Weill Cornell Medicine

Surveillance Cultures to Guide VAP Therapy

- Michael S. Niederman , M.D.
- Professor of Clinical Medicine

  Weill Cornell Medical College

- Clinical Director and Associate Chief

  Division of Pulmonary and Critical Care Medicine

  New York Presbyterian Hospital-

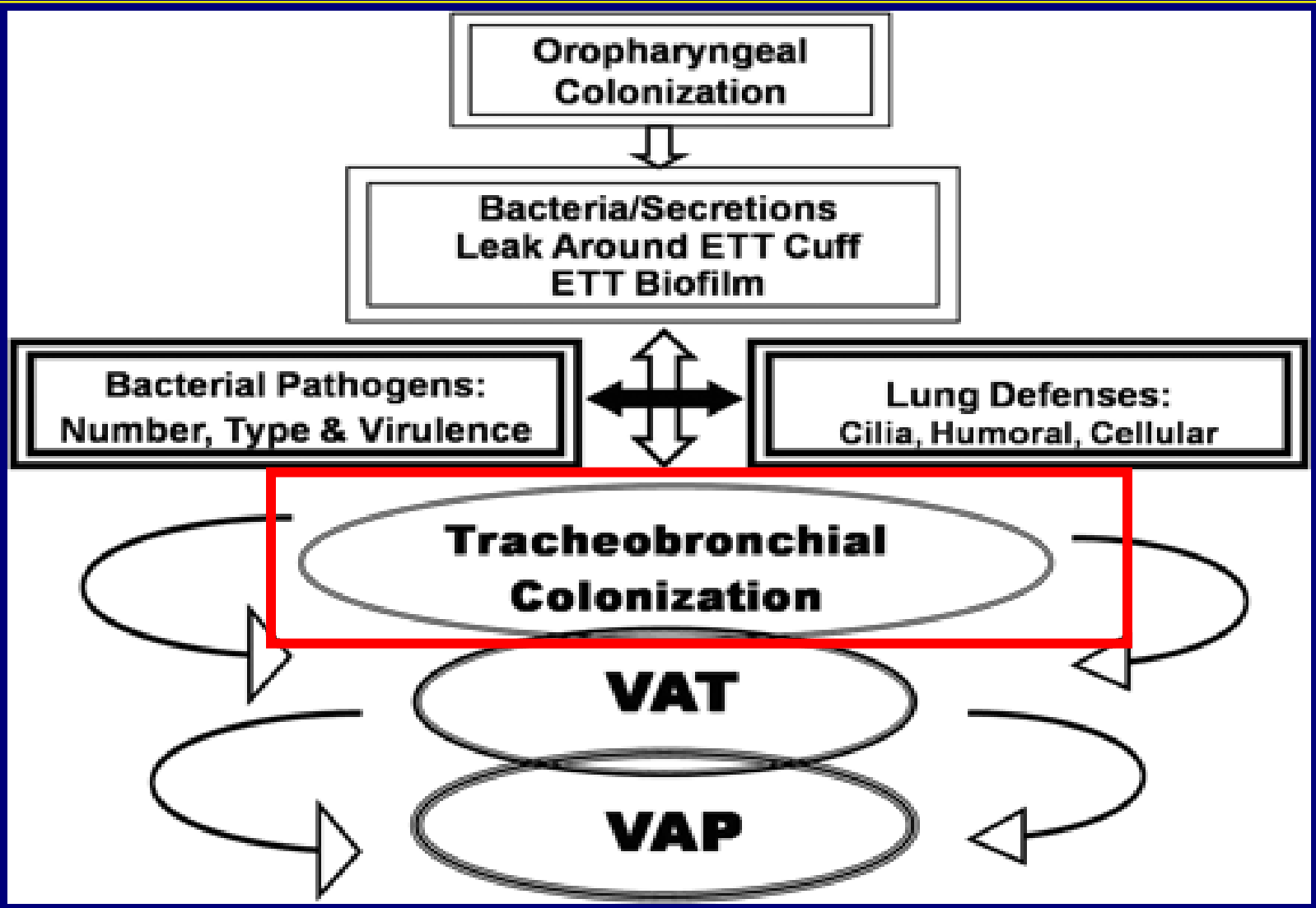
  Weill Cornell Medical Center

- msn9004@med.cornell.edu

FINANCIAL DISCLOSURE

- Dr. Niederman has no disclosures relevant to this lecture

VAP Pathogenesis: Surveillance to Detect Colonization



Is Surveillance Useful to Guide Empiric VAP Therapy?

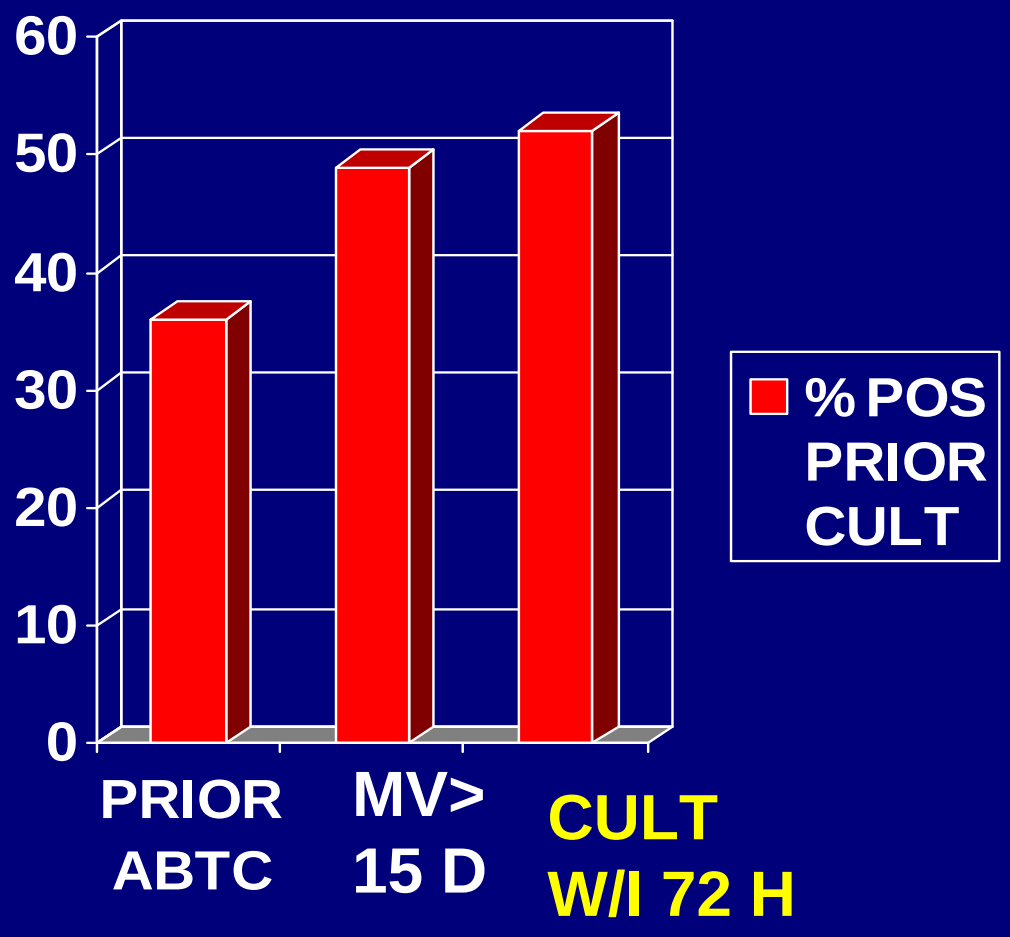
- Studies of surveillance culture and their role in accurate empiric antibiotic choice in VAP
- Can surveillance guide the recognition of VAT and when to START therapy?
- How do rapid diagnostic methods affect this paradigm?
  - MRSA nasal swabs
  - Rapid testing at time of clinical VAP diagnosis
- ICU vs. individual microbiologic surveillance

Is Surveillance Useful to Guide Empiric VAP Therapy?

- Studies of surveillance culture and their role in accurate empiric antibiotic choice in VAP
- Can surveillance guide the recognition of VAT and when to START therapy?
- How do rapid diagnostic methods affect this paradigm?
  - MRSA nasal swabs
  - Rapid testing at time of clinical VAP diagnosis
- ICU vs. individual microbiologic surveillance

SURVEILLANCE CULTURES IN THE ICU: VAP ORGANISMS AND PRIOR CULTURES

- Compare VAP organisms (bronch) with prior cults in 125 episodes (91 patients)
- 220 organisms: 73 in prior cults (53 respiratory)
- 342 organisms in cults and NOT bronch
- 36/102 with prior resp cults (mean 8 days before) had all pneumonia organisms identified
- For MRSA and P. aeruginosa, high Neg pred value of prior cults
- Hayon et al: AJRCCM 2002; 165: 41.



Use of Surveillance EA Cultures To Guide Empiric Therapy of VAP

- 299 MV patients for ≥ 48 hours with twice weekly EA's
- 75 had BAL, 41 with VAP dx by BAL
  - EA taken just before VAP with same organisms (at > 10^3/ml) and susceptibility in 34 (83%)
  - 95% got adequate rx based on EA results
  - 18 patients (45%) with broad spectrum B-lactam rx per EA vs. 76% with Trouillet guideline (p=0.01), 95% with ATS guideline
- Michel et al: Chest 2005; 127; 589-597

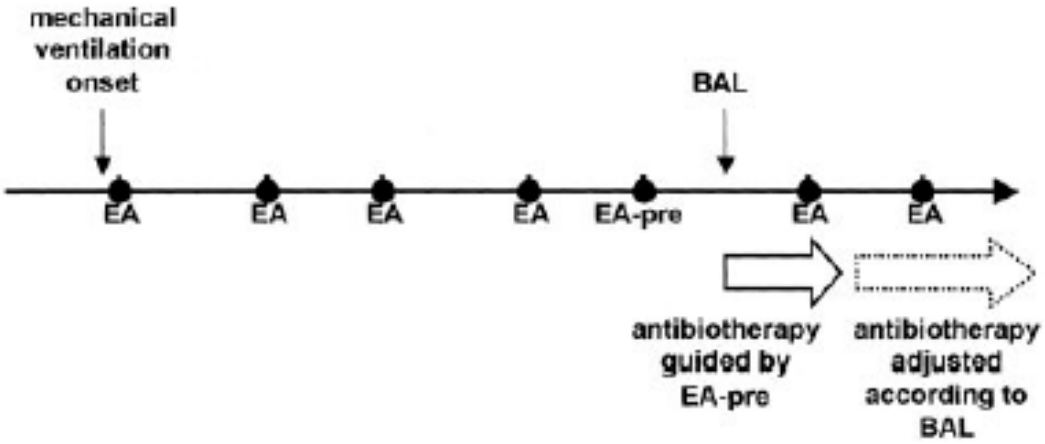


FIGURE 1. Study design.

Accuracy of Surveillance EA Cultures To Guide Empiric Therapy

- Retrospective analysis of prospective data. Routine weekly EA to guide therapy in 90 of 113 with VAP who had EA and BAL. 23 with no EA data.
  - 65/90 with EA and BAL concordant, 35 discordant
- 85% of therapy appropriate when guided by most recent EA. Not as accurate if use guidelines (73% by ATS guideline) or if no EA data available (61% appropriate). NO OUTCOME DIFFERENCES
- Jung B, et al. Intensive Care Med 2009; 35: 101-107.

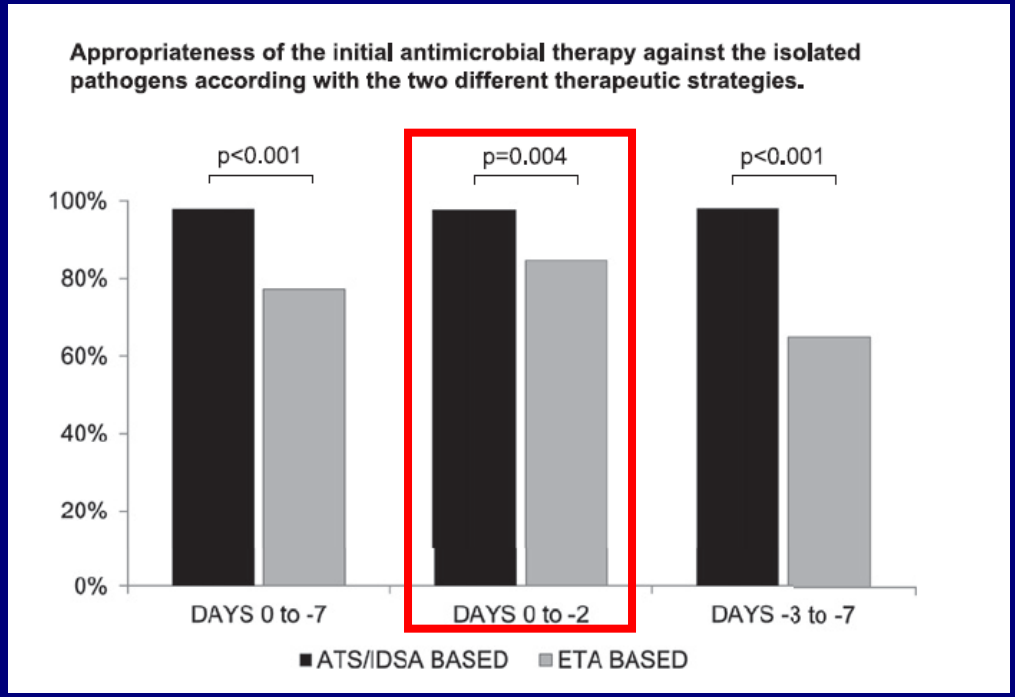
Table 3 Clinical outcome of the patients from the three groups

	All ($n = 113$)	Group concordant BAL/EA ($n = 65$)	Group discordant BAL/EA ($n = 25$)	Group EA not performed ($n = 23$)
Post-VAP length of mechanical ventilation (days)	17 ± 18	16 ± 15	12 ± 11	21 ± 20
Total length of mechanical ventilation (days)	26 ± 23	27 ± 24	22 ± 16	25 ± 26
Post-VAP length of ICU stay (days)	23 ± 20	23 ± 17	19 ± 16	23 ± 17
Total ICU length of stay (days)	36 ± 27	39 ± 27	30 ± 19	33 ± 33
Nonpulmonary ICU-acquired infections, *n* (%)	55 (49)	34 (52)	15 (60)	8 (34)
ICU mortality, *n* (%)	33 (29)	19 (29)	7 (28)	7 (30)

Values are expressed as mean ± standard deviation or number (%)
There was no significant difference between the three groups for the studied parameters

Use of Surveillance EA Cultures To Guide Empiric Therapy of VAP

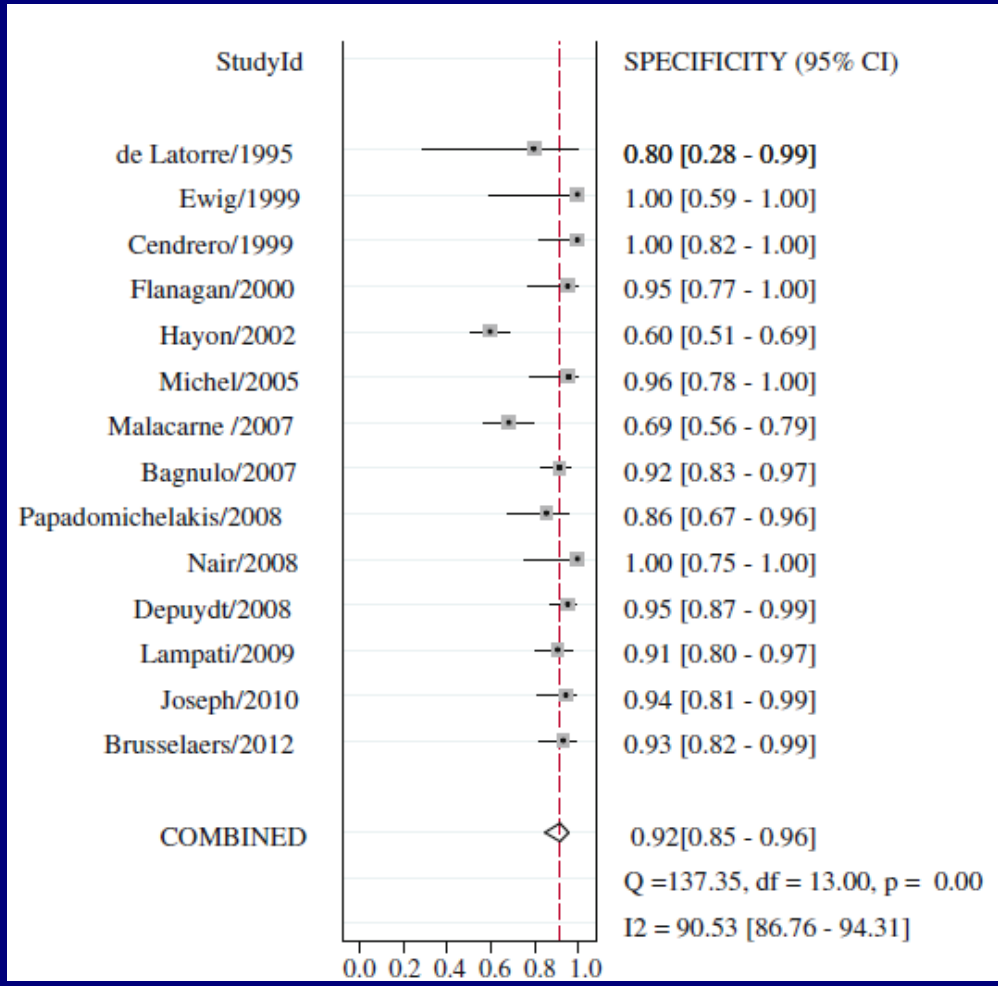
- Prospective, observational study of 283 patients ventilated ≥ 48 hours.
- Twice weekly ETA cultures, BAL when VAP suspected
- 55 patients with 65 VAPs (17% rate)
- ETA predicted BAL in 62.4%: 74% if ≤ 2 days of BAL, 46.2% if 3-7 days of BAL
- Appropriate rx : 97.9% if ATS/IDSA guideline vs. 77.4% if ETA. Fewer antibiotic days if ETA (1557 vs 1942)
- Luna CM, Srquis S, Niederman MS, et al. Chest 2013; 144:63-71.



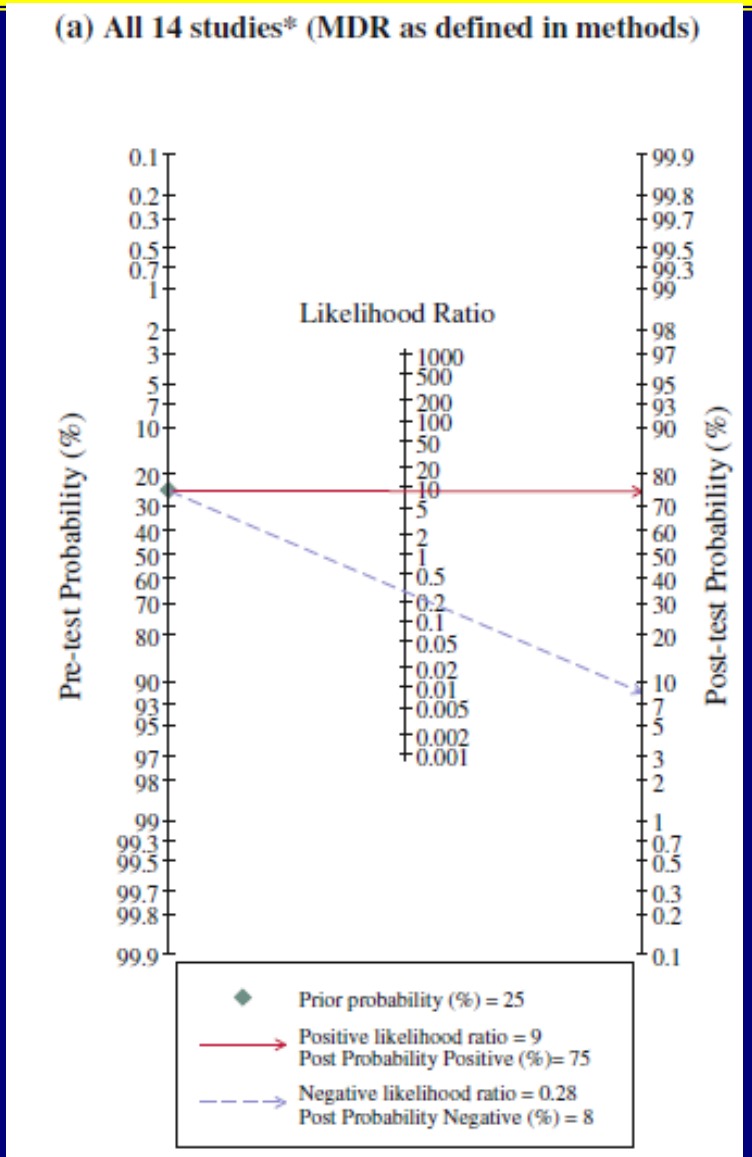
EA most useful if w/i 2 days

Systematic Review and Meta-Analysis of Surveillance Cultures to Predict VAP Pathogens

- 14 studies with LRT samples pre VAP, 791 VAP episodes
- Pooled sensitivity 0.75, specificity 0.92
- Higher accuracy if sample > 2x/week and use recent sample
- Increases likelihood of MDR if cult + for MDR
- High specificity means a high likelihood ratio of NO MDR if negative
- Brusselaers N,, et al. Intensive Care Med 2013; 39:365-75



How the Results of Surveillance Cultures Alter the Post Test Probability of an MDR Pathogen



- Brusselaers N,, et al. Intensive Care Med 2013; 39:365-75

Concordance of Surveillance Cultures with VAP Pathogens

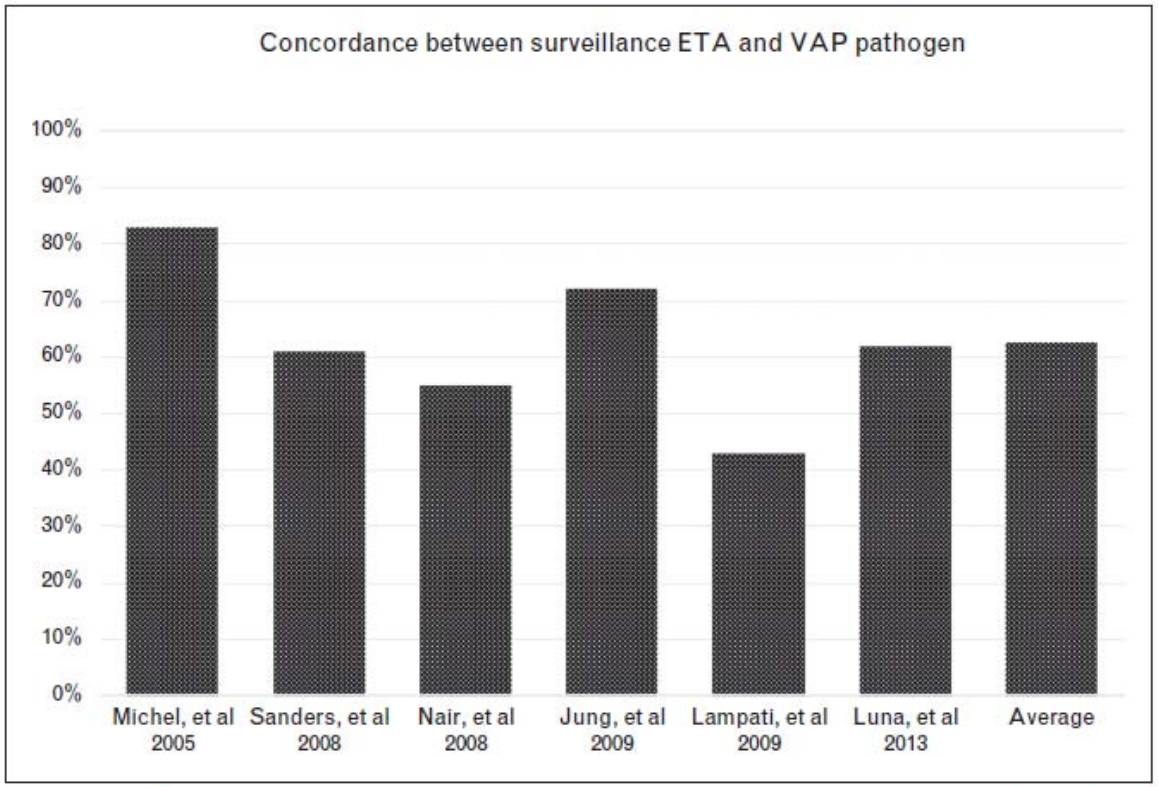
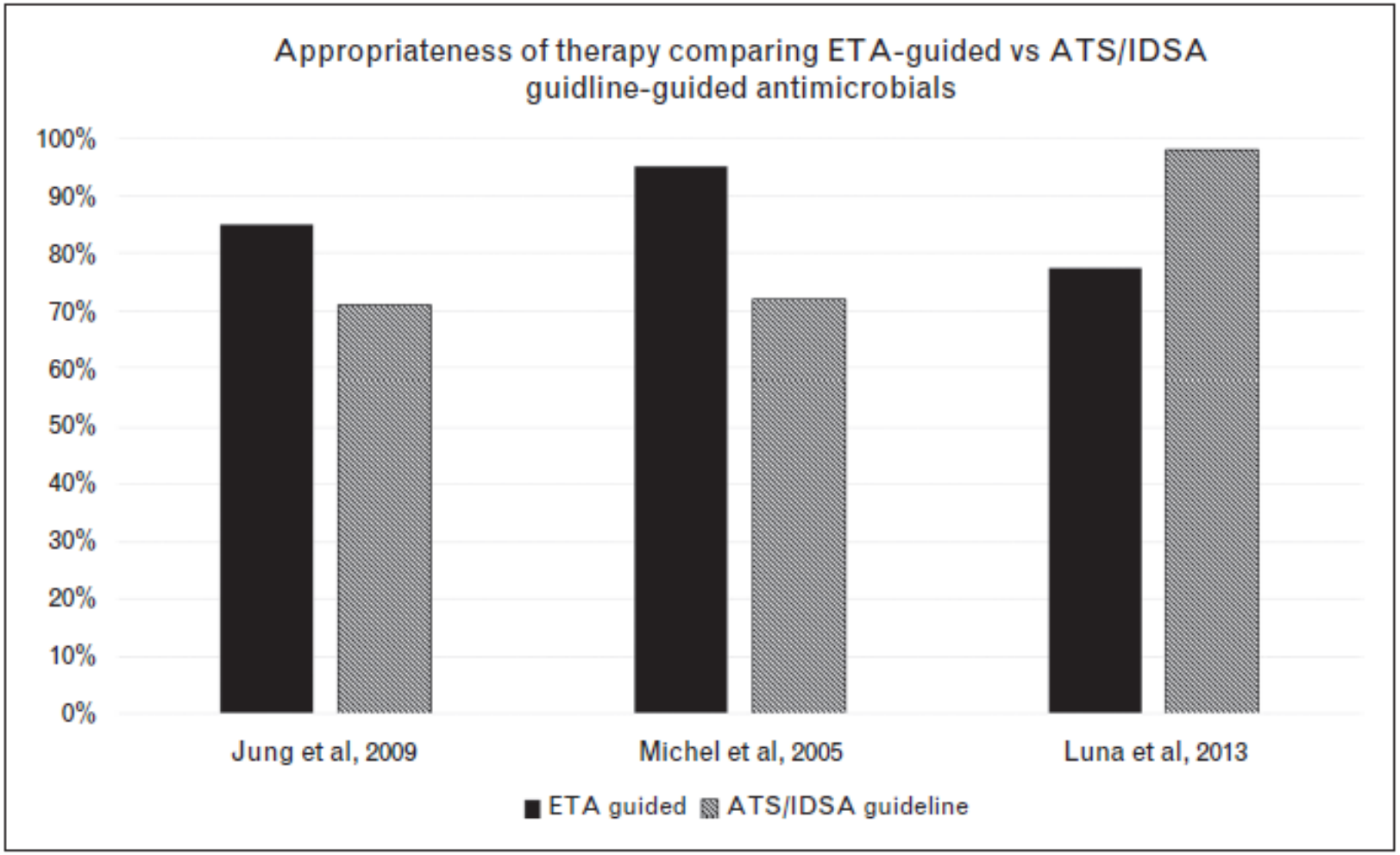


FIGURE 3. The concordance between the pathogen isolated in the surveillance cultures performed usually during the last 0–7 days before, and by the time of VAP diagnosis is displayed according to different authors [15,22,23,24▪▪,25,26]. ETA, endotracheal aspiration; VAP, ventilator-associated pneumonia.

Luna CM , et al. Curr Opin Infect Dis 2014; 27:184-93

Appropriateness of ETA guided Therapy for VAP



Luna CM , et al. Curr Opin Infect Dis 2014; 27:184-93

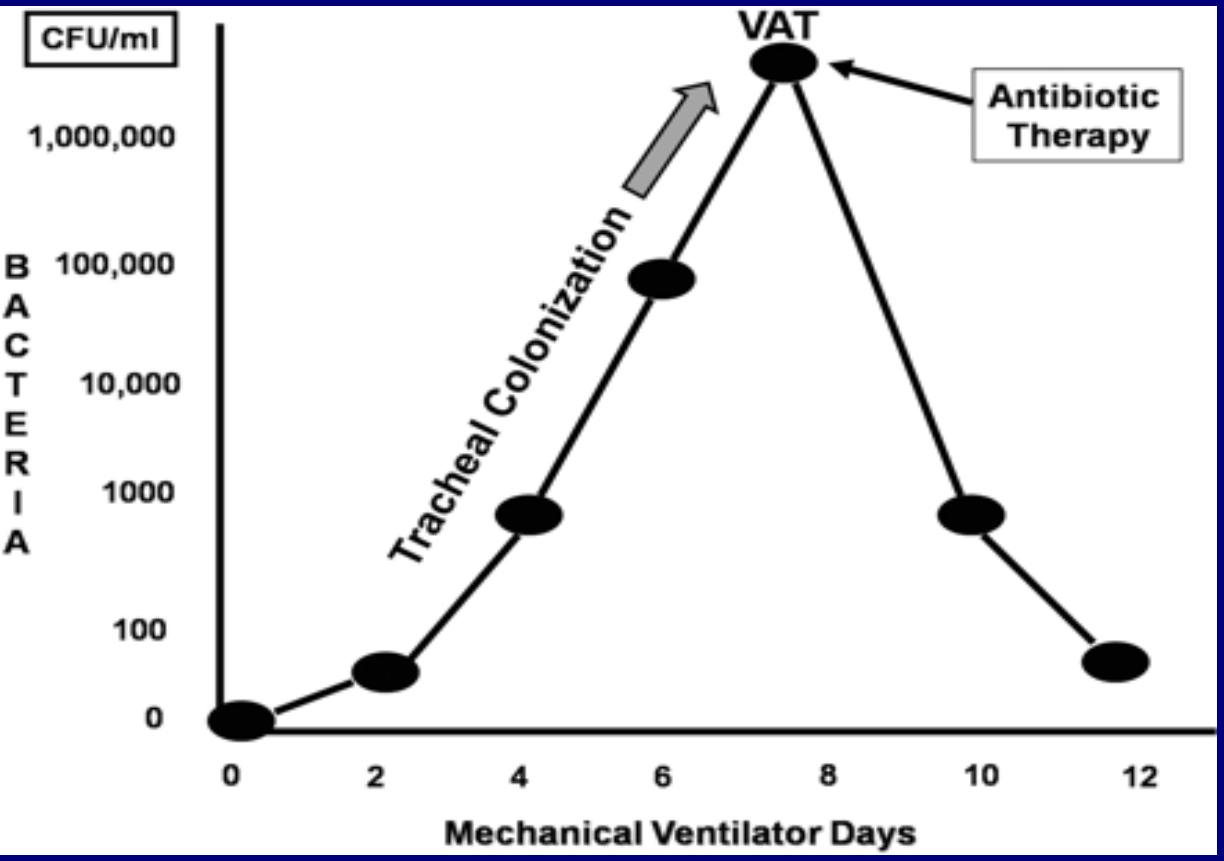
Caveats About Surveillance Culture Studies

- Evaluation of 24 studies and 1 systematic review
- Few prospective studies
- Many with "incorporation bias" , using ETA as BOTH a surveillance method and a diagnostic test, overestimating the value of surveillance cultures
- Surveillance useful for MRSA, esp in high risk units
- Most cost effective in patients at high risk for pneumonia and in ICU with high prevalence of MDR pathogens
- No guidelines recommend their use
  - Scholte JBJ, et al. Curr Opin Pulm Med 2014; 20:259-71

Is Surveillance Useful to Guide Empiric VAP Therapy?

- Studies of surveillance culture and their role in accurate empiric antibiotic choice in VAP
- Can surveillance guide the recognition of VAT and when to START therapy?
- How do rapid diagnostic methods affect this paradigm?
  - MRSA nasal swabs
  - Rapid testing at time of clinical VAP diagnosis
- ICU vs. individual microbiologic surveillance

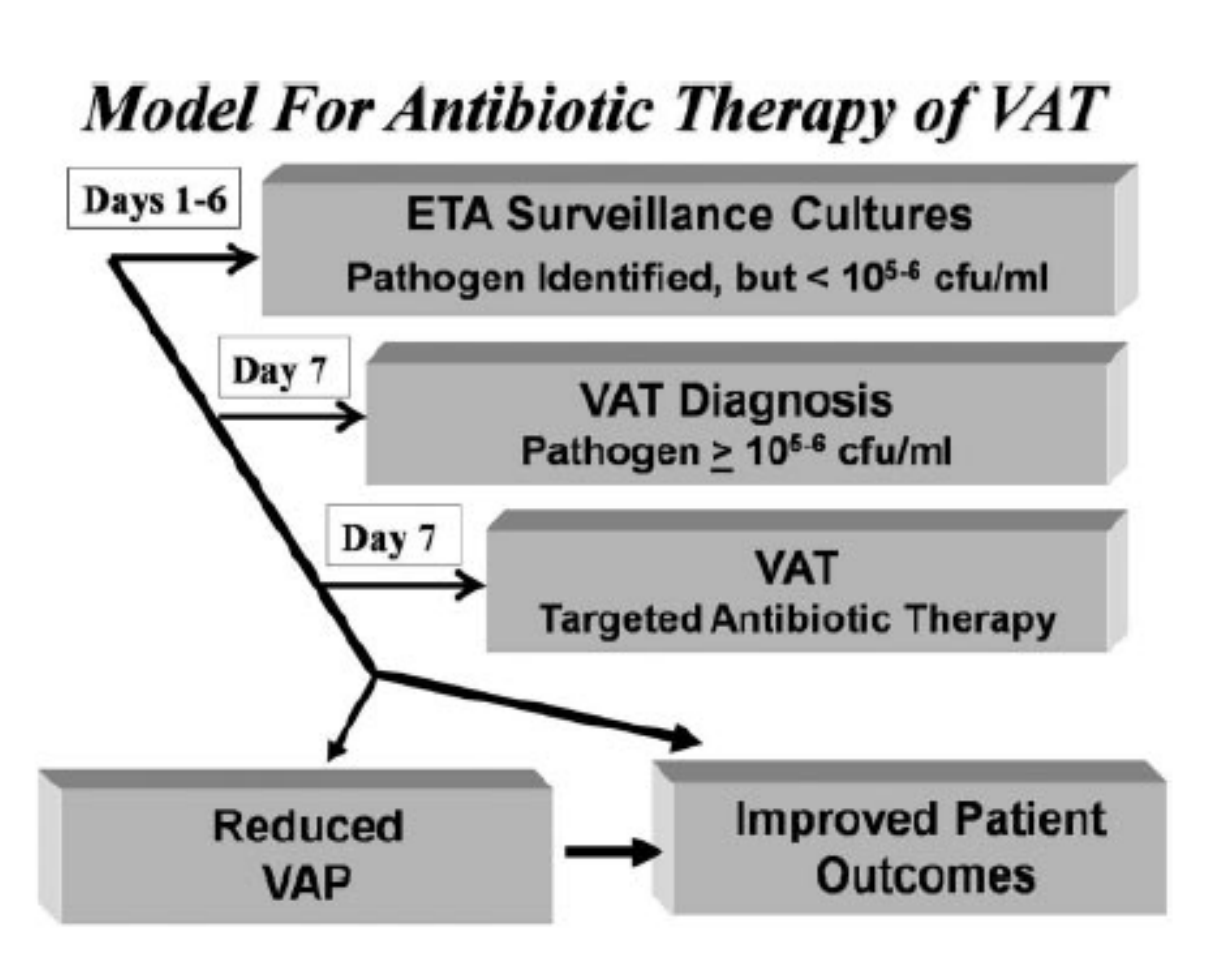
Ventilator-Associated Tracheobronchitis



- Fever, leukocytosis, purulent sputum, no infiltrate.
- Crude incidence 2.7 to 10% of intubated patients.
- Pathogens: P. aeruginosa, Acinetobacter, MRSA.

Craven DE, et al. *Chest* 2009;135:521-528.

Defining When to Treat VAT: Use of Surveillance Cultures



Craven et al. Chest 2008; 135: 521-28

Problems With Basing VAT Therapy on Quantitative Surveillance Cultures

- With strict definitions, the incidence of VAT can be relatively low and yield of surveillance will be low
  - Great cost of prospective surveillance and quantitative cultures vs. targeting only to patients with active symptoms
  - With a more liberal definition the incidence may rise, but lead to over use of antibiotics and less chance of benefit
- Not all VAT progresses to VAP
  - Excess use of antibiotics for limited benefit
  - Therapy of VAT based on surveillance can lead to overuse of antibiotics and promote the development of drug resistance
- VAT may be a process that is independent of VAP

Other Problems With Surveillance Cultures For VAT in Long Term Ventilation

- VAT will be overdiagnosed in long term ventilated patients, and few need therapy
  - Chronic ventilation associated with high colony counts that lead to little clinical harm in most long term ventilated patients
- 39 outpatients with chronic tracheostomy
  - Tracheal cultures 6 times in one year: 83% of samples colonized ; 38 patients colonized at least once.
  - In one year, only 30 episodes of respiratory infection (in 18 patients) requiring antibiotics, of which 5 were pneumonia and 25 were tracheobronchitis.
  - Harlid et al: AJRCCM 1996; 154: 124.
- 14 patients on prolonged ventilation with no suspicion of VAP. 29/32 lobes sampled with > 10^4 cfu/ml on BAL.
  - Baram et al. Chest 2005; 127:1353-1357.

Is Surveillance Useful to Guide Empiric VAP Therapy?

- Studies of surveillance culture and their role in accurate empiric antibiotic choice in VAP
- Can surveillance guide the recognition of VAT and when to START therapy?
- How do rapid diagnostic methods affect this paradigm?
  - MRSA nasal swabs
  - Rapid testing at time of clinical VAP diagnosis
- ICU vs. individual microbiologic surveillance

How Can New Diagnostic Methods Help?

- By providing organism identification, quantitation and susceptibility testing (or resistance gene presence) with high sensitivity, in hours, can promote focused and accurate therapy AS AN ALTERNATIVE TO SURVEILLANCE CULTUERS, IN ORDER TO IMPROVE ACCURACY OF THERAPY
  - Allows appropriate therapy by showing the presence of a resistant pathogen
    - Rapid and accurate quantitation can tell which organisms to treat
    - A negative , highly sensitive test can tell which organisms NOT to treat
    - May not be affected by prior antibiotics
  - Can detect resistance genes (carbapenemase producers)
    - Kim DK, et al. Ann Lab Med 2016; 36:162-165

PCR Methods to Guide Empiric VAP Therapy

- MRSA
  - 400 patients with nasal PCR w/i 48 h ICU admit and suspected NP with LRT sample w/I 7 days of MRSA swab.
  - 22.8% nasal swabs with MRSA, 9.3% NP with MRSA
  - Nasal swab NPV : 99.0%; PPV: 37.4%; SENS: 91.9%; SPEC 84.3%
  - Maintained value over time (4 serial cultures)
  - Smith MN, et al. J Crit Care 2017; 38: 168-71

Table 2
Diagnostic characteristics of MRSA nasal PCR assay

Measurement	Culture 1 (n = 400)	Culture 2 (n = 164)	Culture 3 (n = 68)	Culture 4 (n = 23)
NPV, % (95% CI)	99.03 (97.18-99.8)	96.83 (92.07-99.13)	100 (93.15-100)	87.5 (61.65-98.45)
PPV, % (95% CI)	37.36 (27.44-48.13)	18.42 (7.74-34.33)	6.25 (0.16-30.23)	14.29 (0.36-57.87)
Sensitivity, % (95% CI)	91.89 (78.09-98.3)	63.64 (30.79-89.07)	100 (2.5-100)	33.33 (0.84-90.57)
Specificity, % (95% CI)	84.3 (80.14-87.88)	79.74 (72.49-85.80)	77.61 (65.78-86.89)	70 (45.72-88.11)
Median time to culture, d (IQR)	1.4 (0.2-3.4)	7.4 (4.6-10)	13.4 (10.5-17.7)	21.9 (17.1-30.1)

CI indicates confidence interval; IQR, interquartile range.

Rapid Automated Microscopy (Accelerate Diagnostics) to Diagnose VAP

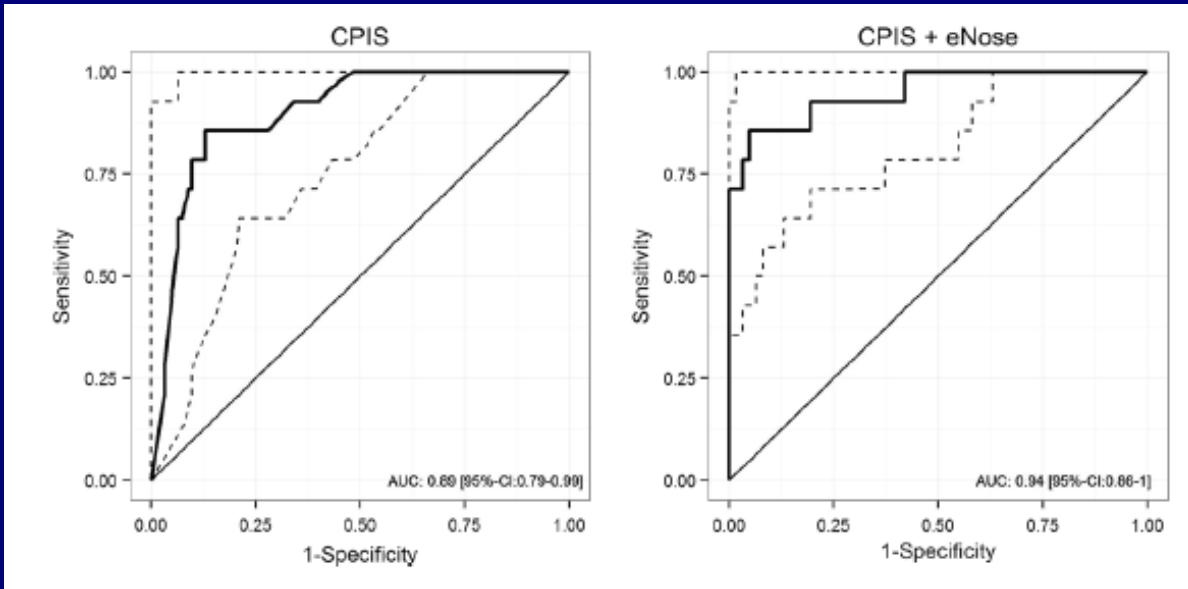
- Alternate day mini-BAL (n=77) in 33 patients with MV > 48 h
  - 1 with VAP
- 73 paired samples (culture and microscopy to give ID and S on BAL). 1 clinically diagnosed VAP
  - 7 with > 10^4 CFU/ml in 5 patients
  - Microscopy (at 5 hours) found all 7 and 64/66 negative cults
  - 100% sensitive, 97% specific for bacteria in clinical cultures

		CLINICAL MICROBIOLOGY PRESENCE/ABSENCE ≥ 1 × 10⁴ CFU/mL	
		Positive	Negative
AUTOMATED MICROSCOPY	Positive	7	2
	Negative	0	64
		Sensitivity=100%	Specificity=97%

Douglas I , et al. Am J Respir Crit Care Med 2015; 191:566-73

Electronic Nose Surveillance For VAP??

- Use eNose to detect Volatile Organic Compound (VOC) fingerprint in "headspace air" from TAs taken q 3 days in 45 MV patients
- 14 VAP, 14 colonized, 17 neither
- eNose could tell VAP vs non-VAP and added to CPIS. NOT affected by colonization .
- Not clear which VOCs responsible
- Bos LDJ, et al. Intensive Care Med 2014; 20:761-762



Is Surveillance Useful to Guide Empiric VAP Therapy?

- Studies of surveillance culture and their role in accurate empiric antibiotic choice in VAP
- Can surveillance guide the recognition of VAT and when to START therapy?
- How do rapid diagnostic methods affect this paradigm?
  - MRSA nasal swabs
  - Rapid testing at time of clinical VAP diagnosis
- ICU vs. individual microbiologic surveillance

Combination Regimens Must Account For Local Microbiology

- 111 patients with HAP
- Most common organisms: *S. aureus, Acinetobacter baumannii, P. aeruginosa*
- Piperacillin resistance more likely after 10 days
- Amikacin more active vs. gram –negatives than quinolones
- Beardsley JR, et al. Chest 2006; 130: 787-793.

Table 4—*Adequacy of Various Antibiotic Combinations Against All Gram-Negative Isolates (n = 139)

Drugs	Additional Antibiotic			
	None	Ciprofloxacin	Gentamicin	Amikacin
Piperacillin-tazobactam	80%	82%	81%	96%
Cefepime	81%	83%	82%	96%
Meropenem	82%	83%	83%	96%

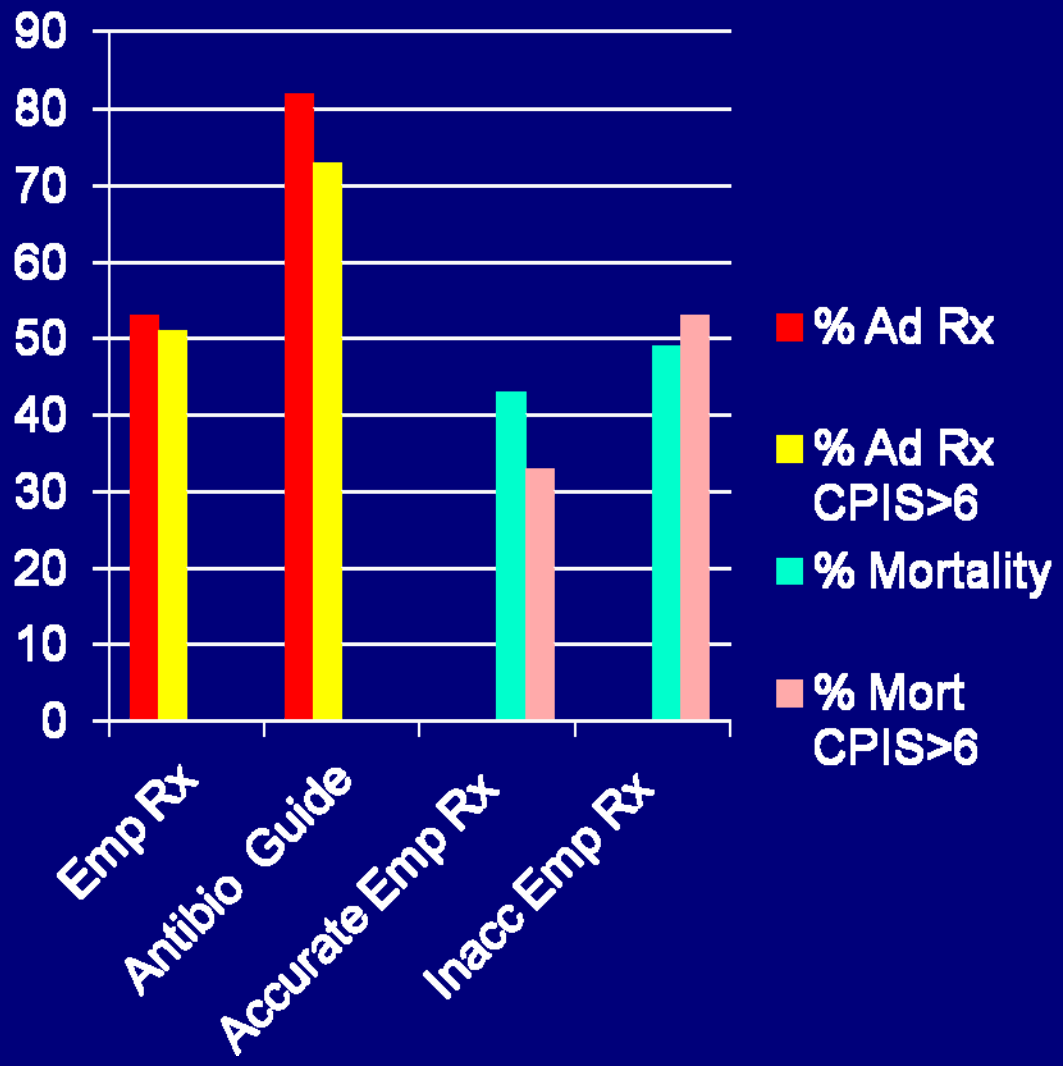
*Data are presented as percentage susceptible to at least one antibiotic.

Using an ICU Antibiogram (Whole ICU Surveillance) to Guide Empiric VAP Therapy

- ICU respiratory tract cultures collected over at least 1 year to get a minimum of 30 isolates.
  - Looked at: MRSA, *P. aerugionosa, K. pneumoniae, E. coli, S. Maltophilia* and *Acinetobacter baumanii*.
  - Based on susceptibility testing the best empiric VAP therapy would be: cefepime, amikacin and vancomycin/linezolid.
  - None good for *A. baumanii* (Amp/sul best at 47%) and TMP/SMX and quinolones for *S. maltophilia.*

Using an ICU Antibiogram (Whole ICU Surveillance) to Guide Empiric VAP Therapy

- 138 patients with a respiratory tract culture and antibiotic therapy (53 with CPIS ≥ 6)
  - Empiric therapy correct in 53% (51% if CPIS ≥6)
  - Antibiogram algorithm correct in 82% (73% if CPIS ≥6)
  - Accurate empiric therapy: 43% mortality (33% if CPIS ≥6)
  - Inaccurate empiric therapy: 49% mortality (53% if CPIS ≥6)
    - When antibiogram wrong,often due to a new outbreak of *Stenotrophomonas maltophila*.



Conclusions

- ETA surveillance cultures can improve the use of antibiotics and maybe lead to more accurate empiric therapy, if collected within 2 days of VAP onset
  - Limited role of surveillance for VAT
- Surveillance more valuable if high risk for VAP and high prevalence of MDR pathogens
- New PCR methods may enhance the value of surveillance, but may also improve antibiotic use at the time of VAP diagnosis
  - High NPV of surveillance cultures /PCR can reduce antibiotic use
- Whole ICU surveillance and antibiograms can also improve empiric VAP therapy