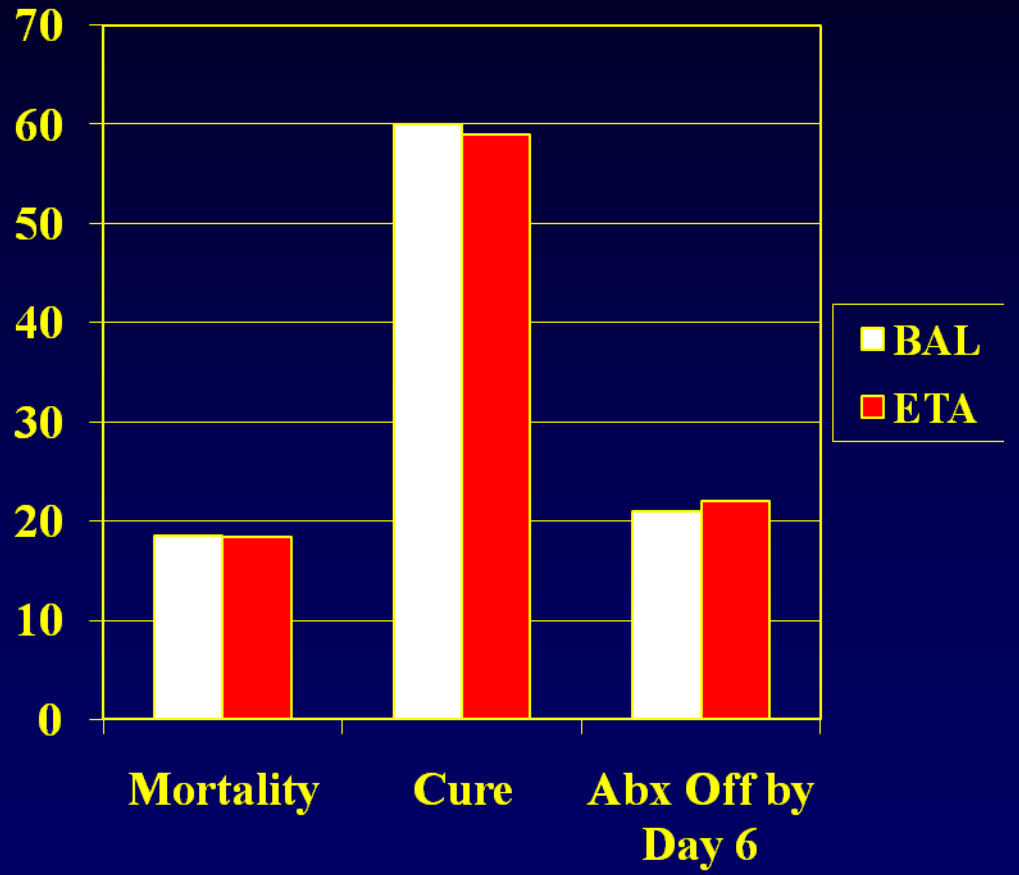


*Random effects model; Test of heterogeneity p=0.493, for Odds ratio p=0.002

#Fagon, et al. did not report how frequently invasive testing altered antibiotic management

VAP Diagnosis

- RCT
- Subjects:
  - Pt's at risk for VAP
  - Mean duration of MV prior to enrollment: 7
- N= 739
- Interventions
  - LRT cult vs. trach asp
  - Mono vs dual tx for GNR



CCTG. NEJM 2006: 355: 2619-30.

VAP Diagnosis

- Limitation of CCTG study
  - Excluded patients likely to have high-risk organisms
  - Fewer than 2% MRSA and 6% P. aeruginosa
  - De-escalation formalized
  - Study nurse reminded investigators to alter/stop abx
- Overall, study's generalizability to US ICUs limited

Pathogenesis of HAP and VAP

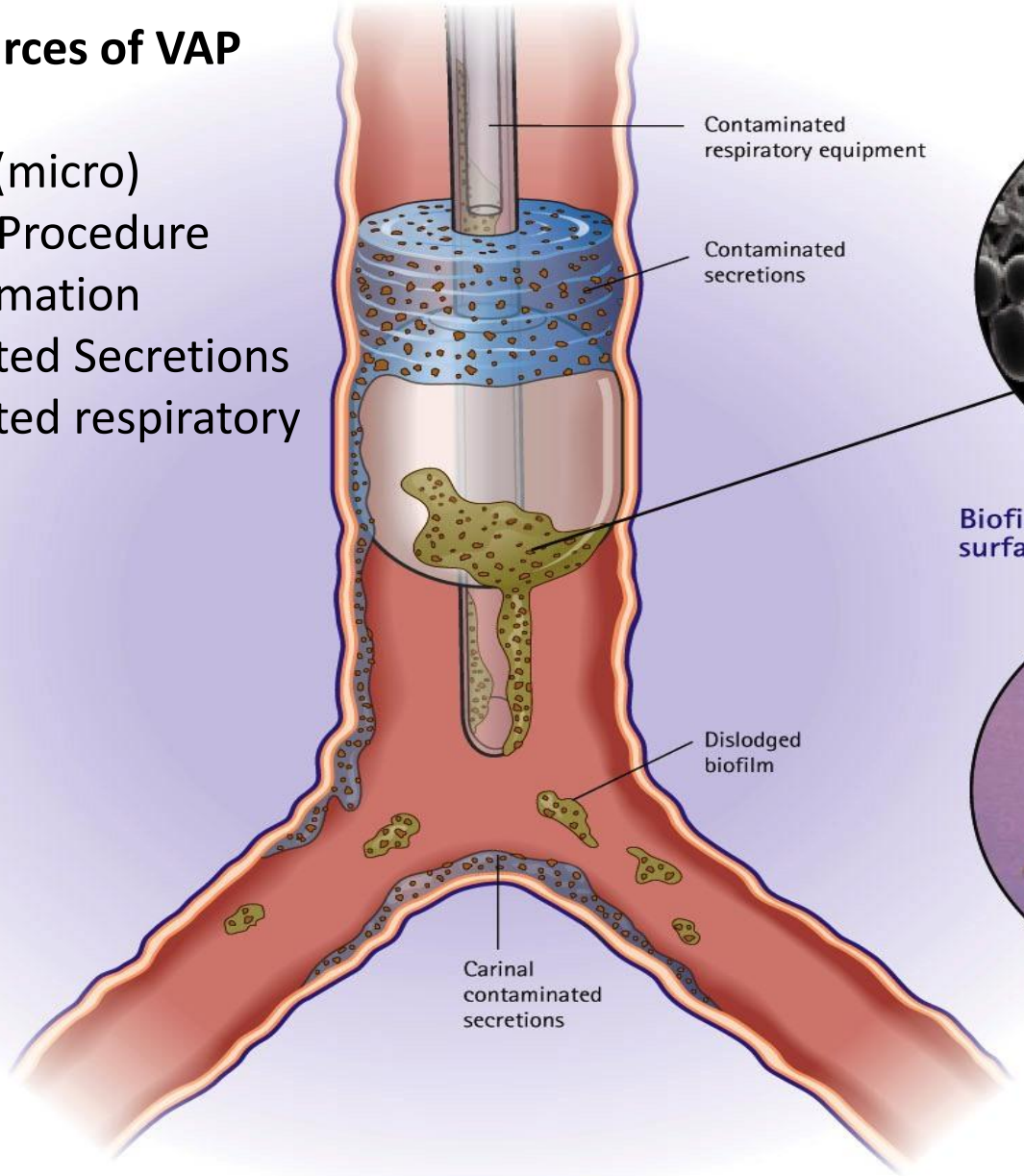
Usually requires that two important processes take place:

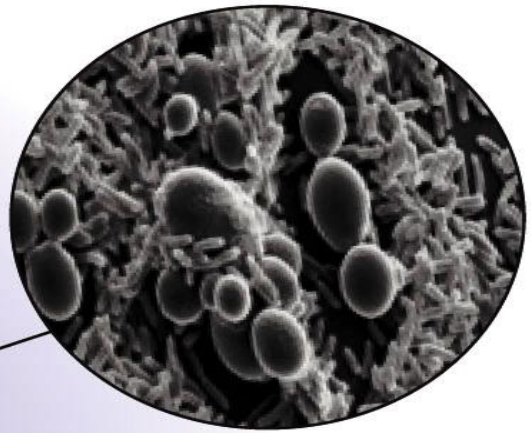
1. **Bacterial colonization** of the aerodigestive tract
2. **Aspiration** of contaminated secretions into the lower airway

VAP Pathogenesis

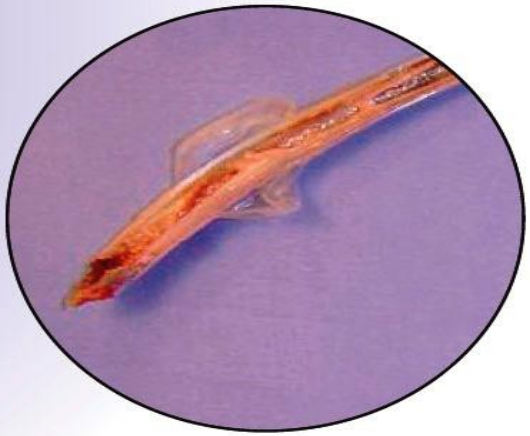
Common Sources of VAP Pathogens:

- ❑ Aspiration (micro)
- ❑ Intubation Procedure
- ❑ Biofilm Formation
- ❑ Contaminated Secretions
- ❑ Contaminated respiratory equipment





Biofilm formation on inner and outer surface of the endotracheal (ET) tube

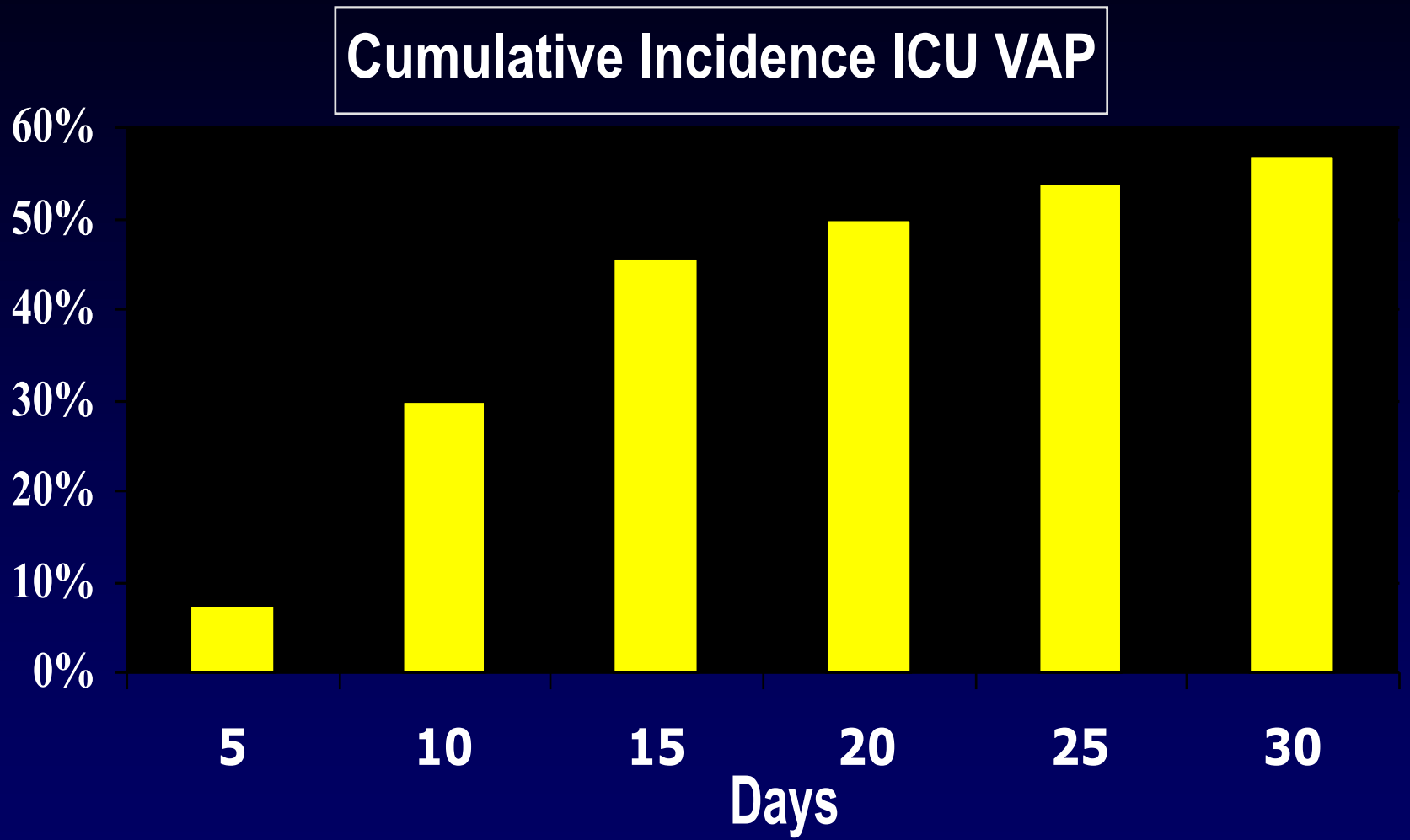


ET tube upon extubation

VAP: Increased Risk

- Intubation
  - Organisms carried from the oropharynx into the trachea
  - Bacteria aggregate on surface of tube over time and form a biofilm that protects from host defenses
  - Bacterial aggregates become dislodged by ventilator flow/suctioning and embolize into the lower respiratory tract
  - Leakage around the cuff allows pooled secretions to enter the trachea
- **Mechanical ventilation increases the risk of nosocomial pneumonia by 6-21 fold**

VAP: Time Course



PPIs and VAP

- PPIs affect gut pH more so than H2 blockers
- No evidence PPIs more effective at prevention of stress ulcer bleeding
- PPIs widely employed in US ICUs
  - Associated with increasing rates of *C. difficile*

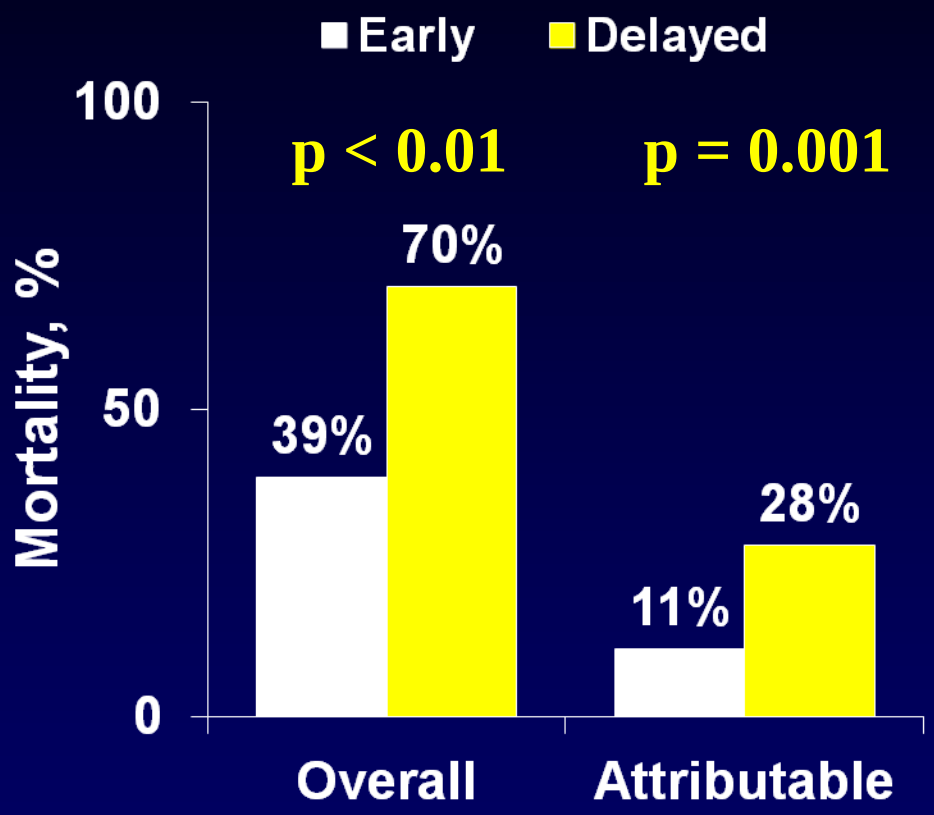
Table 4. Rates of Hospital-Acquired Pneumonia According to Type of Acid-Suppressive Medication

	Acid-Suppressive Medication	No Acid-Suppressive Medication	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
		Proton-Pump Inhibitors[a]		
Total admissions, No.	25374	30956	56330	56330
Hospital-acquired pneumonia, No. (%)	1340 (5.3)	610 (2.0)	2.8 (2.5-3.1)	1.3 (1.1-1.4)[b]
		$Histamine_2$ Receptor Antagonists[c]		
Total admissions, No.	5686	30956	36642	36642
Hospital-acquired pneumonia, No. (%)	176 (3.1)	610 (2.0)	1.6 (1.3-1.9)	1.2 (0.98-1.4)[b]

Herzig SJ, et al. JAMA 2009; 301: 2120-8.

Early Appropriate Therapy is Critical in NP

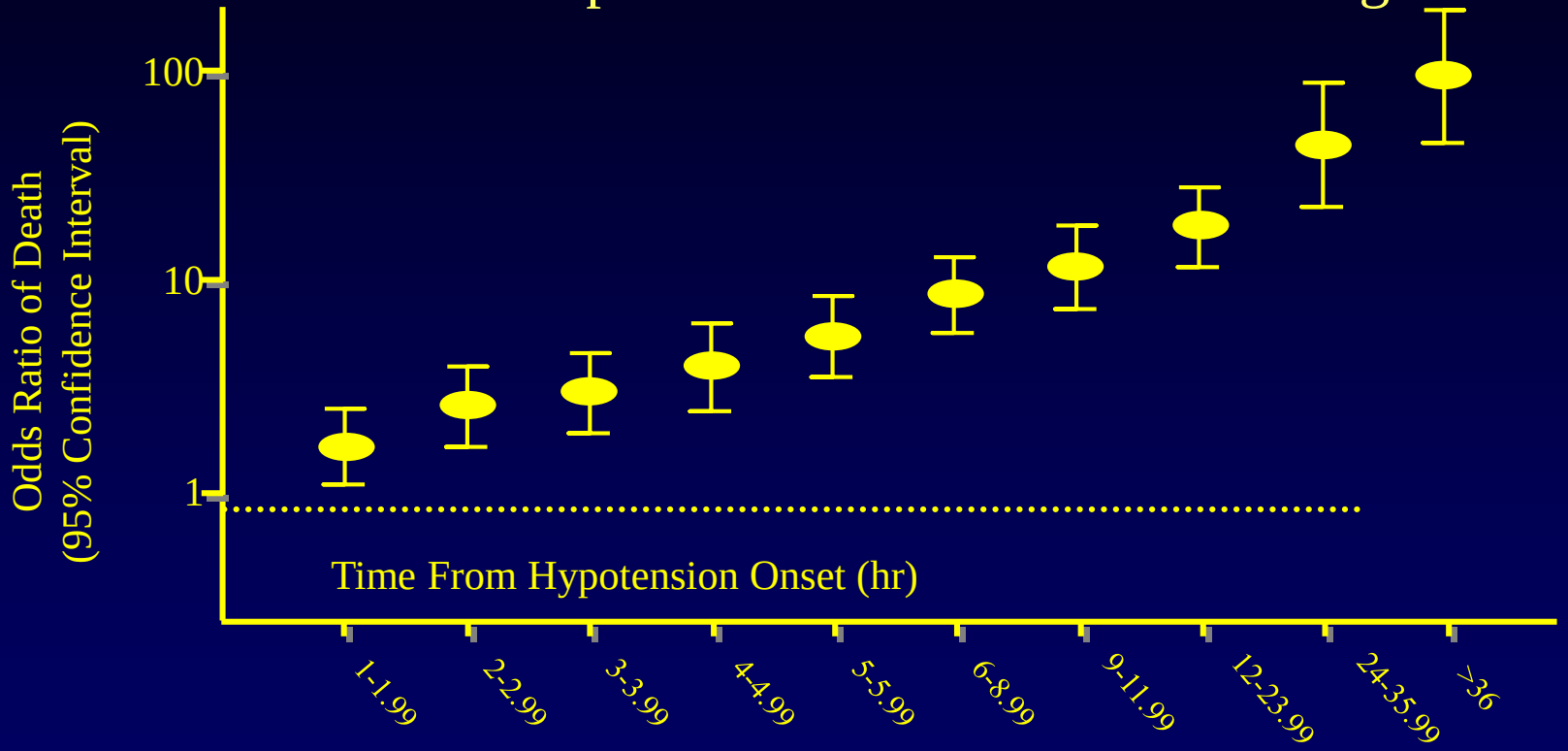
- 107 patients with VAP
- Mean time from diagnosis of VAP to initiation of appropriate therapy was 28.6 hr in delayed group vs. 12.5 hr in early group



Iregui M, et al. Chest 2002;122:262-268.

Appropriate Initial Therapy

- An earlier study of septic shock (n = 2,731) explicitly demonstrated the importance of antimicrobial timing



- Every hour's delay until appropriate therapy resulted in a 12% increase in mortality
- Compared with starting appropriate therapy within 1 hour of the onset of hypotension, the OR for mortality increased from 1.67 in Hour 2 to 92.54 with delays >36 hours

Kumar A, et al. Crit Care Med. 2006;34:1589-1596.

Duration of Therapy

- Prospective RCT
- 51 French ICUs
- N=401
- Bronchoscopically confirmed VAP
- Randomized to
  - 8 days of abx
  - 15 days of abx
- Repeat BAL if recurrence (superinfection or relapse) suspected

- Mean SOFA: 7.3
- Mean duration of MV before VAP: 13.6 days
- 7% bacteremic
- Approximately 1/3rd in shock
- More than 25% of isolates S. aureus
- If patient given inappropriate antibiotics, excluded from trial

Chastre J, et al. JAMA 2003: 290: 2588-98.

Short Course Therapy

	8-Day Regimen	15-Day Regimen	Difference (95% CI)
All cause mortality	18.8%	17.2%	1.6% (-3.7 to 6.9)
All cause mortality (MRSA)	28.6%	23.8%	-6.7% (-17.5 to 4.1)
Recurrence (All)	28.9%	26.0%	2.9% (-3.2 to 9.1)
Recurrence (NF GNRs)	40.6%	25.4%	15.2% (3.9 to 26.6)
Abx Free days	13.1±7.4	8.7 ±5.2	4.4 (3.1 to 5.6)
ICU LOS, days	30.0±20.0	27.5 ±17.5	2.5 (-0.7 to 5.2)

Management Strategies and Evidence-based Treatment Recommendations: New 2016 ATS/IDSA Guidelines

Changes to the Guidelines

- Generally recommend shorter courses of therapy
- Continue emphasis on need to prevent under-treatment but must balance against concerns about promoting resistance
- Elimination of concept of HCAP
  - New concept: Community-onset pneumonia with risk factors for resistance

Guiding Principles of the ATS/IDSA Guidelines: 2005 vs 2016

2005

"…selection of initial appropriate antibiotic therapy (ie, getting the antibiotic treatment right the first time) is an important aspect of care for hospitalized patients with serious infections."

2016

" …..resistant pathogens lead to a significant risk of inadequate initial empiric antibiotic therapy, which is associated with an increased risk of mortality…"

NP, nosocomial pneumonia.

ATS/IDSA. *Am J Respir Crit Care Med*. 2005;171(4):388-416. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. CID. 2016; 63 (5): e61-111.

Common Principles Between 2005 and 2016

- Strive to avoid untreated or inadequately treated NP
  - Inappropriate or delayed therapy is associated with higher mortality
- Take local microbiologic data into account when determining appropriate treatment regimens – strong recommendation for reliance on local antibiograms
- Avoid overuse of antibiotics
  - Focus on accurate diagnosis – always culture to include blood cultures
  - Tailor therapy to culture results
  - Keep course of therapy to a minimum effective period

New Emphasis in 2016

- Recognize need to prevent resistance
  - It is imperative "to balance the need for effective initial antibiotic therapy against the risks of excessive antibiotic use." (p. e57 2016 Guidelines)
- Shorter courses of therapy
  - "For patients with VAP, we recommend a ***7-day*** course of antimicrobial therapy rather than a longer duration (strong recommendation, moderate-quality evidence)." p. e58 2016 Guidelines)

Treatment Recommendation for VAP

Table 3. Suggested Empiric Treatment Options for Clinically Suspected Ventilator-Associated Pneumonia in Units Where Empiric Methicillin-Resistant *Staphylococcus aureus* Coverage and Double Antipseudomonal/Gram-Negative Coverage Are Appropriate

A. Gram-Positive Antibiotics With MRSA Activity	B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam–Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Glycopeptides[a] Vancomycin 15 mg/kg IV q8–12h (consider a loading dose of 25–30 mg/kg × 1 for severe illness)	Antipseudomonal penicillins[b] Piperacillin-tazobactam 4.5 g IV q6h[b]	Fluoroquinolones Ciprofloxacin 400 mg IV q8h Levofloxacin 750 mg IV q24h
OR	OR	OR
Oxazolidinones Linezolid 600 mg IV q12h	Cephalosporins[b] Cefepime 2 g IV q8h Ceftazidime 2 g IV q8h	Aminoglycosides[a,c] Amikacin 15–20 mg/kg IV q24h Gentamicin 5–7 mg/kg IV q24h Tobramycin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems[b] Imipenem 500 mg IV q6h[d] Meropenem 1 g IV q8h	Polymyxins[a,e] Colistin 5 mg/kg IV × 1 (loading dose) followed by 2.5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135] Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams[f] Aztreonam 2 g IV q8h	

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. CID. 2016; 63 (5): e61-111.

European Guidelines

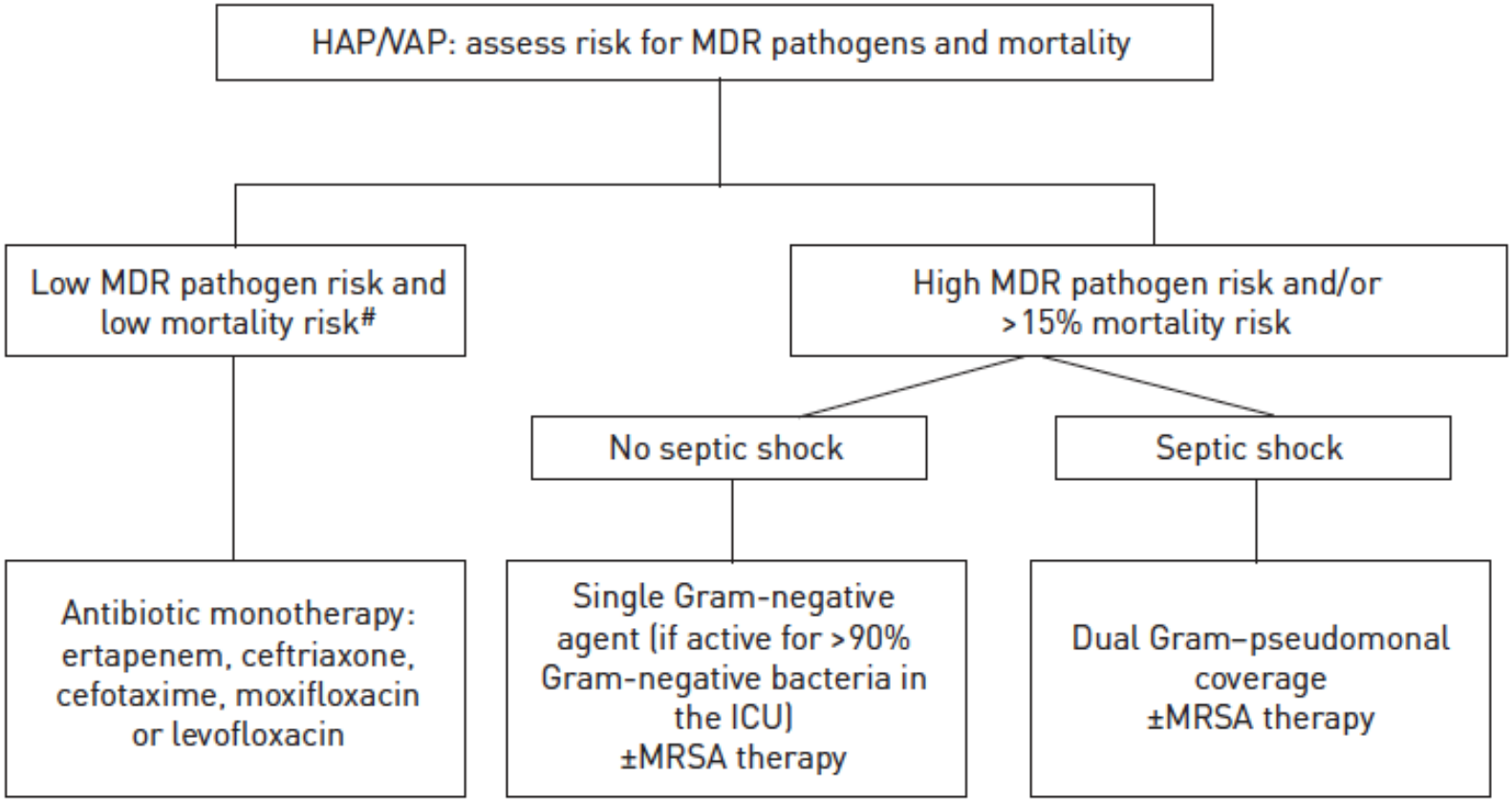


FIGURE 2 Empiric antibiotic treatment algorithm for hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP). MDR: multidrug-resistant; ICU: intensive care unit; MRSA: methicillin-resistant *Staphylococcus aureus*. #: low risk for mortality is defined as a ⩽15% chance of dying, a mortality rate that has been associated with better outcome using monotherapy than combination therapy when treating serious infection [80].

ERJ 2017; 50: 1700582.

European Guidelines

We recommend broad-spectrum empiric antibiotic therapy targeting *P. aeruginosa* and extended-spectrum β-lactamase (ESBL)-producing organisms, and, in settings with a high prevalence of *Acinetobacter* spp., in patients with suspected early-onset HAP/VAP who are in septic shock, in patients who are in hospitals with a high background rate of resistant pathogens present in local microbiological data and in patients with other (nonclassic) risk factors for MDR pathogens (see Question 3). (Strong recommendation, low quality of evidence.)

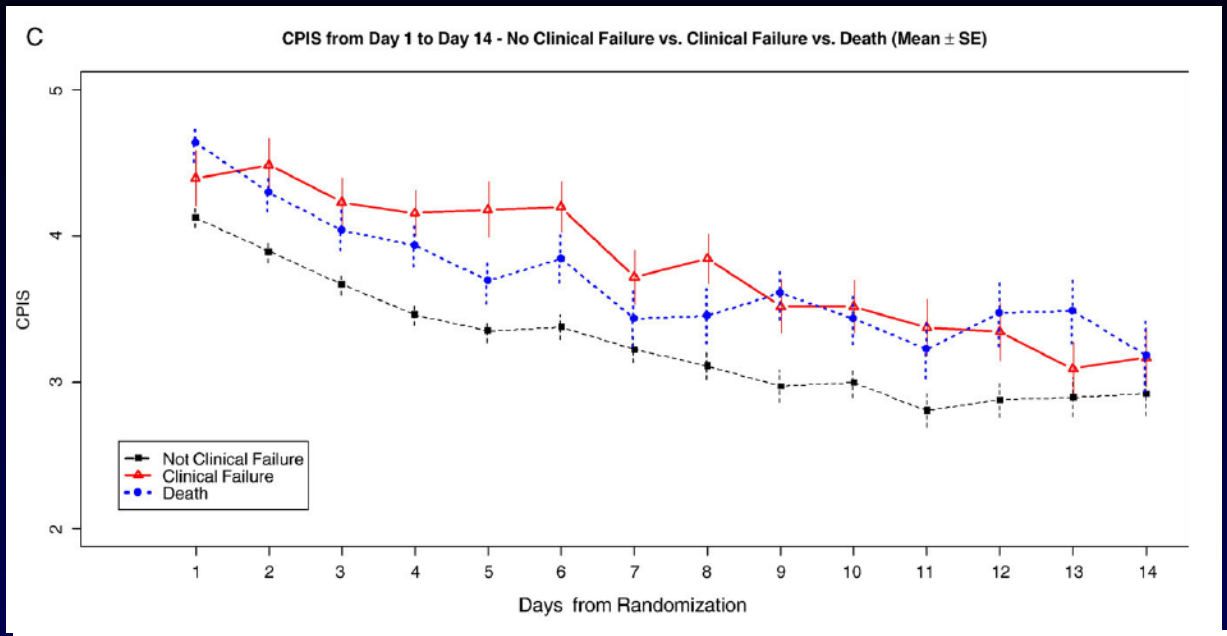
The panel believes that tailoring antibiotic therapy to the susceptibility data of the aetiological pathogen once microbiological and clinical response data become available (day 3) represents good practice. (Good practice statement.)

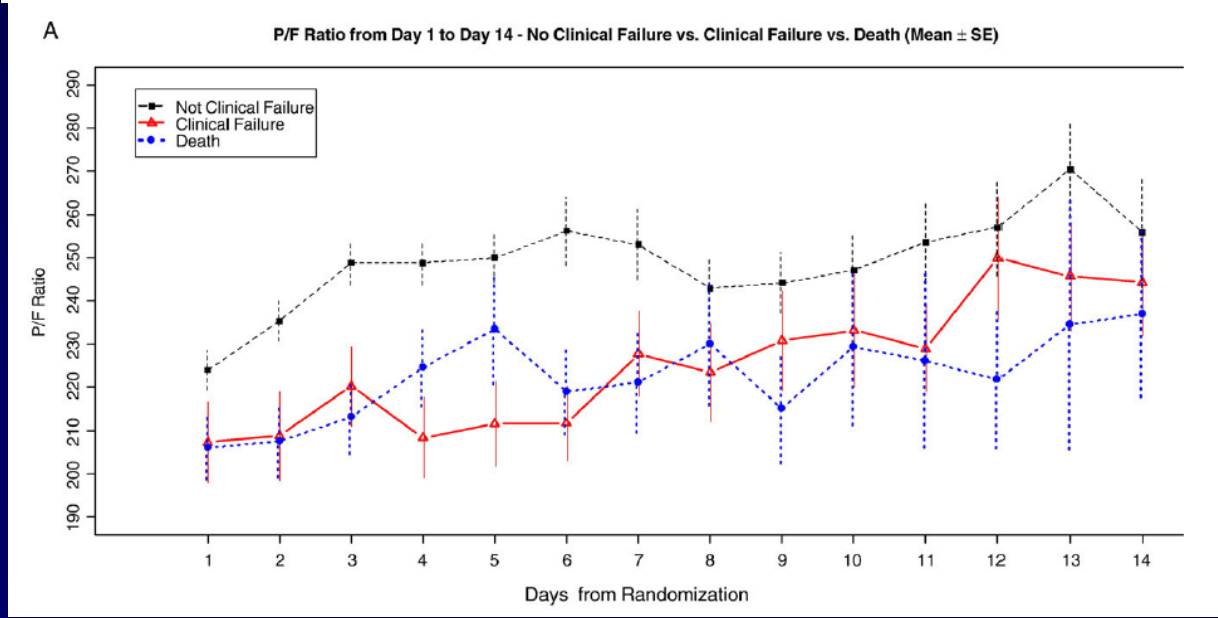
ERJ 2017; 50: 1700582.

CPIS vs P/F Ratio

-Secondary analysis of large, prospective RCT n=563)
-Serial evaluation of CPIS and its components

Changes in P/F ratio drive CPIS changes





Shorr AF, et al. JCC 2008; 23: 64-73.

Lack of Improvement in P/F Represents Early Predictor of Clinical Failure

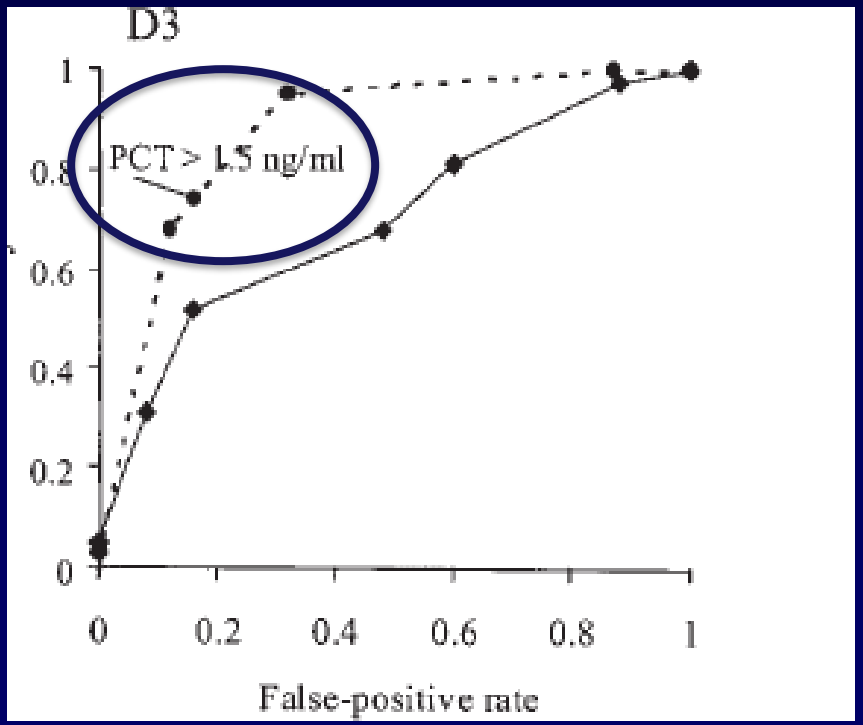
Table 3 Independent factors associated with clinical failure

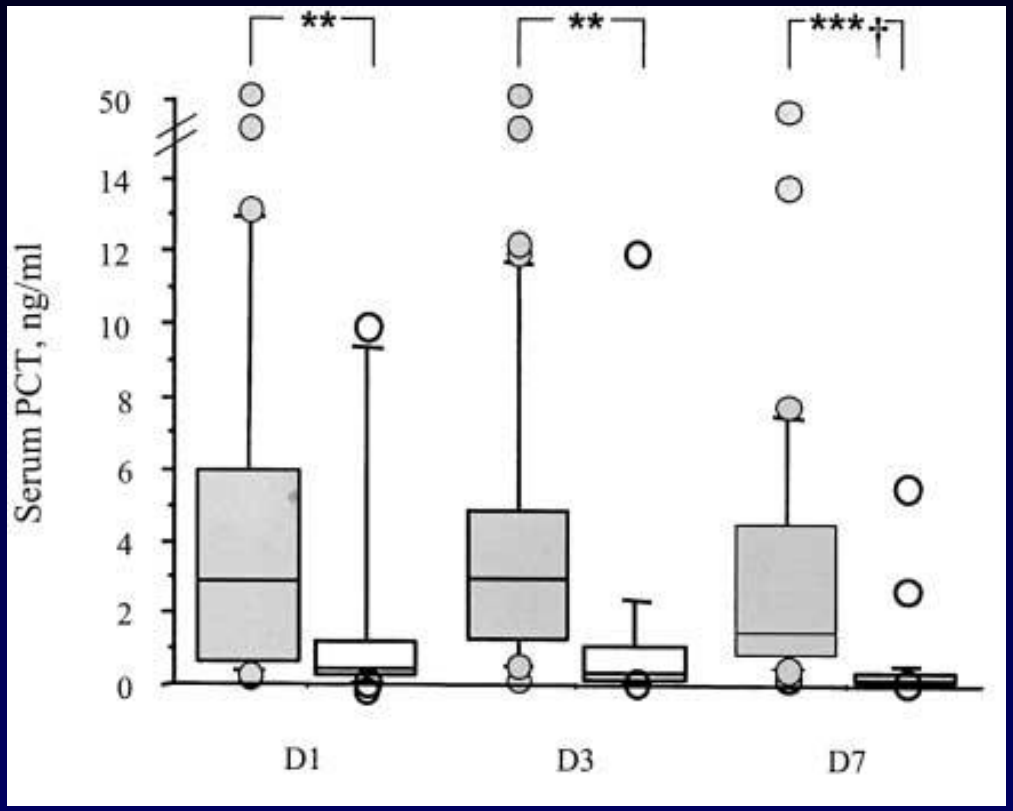
Variable	OR (95% CI)	*P*
Failure to improve between enrollment and day 3		
In temperature (yes vs no)	1.65 (0.98-2.76)	.06
In vasopressor (yes vs no)	1.55 (0.83-2.91)	.17
In Pa_{O_2}/F_{IO_2} ratio (yes vs no)	1.71 (1.04-2.81)	.04
In purulence of endotracheal secretions (yes vs no)	0.62 (0.33-1.16)	.13
Time from VAP suspicion to the start of study drug	1.00 (0.99-1.02)	.64

Shorr AF, et al. JCC 2008; 23: 64-73.

PCT

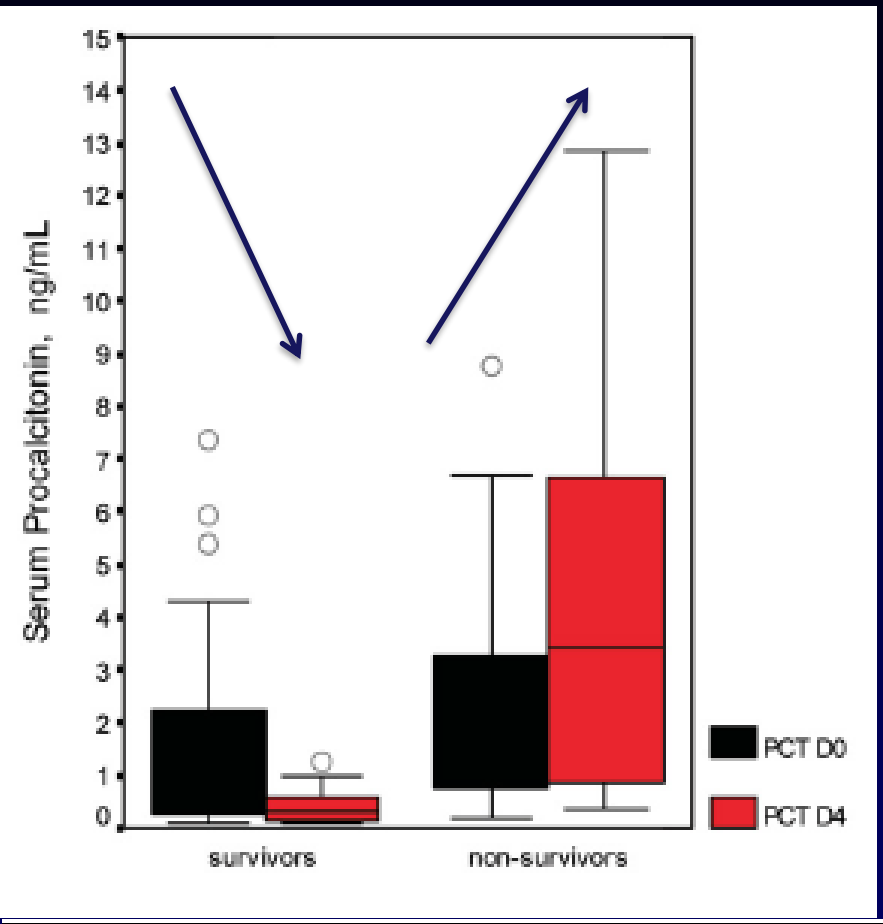
- Prospective, observational n=63
- Subjects: VAP
- PCT kinetics
- Endpoint: Unfavorable response





Luyt CE, et al. AJRCCM 2005; 171: 48-53.

PCT Kinetics

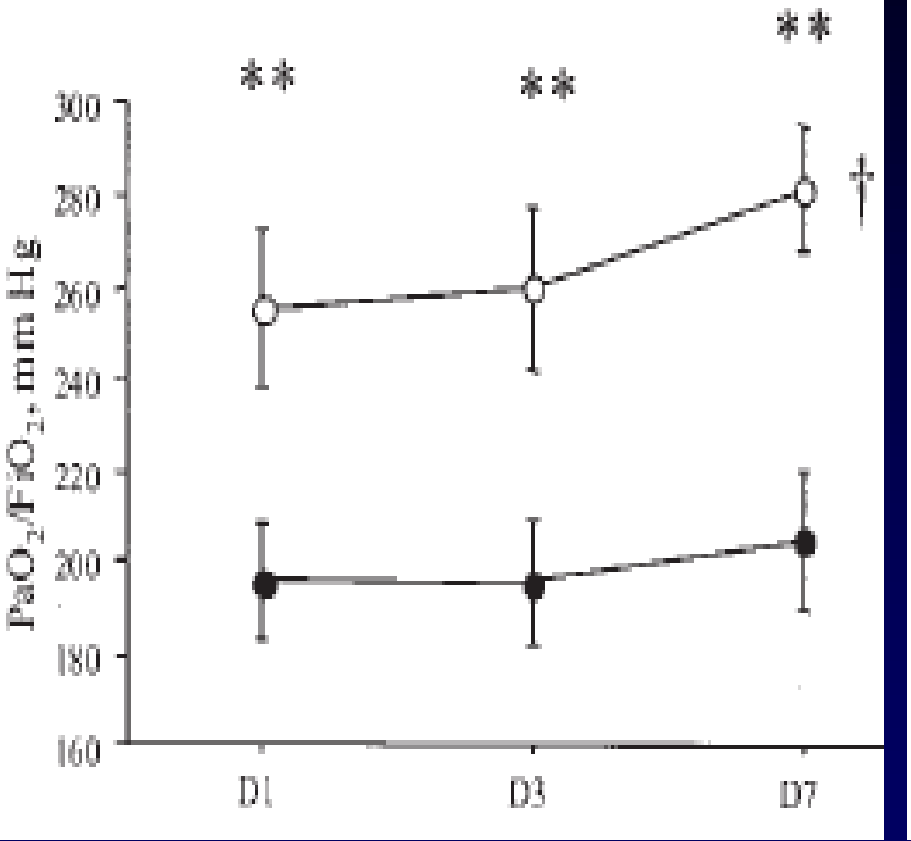


- Prospective, observational study
- All subjects with VAP
- n=75
- Endpoint: Mortality
- Serial, daily PCT measurements

Parameter	Survivors ($n = 45$)	Non-survivors ($n = 23$)	p
Procalcitonin D0	0.58 (0.08–19.60)	2.18 (0.19–21.33)	0.003
Procalcitonin D4	0.30 (0.08–36.19)	3.44 (0.39–17.00)	<0.001

Seligman R, et al. Crit Care 2006: 10; R125.

Clinical vs Biomarker: Does it Matter?



Factors Associated with Outcome	OR	95% CI	p Value
Day 1*			
Pa_{O_2}/Fi_{O_2} < 215 mm Hg	3.6	1.1–12.1	0.04
Procalcitonin > 1 ng/ml	12.3	2.4–62.2	0.002
Day 3†			
Pa_{O_2}/Fi_{O_2} < 210 mm Hg	25.9	3.9–173.2	0.0008
Procalcitonin > 1.5 ng/ml	24.6	4.6–122.3	< 0.0001
Day 7‡			
Pa_{O_2}/Fi_{O_2} < 235 mm Hg	6.4	1.1–37.9	0.04
Procalcitonin > 0.5 ng/ml	64.2	11.1–375.5	< 0.0001

Luyt CE, et al. AJRCCM 2005; 171: 48-53.

Considerations When Switching

- What pathogens might I have missed?
  - Local resistance?
  - Polymicrobial infection?
- Am I giving a drug with reliable pharmacokinetics?
  - Consider issues with dosing for augmented renal clearance, tissue penetration, etc?
- Is there a pleural complication (undrained abcess)?

Conclusions

- HAP and VAP remain associated with substantial morbidity
- Pattern seen globally
- Inappropriate therapy
- Many controversies remain but evidence improving