# Ventilator-Associated Pneumonia (VAP)
# Hospital-Acquired Pneumonia (HAP)
# Definitions, Diagnostics & Outcomes

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IDSA

VAP-FDA 10-31-11

IDSA

# Craven Disclosures

- **Speakers Bureau/Honoraria:**

  Sanofi Pasteur & Merck, Pfizer

- **Research:**

  Bard, Pfizer

- **Honoraria/Consulting:**

  Merck, Pfizer, Covidien, Cubist

# Definitions/Abbreviations

Diagnoses:

- VAP – ventilator-associated pneumonia
- VAT – ventilator-associated tracheobronchitis
- HAP – hospital-acquired pneumonia

Sputum Cultures:

- QTA – quantitative tracheal aspirate (TA)
- SQTA – semi-quantitative TA
- BAL – quantitative bronchoalveolar lavage

# Frequent Abbreviations (2)

Microbiology

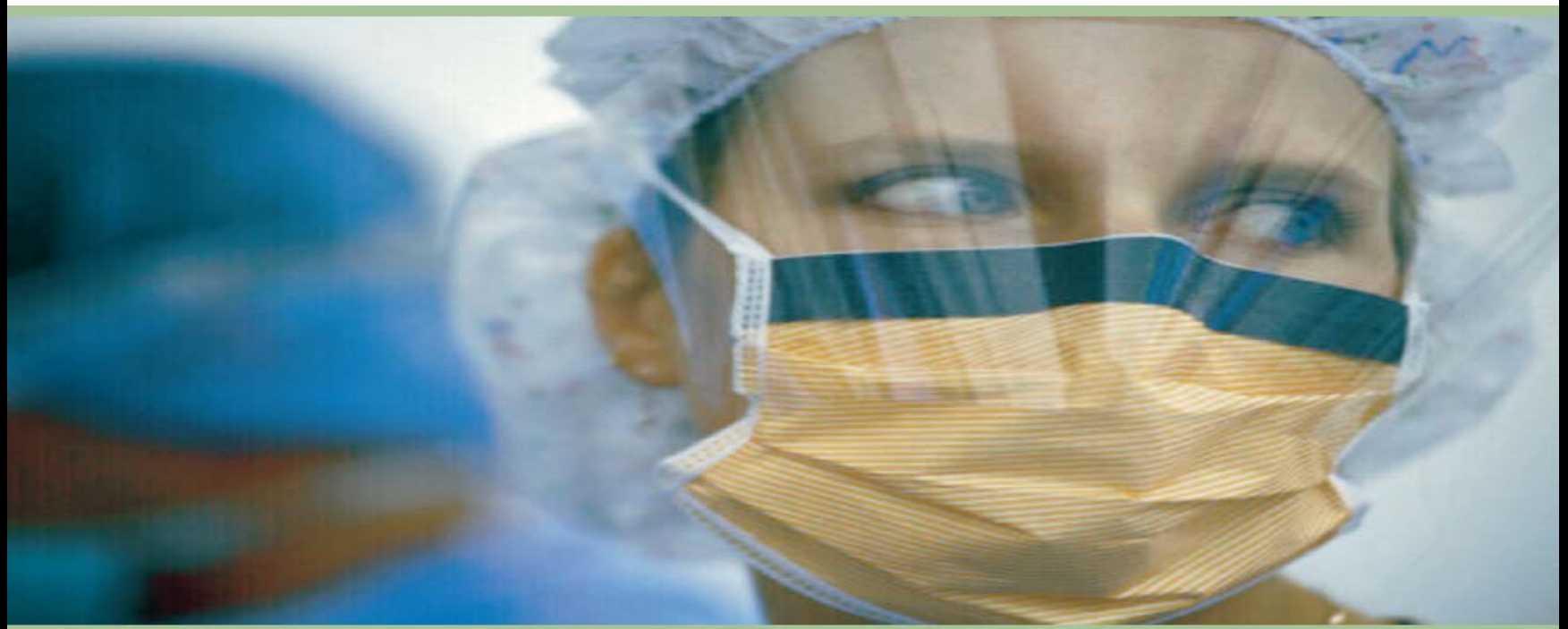
- MRSA – methicillin-resistant *S. aureus*
- GNR – Gram-negative rod
- ESBL+ = extended-spectrum B-lactamase +
- KPC + = Klebsiella producing carbepenemase
- CPE+ = carbepenem-resistant Enterobactereaceae
- MDR – multi-drug resistant

Clinical Markers:

- CRP – C-reactive protein
- PCT – procalcitonin
- CS – Clinical signs of VAP
- CPIS – Clinical Pulmonary Infection Score

# Bad Bugs, No Drugs

As Antibiotic Discovery Stagnates ...
A Public Health Crisis Brews



IDSA
Infectious Diseases Society of America

July 2004

Boucher. Clin Infect Dis 2009; 48:1-12

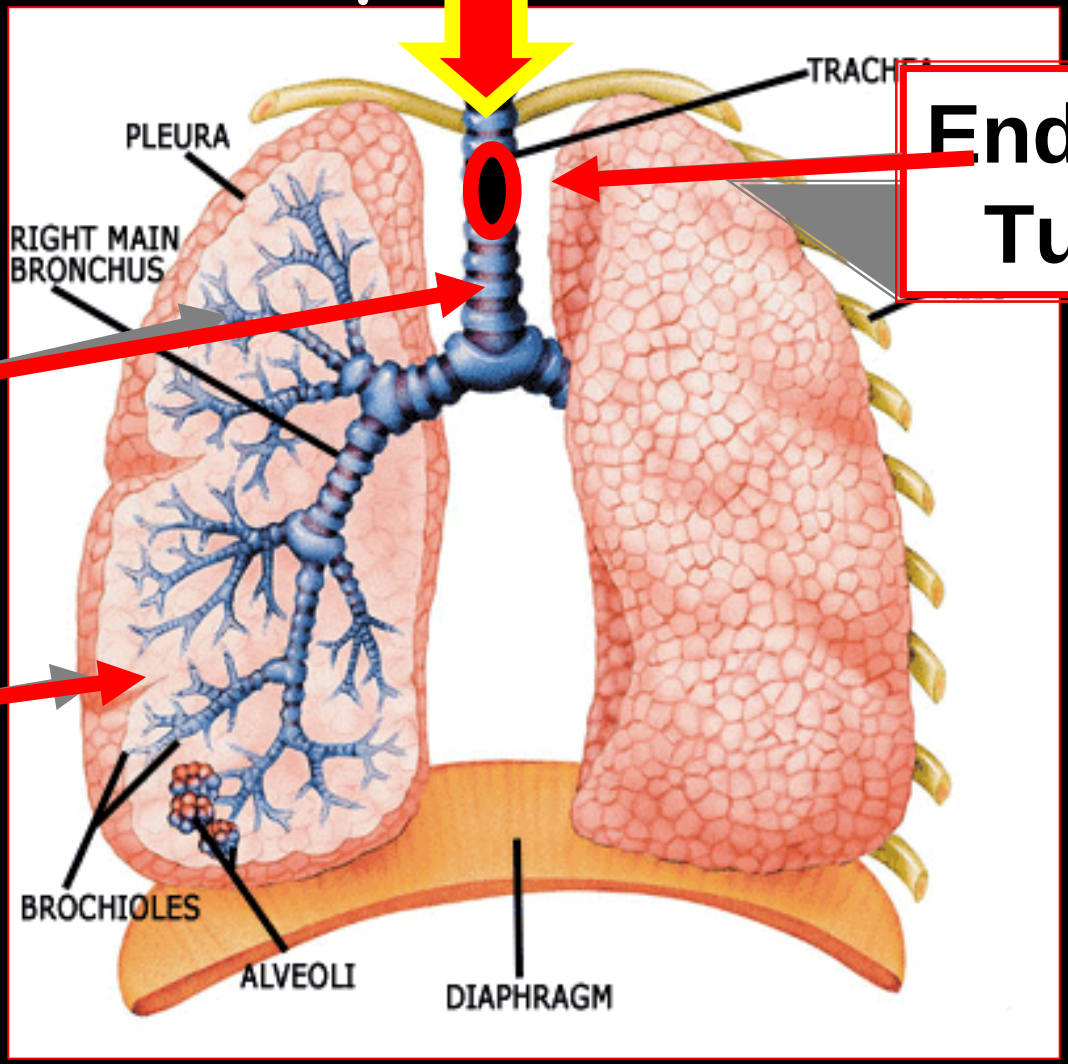
# IDSA Goals: Improved Clinical Trials

1. Enrollment: extend prior antibiotics: 24-36 hr
2. Sputum microbiology: quantitative tracheal aspirates *(TA) or bronchoalveolar lavage (BAL) samples needed for diagnosis.*
3. Outcomes: mortality + clinical endpoints (clinical response, patient outcomes, etc.).
4. VAP data is applicable to HAP

Spellberg, Clin Infect Dis, 2010; 51:150 Supplement

# BACTERIA: Lung Entry & Exit

One Way In & Out




Endotracheal Tube Cuff

VAT

VAP or HAP

# HAP/VAP/VAT: Pathogens

## Bacteria

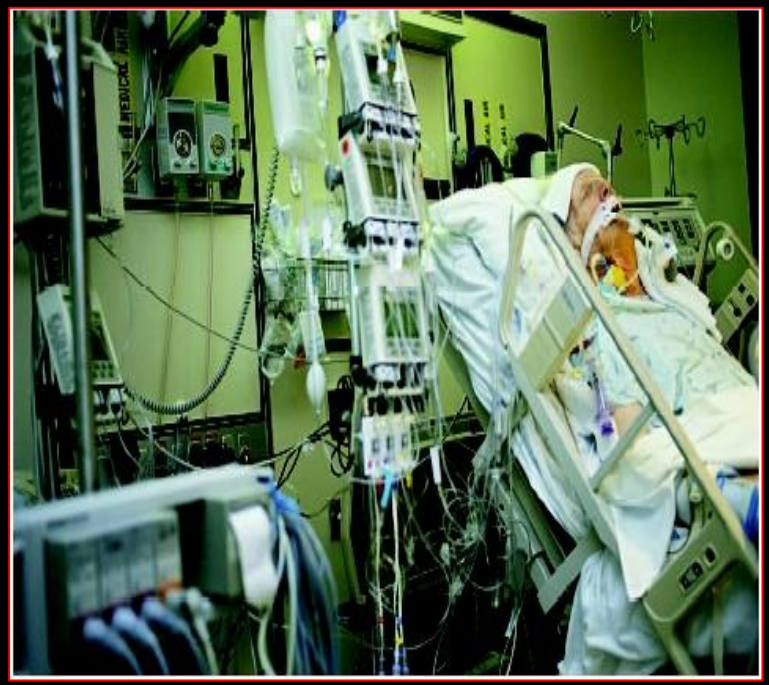
- Pneumococcus
- *Haemophilus spp*
- *S. aureus (MSSA)*
- E. coli
- Legionella**

## Resistant

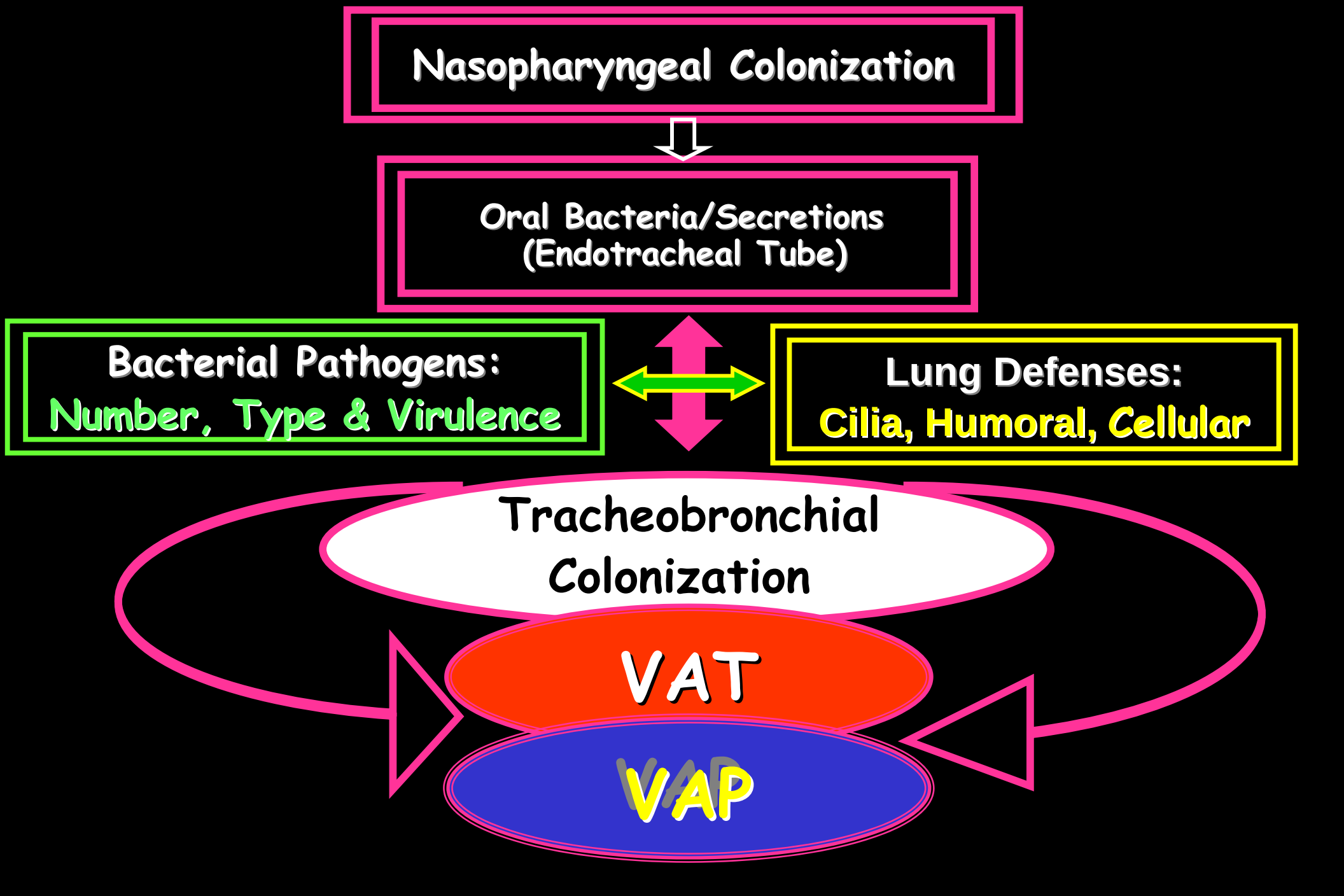
- S. aureus (MRSA)
- *P. aeruginosa*
- *ESBL+, KPC/CPE+ GNR*
- *Acinetobacter spp*
- *Stenotrophomonas spp*

# VAP: Sickest Patients!

- Endotracheal tube increases risk >6-21-fold; good microbiology
- VAP >50% of ICU antibiotics
- Crude Mortality = 20%-40%
- Morbidity = huge
- Acute Cost/Case = $15K-$40K



Chastre, Am J Resp Crit Care Med 2002: 165:867-03


Nasopharyngeal Colonization
Oral Bacteria/Secretions
(Endotracheal Tube)
Bacterial Pathogens:
Number, Type & Virulence
Lung Defenses:
Cilia, Humoral, Cellular
Tracheobronchial
Colonization
VAT
VAP

# Thinking Outside the Box

- **Pathogenesis**: Hospital-Acquired Pneumonia (HAP)A Ventilator-associated tracheobronchitis (VAT) & Pneumonia (VAP)
- **Diagnosis** = clinical + microbiology data
- **Outcomes**: mortality + clinical outcomes & response
- **Biomarkers**: (e.g. CRP, PCT) helpful

Craven, Clin Infect Dis 2010: 51: S59

# I. HAP/VAP/VAT Definitions

## Sensitivity vs Specificity

## No Gold Standard!

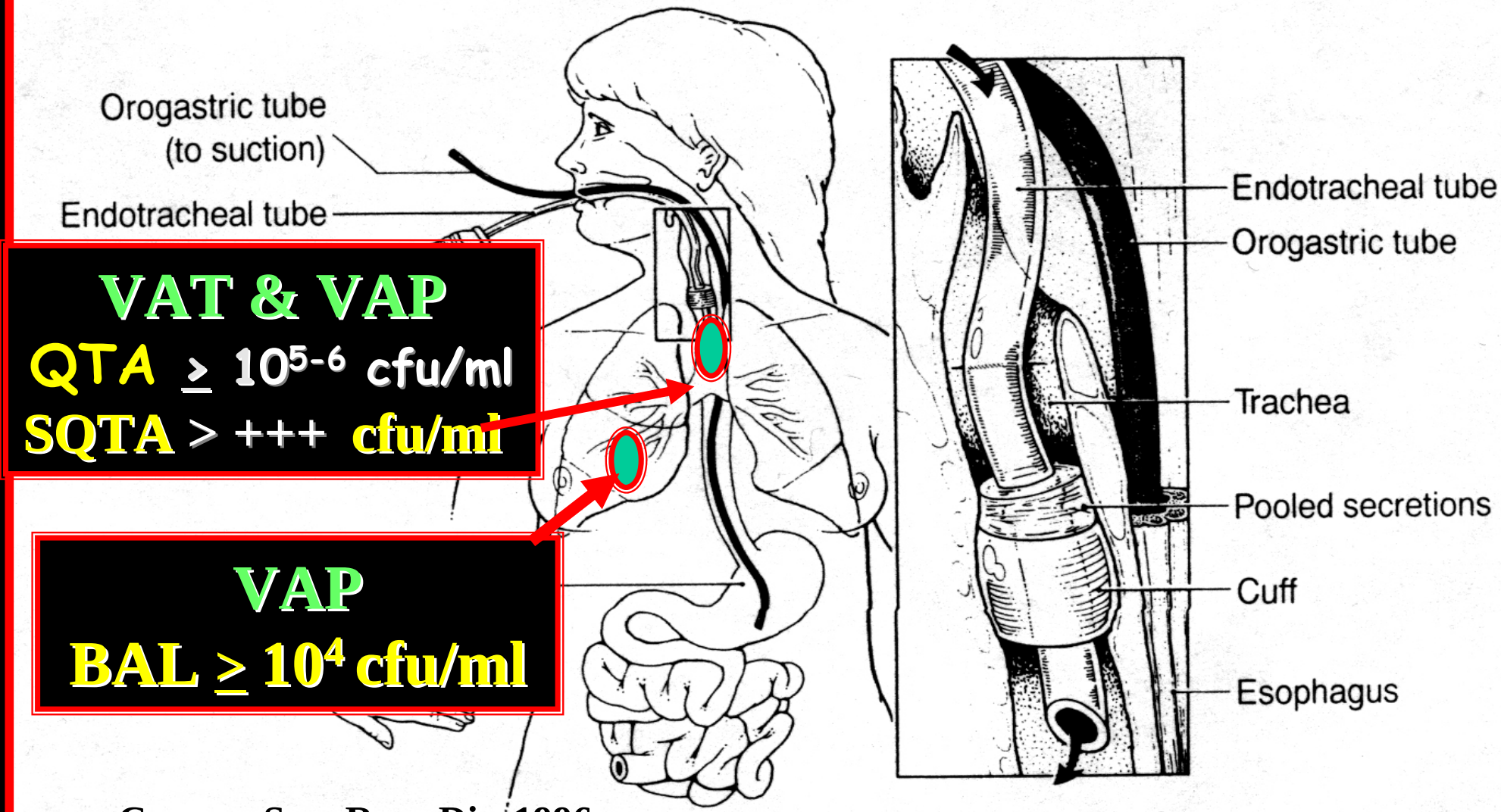
**Microbiology**

**+**

**Clinical Data**

# Quantitative Microbiology

## Infection = A Numbers Game!




**VAT & VAP**

**QTA $\geq 10^{5-6}$ cfu/ml**

**SQTA > +++ cfu/ml**

**VAP**

**BAL $\geq 10^{4}$ cfu/ml**

Craven, Sem Resp Dis, 1996

| VAP | vs | VAT |
|---|---|---|
| Temperature, WBC, sputum<br>Δ in Oxygen Levels | | Temperature, WBC,<br>purulent sputum |
| + Bacterial Pathogen | | + Bacterial Pathogen |
| Chest X-RAY Infiltrate | | Chest X-RAY Normal |
| **Quant-Microbiology**<br>▪ QTA: $>10^{5-6}$ cfu/mL<br>▪ SQTA: ≥ +++ growth<br>▪ BAL $\geq 10^4$ cfu/mL | | **Quant-Microbiology**<br>▪ QTA $>10^{5-6}$ cfu/mL<br>▪ SQTA: ≥+++ growth<br>▪ BAL $< 10^4$ cfu/mL |

# Microbiologic "Standards"

## Ventilator-Associated Pneumonia (VAP) Only

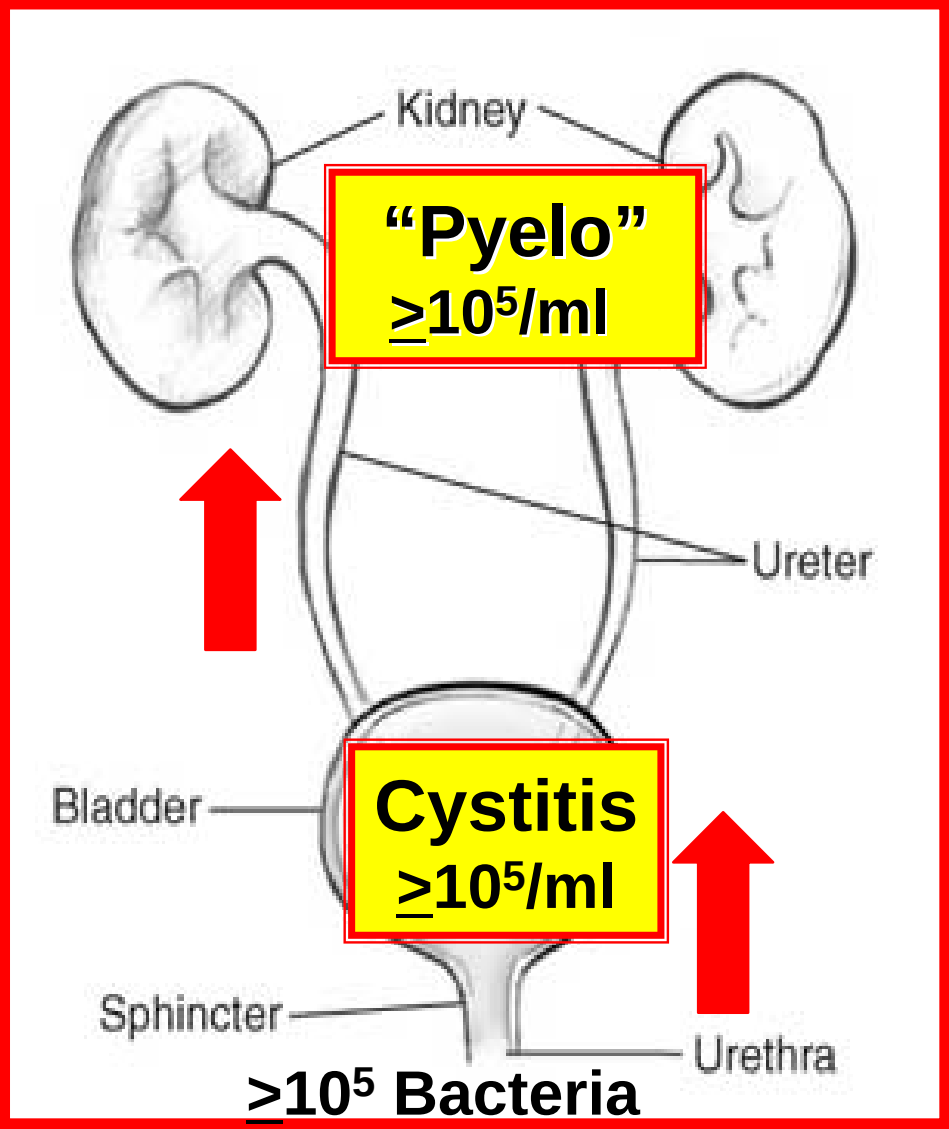
- Bronchoalveolar lavage (BAL) $\geq 10^4$ cfu/ml
- Protected specimen brush (PSB) $\geq 10^3$ cfu/ml

## Ventilator-Associated Tracheobronchitis (VAT) & Pneumonia (VAP)

- QTA $\geq 10^5$ cfu/ml - good sensitivity (VAT/VAP)
- QTA $\geq 10^6$ cfu/ml – better specificity
- SQTA cultures: good agreement with QTA culture

# Universal Definitions:
# Urinary Tract Infections (UTI) vs VAP

- "Kass's #" ">$10^5$cfu/ml"
- UTI symptoms + pyuria
  & urine culture >$10^5$ cfu/ml
- Diagnosis & Treatment:
  - Cystitis (VAT)
  - Pyelonephritis (VAP)



# Randomized Trial of Antibiotic Therapy For Ventilator-Associated Tracheobronchitis (VAT)

- Randomized cliinical trial of antibiotic therapy for VAT vs no (delayed) therapy (n=50):
- Patients treated for VAT had reduced:
  - VAP 14% vs 47%, (p =.01)
  - ICU mortality (p <.05)
  - Ventilator-free days (p <.001)

Nseir, *Crit Care* 2008:12:R62

# Ventilator-Associated Tracheobronchitis (VAT)

## *KEY POINTS FOR CLINICAL TRIALS*

- **Natural history of infection: shown in next 3 slides:**
  - **VAT: diagnosis requires microbiology + clinical data**
  - **VAT is a precursor to VAP**
  - **VAT is associated with poor outcomes**
- **VAT may overlap with VAP**
- **VAT is a potential target for antibiotic therapy**
- **VAT is a logical target for clinical antibiotic trials**

# VAP: Natural History Study n = 188 (>48 hr)

**Heavy EA Colonization**
QTA >$10^5$ 85 (45%)
SQTA +++ 82 (44%)

**Heavy EA Colonization**
QTA >$10^6$ 59 (31%)
SQTA ++++ 51 (27%)

**VAT (+CS)**
QEA $10^5$ 44 (23%)
SQTA 47 (25%)

**VAT (+CPIS)**
QEA $10^5$ 38 (20%)
SQTA 39 (21%)

**VAT* (+CS)**
QTA $10^6$ 32 (17%)
SQTA 28 (15%)

**VAT* (+CPIS)**
QTA $10^6$ 28 (15%)
SQ TA 24 (13%)

Chest –Xray

**VAP (+CXR)**
QTA $10^5$ 15 (8%)
SQTA 14 (7%)

**VAP* (+CXR)**
QTA $10^5$ 12 (6%)
SQTA 10 (5%)

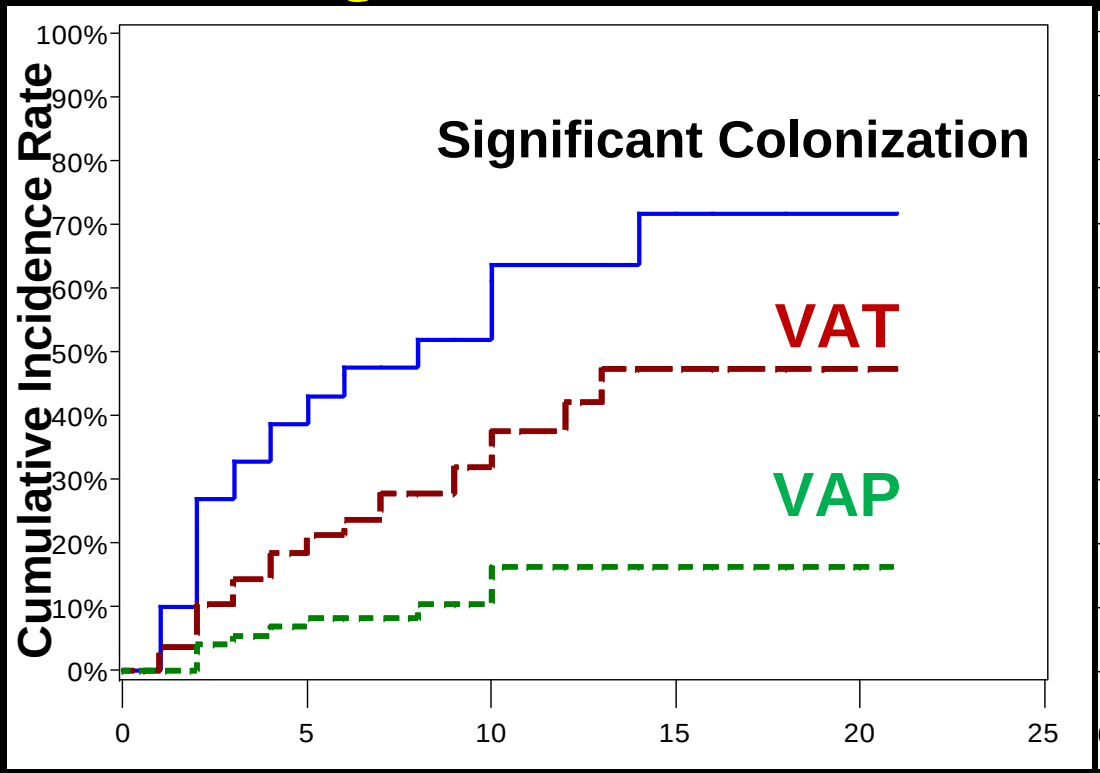
**VAP (+CXR)**
QTA $10^6$ 8 (4%)
SQTA 9 (5%)

**VAP* (CXR)**
QTA $10^6$ 6 (3%)
SQTA 5 (3%)

**VAP diagnosed by BAL in 13/51 (7%) of patients****

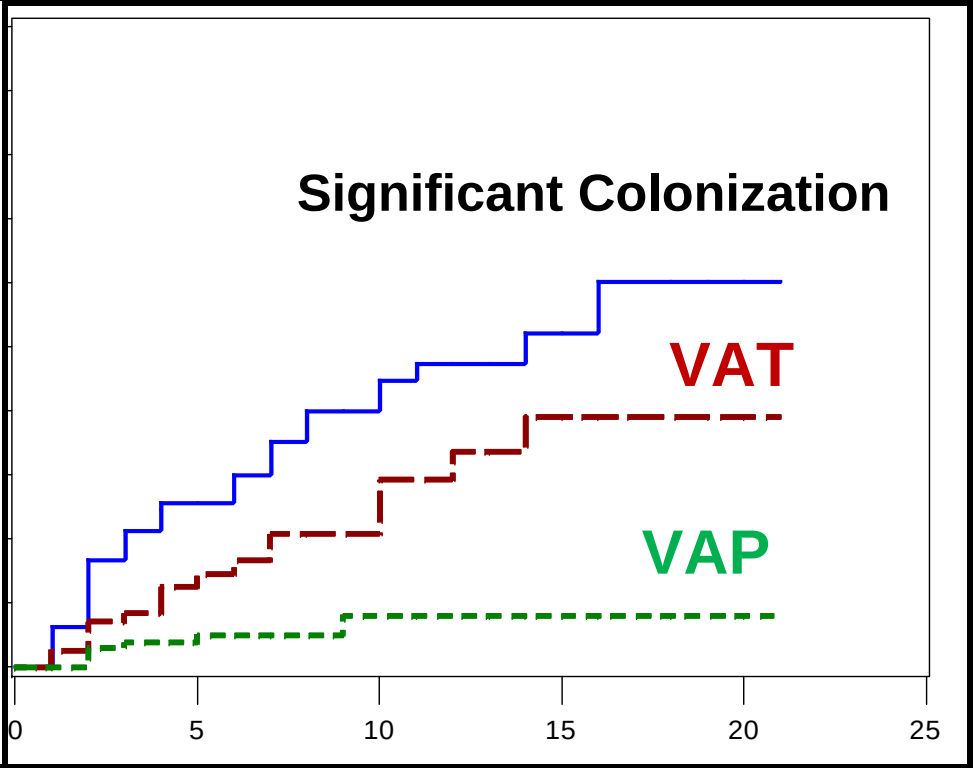
Craven, VAP Natural History Study, IDSA, BOSTON 2010-2011

# A. QEA >$10^5$ cfu/ml




Study Days

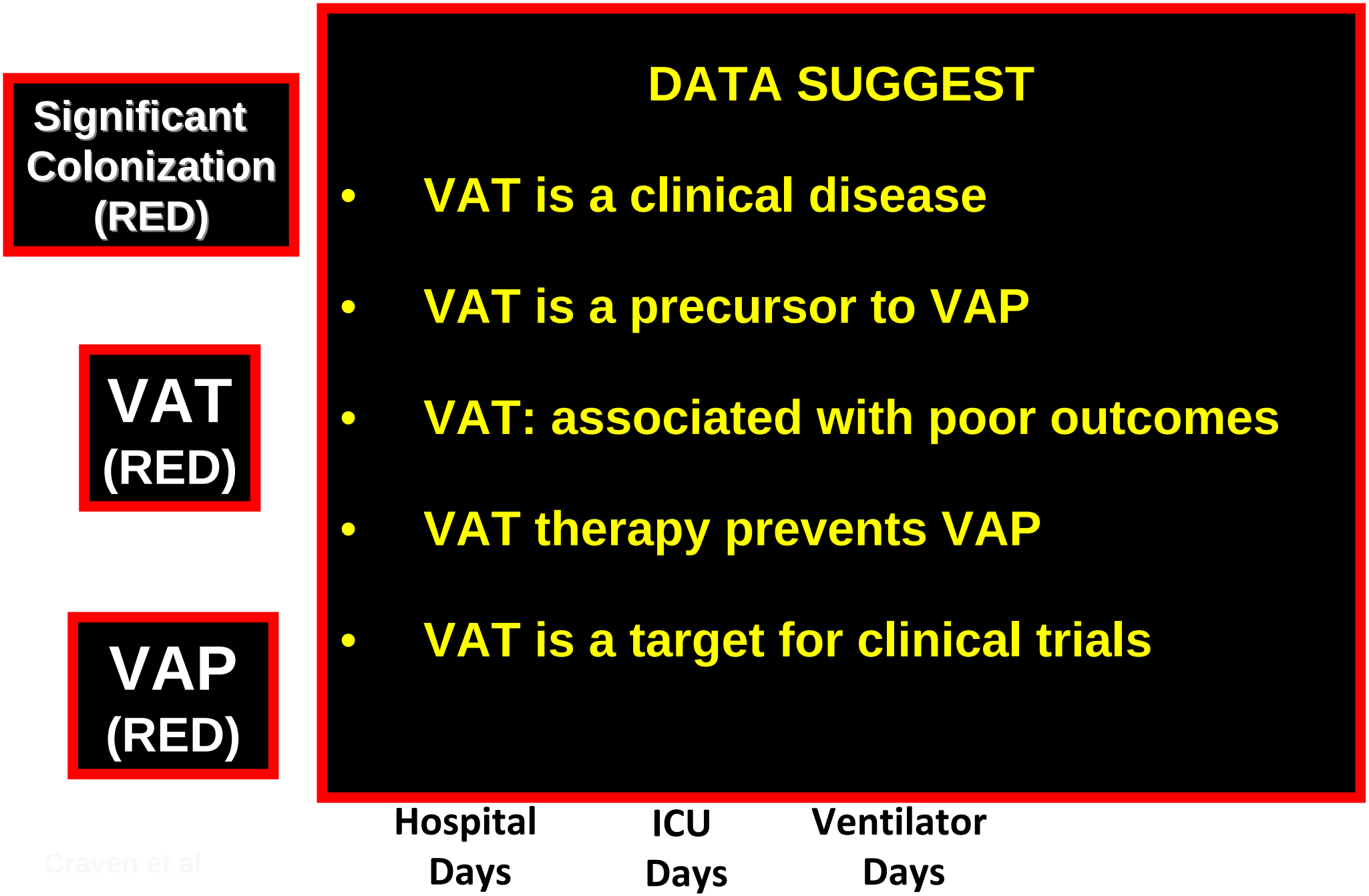
# B. QEA >$10^6$ cfu/ml




Study Days

**Tracheobronchitis Precedes Pneumonia**

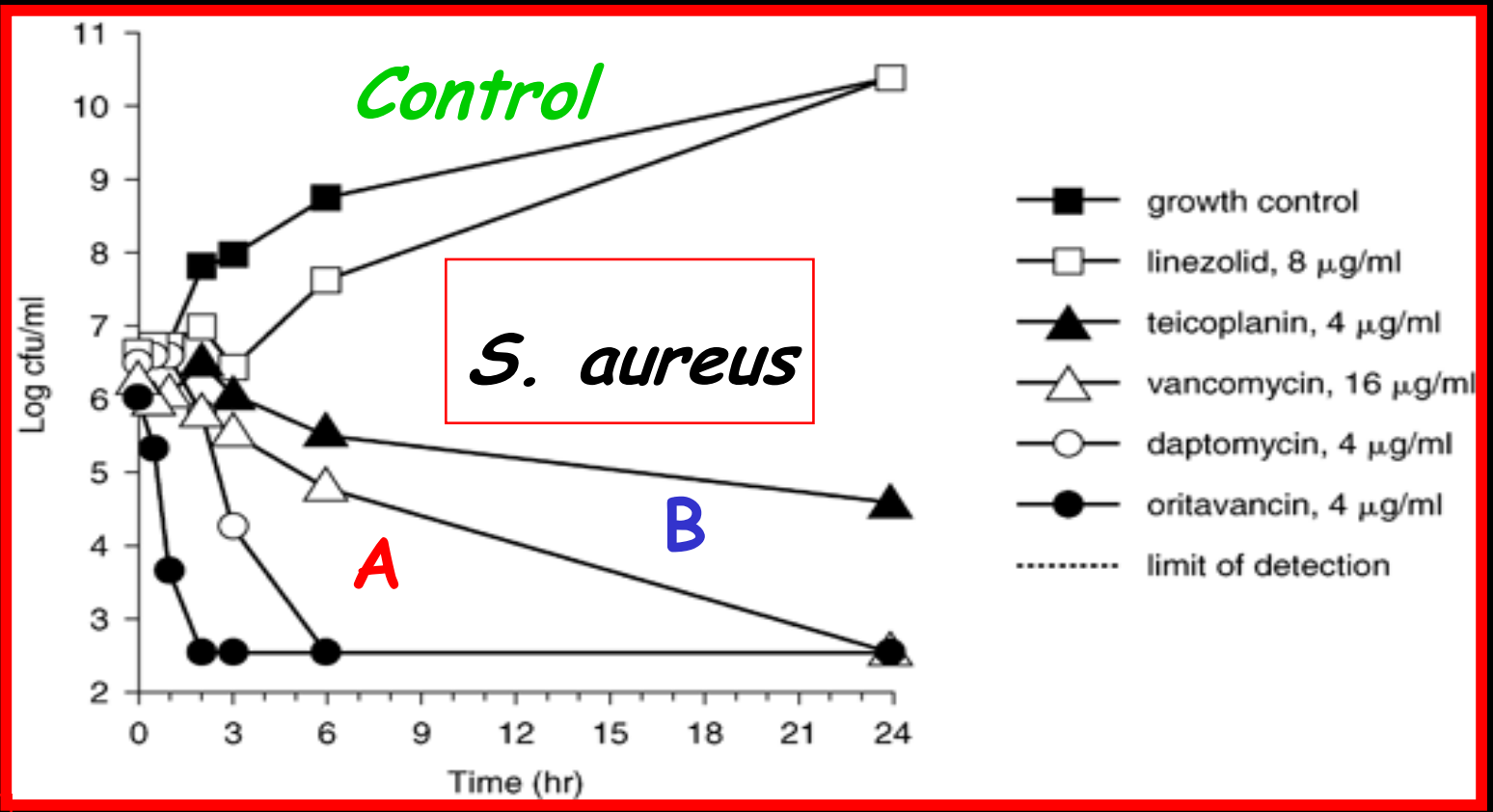
Craven, VAP Natural History Study, IDSA, Boston, 2010-2011


Significant Colonization (RED)
VAT (RED)
VAP (RED)
DATA SUGGEST
• VAT is a clinical disease
• VAT is a precursor to VAP
• VAT: associated with poor outcomes
• VAT therapy prevents VAP
• VAT is a target for clinical trials
Hospital Days
ICU Days
Ventilator Days
Craven et al

# In-vitro vs *In-vivo* Antibiotic Killing Curves

## Opportunities for VAT & VAP

Antibiotic $Log_{10}$ Killing Models




Antibiotic A

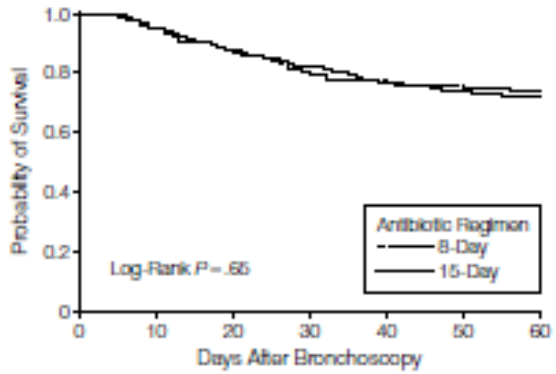
Antibiotic B

Time (HR)

# II. Outcomes
## Mortality (14 vs 28 days) & Non-Mortality Endpoints

- Clinical Response to Therapy
- Clinical Outcomes & Response
- Biomarkers
- Pharmacology Modeling

**Figure 2.** Kaplan-Meier Estimates of the Probability of Survival



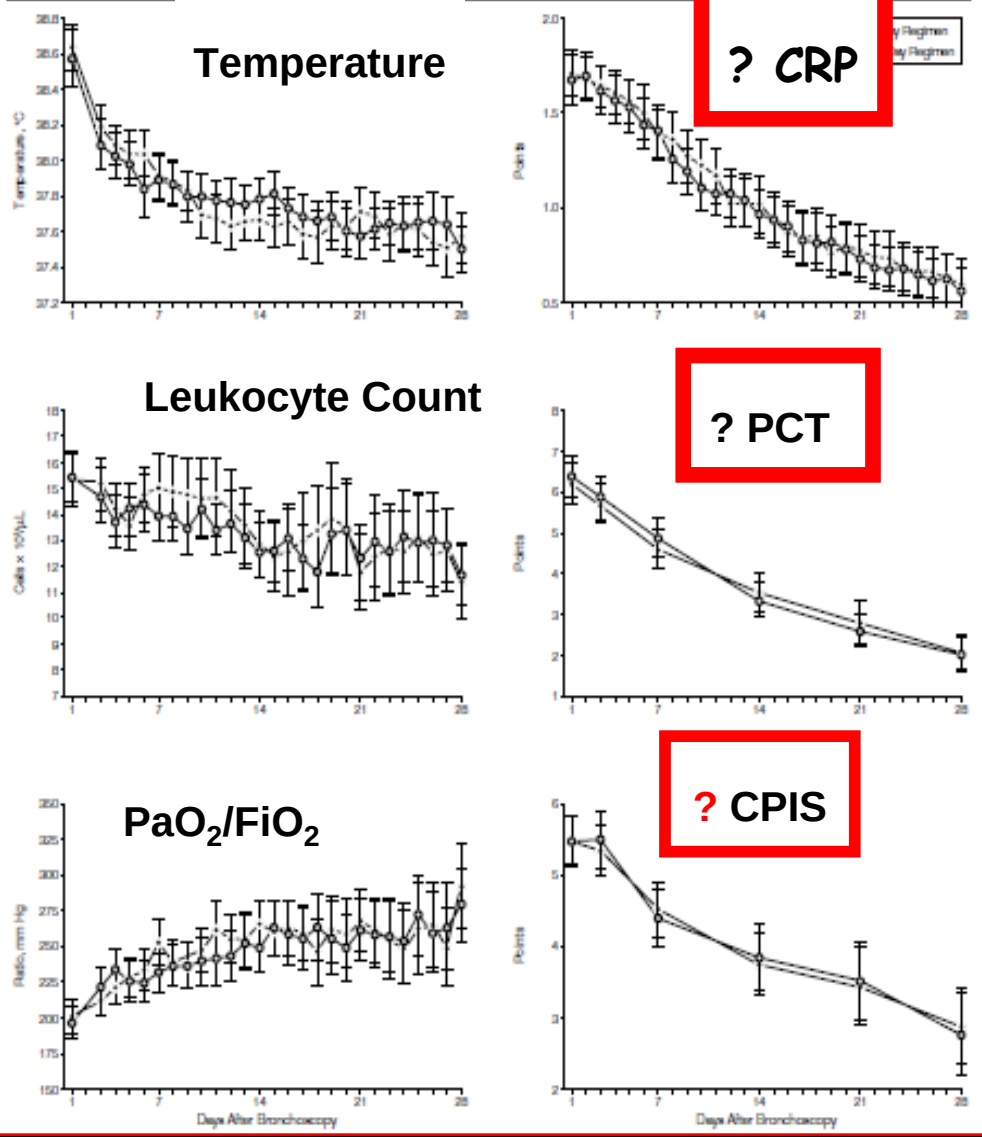

| No. at Risk | | | | | | | |
|---|---|---|---|---|---|---|---|
| 8-Day Antibiotic Regimen | 197 | 187 | 172 | 158 | 151 | 148 | 147 |
| 15-Day Antibiotic Regimen | 204 | 194 | 179 | 167 | 157 | 151 | 147 |

Probability of survival is for the 60 days after ventilator-assisted pneumonia onset as a function of the duration of antibiotic administration.

# Results of a RCT: 7 vs 14 days Of Therapy for VAP

Chastre, JAMA 2003; 290/2588

**Figure 3.** Physiological and Functional Score Changes From Day 1 to Day 28



# IDSA: VAP/VAT/HAP Recommendations

1. Enrollment: accept prior antibiotics >24-36 hr
2. Quantitative microbiology: to define pathogen & antibiotic sensitivity.
3. Outcomes: mortality, clinical response, bacterial load, ventilator/ICU/hospital days, serial biologic markers, relapse rates, etc.
4. VAP/VAT efficacy data: can extrapolate to HAP

# Summary Points

1. Microbiology = key for assessing antibiotic efficacy
3. VAT & VAP may overlap; VAT precedes VAP, and could be a target for clinical antibiotic trials & VAP prevention studies.
4. Endpoints should include mortality plus clinical response to therapy, outcomes & serial biomarkers should be assessed.
5. Focus on VAP: can extrapolate to HAP
6. Pharmacology data & models are valuable
7. A "ACTG" clinical evaluation model for therapy and prevention, with pharma, is recommended!

# The Future of Antibiotic Trials for HAP & VAP....

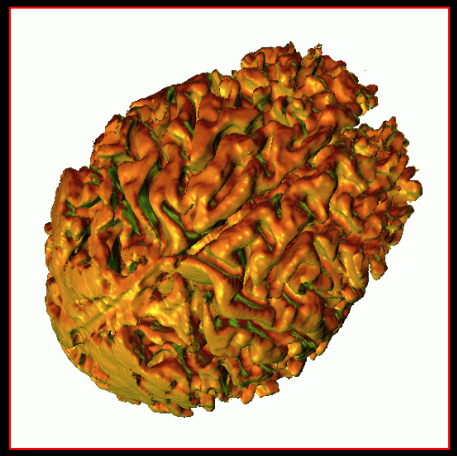
If you keep doing the same thing, you will keep getting the same results.....

"BAD BUGS....NO DRUGS"

**If you want to do better.....**

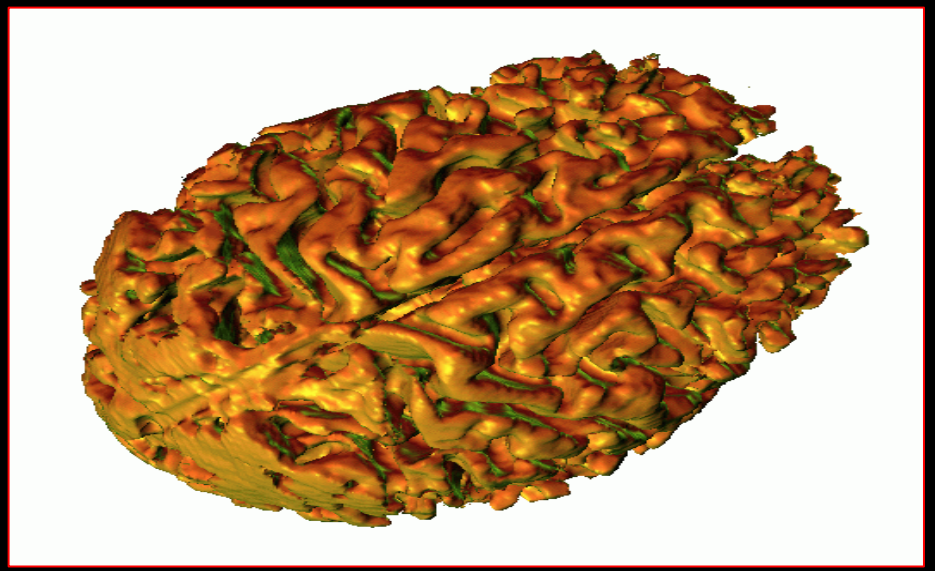
**try something new!**

Man's mind, once stretched
by a new idea,
never regains its original dimension.
-- Oliver Wendell Holmes



Before

After



# ISSUES IN CLINICAL TRIALS FOR HAP/VAP

## Anti-infective Advisory Committee
## November 4, 2011

James Floyd, MD, MS
University of Washington
Public Citizen

# OUTLINE

Background

1. Endpoints
2. Noninferiority margin
3. Study population
4. Conduct of trial

# HAP/VAP

- 2010 FDA Draft Guidance
  - Mortality as endpoint
  - Micro ITT as primary analysis
  - No prior antibiotics

# TRIAL DESIGN FOR HAP/VAP

- There are a number of options
  - Superiority: EXP vs. active-control
  - Superiority: EXP vs. placebo as add-on therapy
  - Noninferiority: EXP vs. active-control

# ELEMENTS OF A NI TRIAL

- Reliable evidence of a treatment effect of the active control
- Choose clinically meaningful NI margin
- Similar patient characteristics, concomitant treatments, and same outcome
- Design and conduct trial to minimize bias toward similar treatment effect

# ENDPOINTS: HAP/VAP

- Mortality
  - Only reliable evidence of a treatment effect for antibiotics on a valid outcome
- Test-of-cure (TOC)
  - Poorly-defined outcome that includes biomarkers
  - Not a valid clinical endpoint or surrogate endpoint

# NONINFERIORITY MARGIN

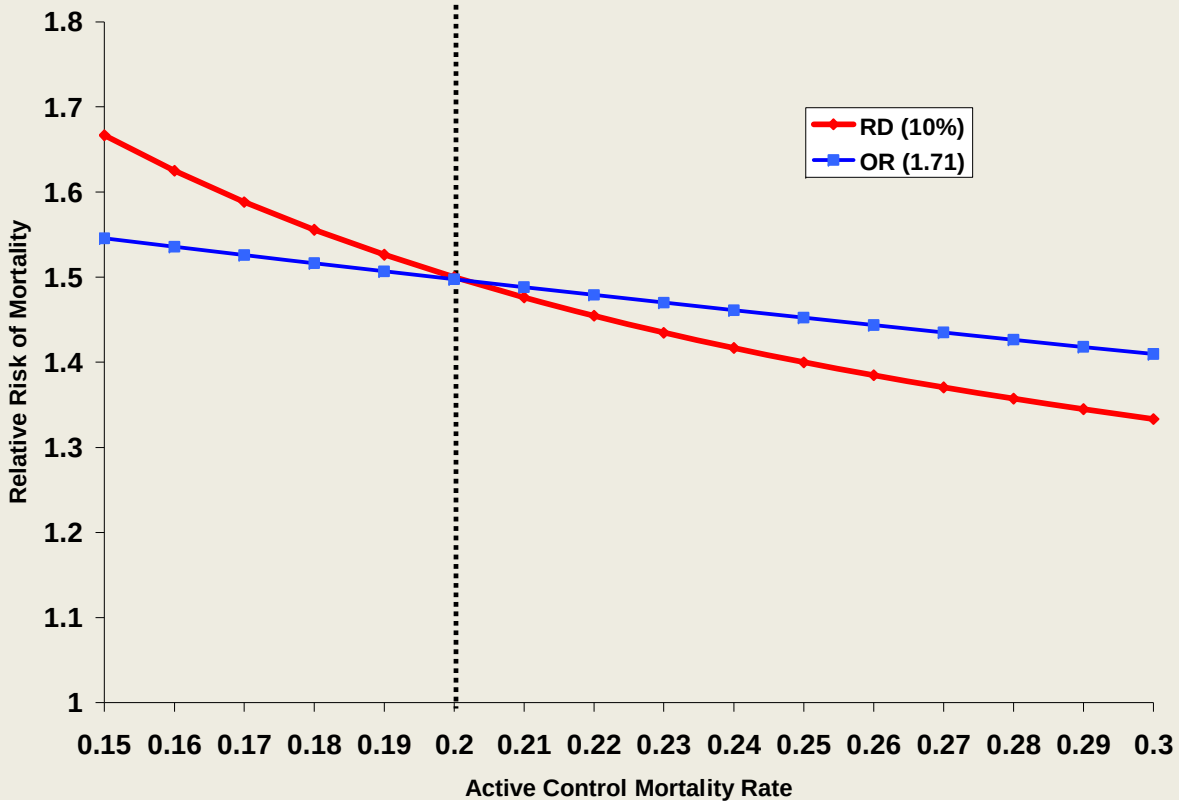
- First, need reliable statistical evidence of a treatment effect for the active control (M1)
- Next, decide how much harm is tolerable (M2)
- It is difficult to justify > 10% M2 on an important outcome like mortality when treatments that reduce absolute risk by 2-3% are considered highly effective

# NI MARGIN: HAP/VAP

- M1: ~ 20% reduction in mortality with Abx in a population with 20% mortality
- To preserve half of this benefit when control group mortality = 20%, M2 is 10%
- If control group mortality < 20%, M2 of 10% preserves < half the treatment effect
- If control group mortality only 10%, M2 of 10% preserves NONE of the treatment effect

# NI MARGIN: HAP/VAP

- Can use margin based on odds ratio rather than risk difference (OR = 1.71)



# STUDY POPULATION

- Subjects must have evidence of infection with bacterial pathogens
  - Micro ITT is the appropriate primary analysis
  - Use of non-culture methods should be encouraged

# STUDY POPULATION

- Separate trials for HAP/VAP ideal
- A single HAP/VAP trial would requires independent confirmation in another trial
  - Could be for a related indication, such as CABP, but would require mortality endpoint
- Each trial should be powered to evaluate M2 ≤ 10% for micro ITT population
- Conducting two HAP/VAP trials with a single pooled analysis of micro ITT population is inadequate

# AN EXAMPLE: XIGRIS

- Approved on basis of a subgroup of a single trial (PROWESS)
  - Reduced risk of death in severe sepsis

**FDA Drug Safety Communication: Voluntary market withdrawal of Xigris [drotrecogin alfa (activated)] due to failure to show a survival benefit**

**Safety Announcement**

**[10-25-2011]** The U.S. Food and Drug Administration (FDA) is informing healthcare professionals and the public that on October 25, 2011, Eli Lilly and Company announced a worldwide voluntary market withdrawal of Xigris [drotrecogin alfa (activated)]. In a recent study, Xigris failed to show a survival benefit for patients with severe sepsis and septic shock.

# TRIAL CONDUCT

- Prior antibiotics active against HAP/VAP pathogens – an exclusion criterion
  - Even if common, biases trial towards NI
  - Might be reasonable to reduce period when prior Abx prohibited if this helps enrollment
- Concomitant antibiotics
  - Also problematic, biases trial towards NI
  - Difficult to interpret trial if high rate of concomitant Abx usage

# AN EXAMPLE: DORIPENEM

| | Doripenem (N=134) | | | | Piperacillin/tazobactam (N=119) | | | |
|---|---|---|---|---|---|---|---|---|
| | Total | Baseline *P. aeruginosa*, n (%) | | | Total | Baseline *P. aeruginosa*, n (%) | | |
| | n (%) | Yes | No | Unk | n (%) | Yes | No | Unk |
| Use of any adjunctive anti-pseudomonal therapy | | | | | | | | |
| No | 29 (22) | 2 (7) | 26 (90) | 1 (3) | 18 (15) | 2 (11) | 15 (83) | 1 (6) |
| Yes | 105 (78) | 16 (15) | 88 (84) | 1 (1) | 101 (85) | 17 (17) | 83 (82) | 1 (1) |
| ≤2 days | 10 (7) | 1 (10) | 9 (90) | 0 | 11 (9) | 0 | 10 (91) | 1 (9) |
| 3 to 5 days | 52 (39) | 5 (10) | 47 (90) | 0 | 50 (42) | 2 (4) | 48 (96) | 0 |
| > 5 days | 43 (32) | 10 (23) | 32 (74) | 1 (2) | 40 (34) | 15 (38) | 25 (63) | 0 |
| Use of amikacin | | | | | | | | |
| Yes | 104 (78) | 16 (15) | 87 (84) | 1 (1) | 100 (84) | 17 (17) | 82 (82) | 1 (1) |
| ≤2 days | 9 (7) | 1 (11) | 8 (89) | 0 | 11 (9) | 0 | 10 (91) | 1 (1) |
| 3 to 5 days | 52 (39) | 5 (10) | 47 (90) | 0 | 49 (41) | 2 (4) | 47 (96) | 0 |
| > 5 days | 43 (32) | 10 (23) | 32 (74) | 1 (2) | 40 (34) | 15 (38) | 25 (63) | 0 |

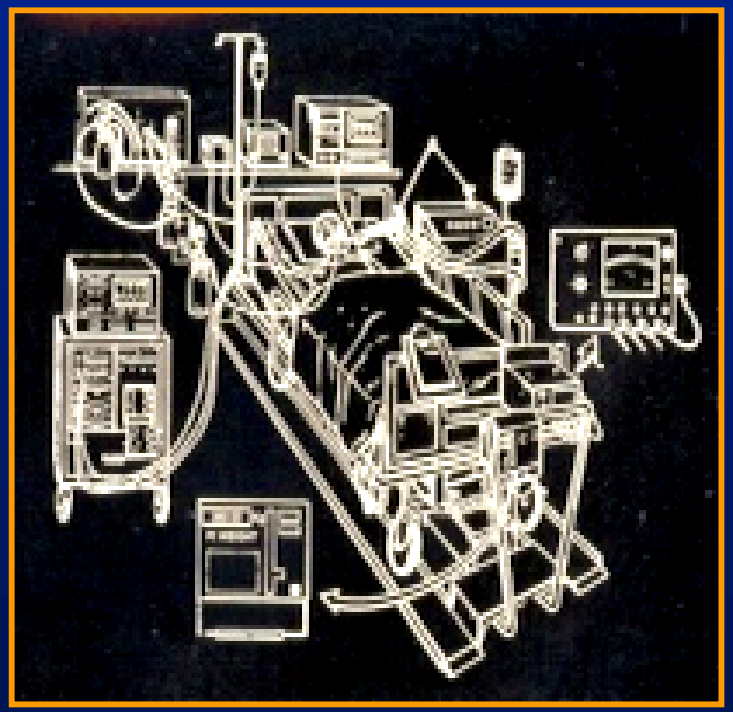
| **TOC** | Doripenem n/N (%) | Piperacillin/tazobactam n/N (%) | Difference % (95% CI) |
|---|---|---|---|
| Clinically evaluable | 109/134 (81.3) | 95/119 (79.8) | 1.5 (-9.1, 12.1) |
| Clinical MITT | 148/213 (69.5) | 134/209 (64.1) | 5.4 (-4.1, 14.8) |

| **MORTALITY** | Doripenem (N=223) n (%) | Piperacillin/tazobactam (N=221) n (%) | Relative Risk (Dori/Pip-tazo) (95% CI) |
|---|---|---|---|
| During iv therapy | 21 (9.4) | 9 (4.1) | 2.3 (1.1, 4.9) |

# CONCLUSION

- FDA has made great advances in regulation of HAP/VAP trials
- Only valid endpoint for NI trial in HAP/VAP is mortality
- NI margin should be justified (≤10% for RD, 1.71 for OR)
- Study population should be valid (micro ITT)
- Use of additional Abx is problematic

# Endpoints and Clinical Trial Issues in Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia



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- Scientific Advisory Board/Consultant—Astellas, Bayer, Cerexa/Forest, DaiichiSankyo,Merck, Nabriva, Pfizer, Tetraphase

# HAP/VAP-Clinical trials Issues

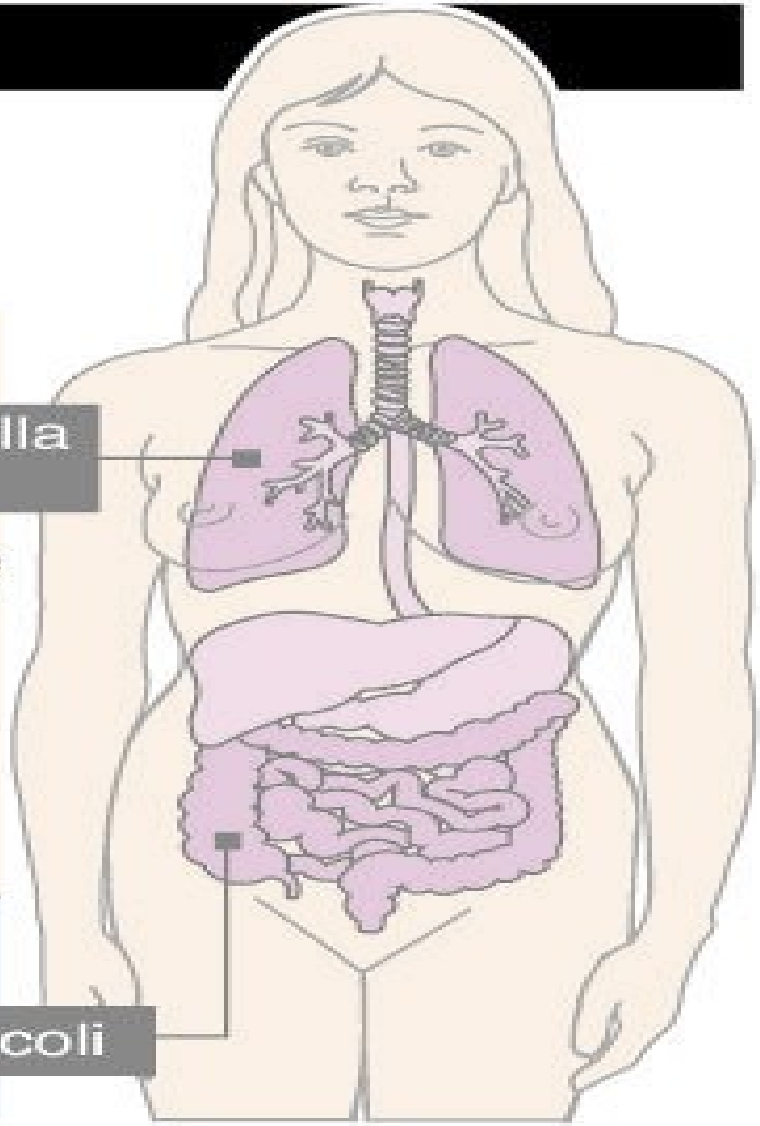
- Clinical crisis
  - Lack of effective antimicrobial agents for MDR pathogens
  - Lack of development
    - » Many companies withdrawing due to uncertainty of guidance
    - » Abstract LB-27 IDSA 2011: 7 new agents for GNR in early development, none for HAP/VAP studies (Boucher et al.)
- Need FEASIBLE clinical study guidance
  - Will require innovative approaches-not business as usual
  - Reflect standard of care (Guideline principles)
  - Pt safety optimal-Requires individualized care; difficult to generalize to any one specific regimen

# SUPERBUGS

## A Global Attack

# New superbug in UK

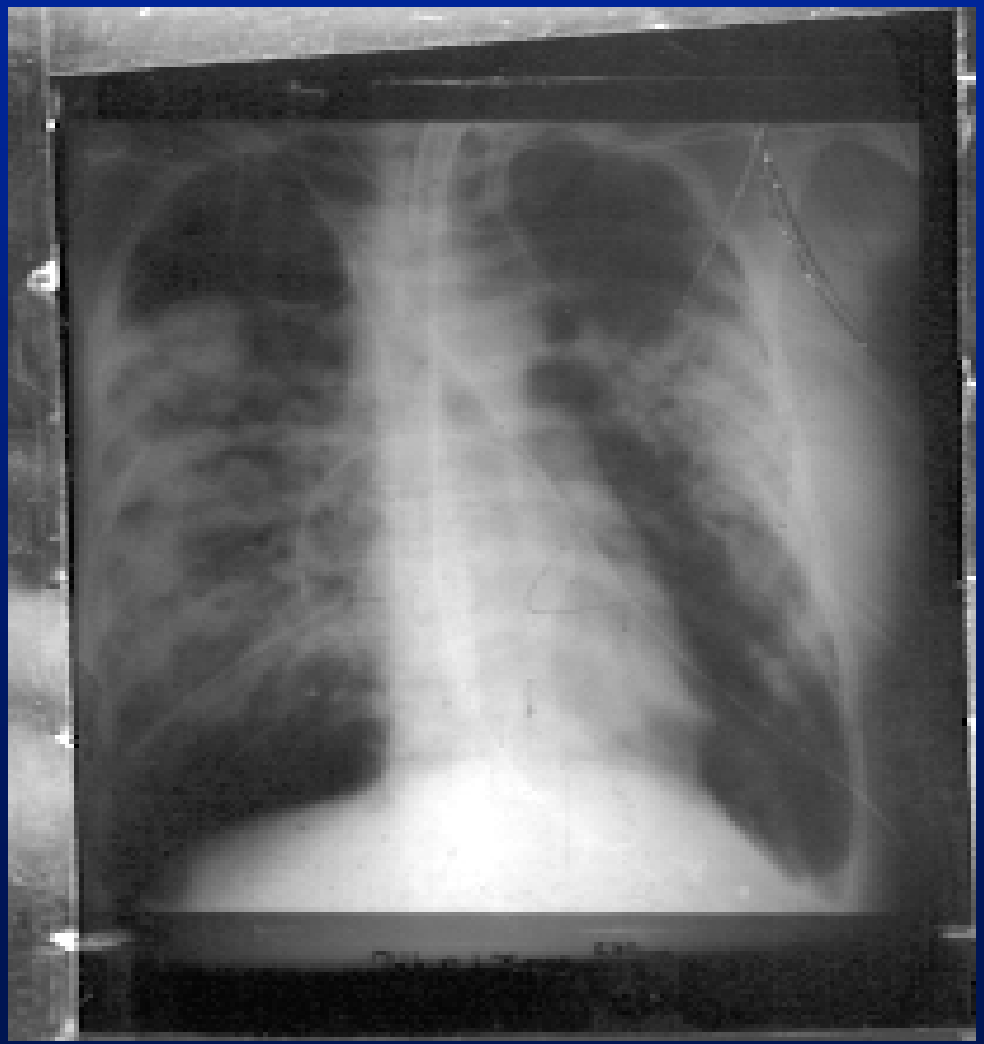
**New Delhi metallo- -lactamase-1**, or NDM-1 for short, is an enzyme that can live inside different bacteria. Any bacteria that carry it will be resistant to antibiotics


**Two types of bacteria have been host to NDM-1:** the gut bacterium E.coli and another that can invade the lungs called Klebsiella pneumonia. Both can lead to urinary tract infections and blood poisoning

Press Association Graphic

# Case : 68 y/o male in ICU on ventilator for 21 days (Post-op infection)



- Prior ABX for Abdominal infection (MDR in ICU)
- Develops fever, pulmonary infiltrates.  Has NG tube.
- T-102$^{0}$F; P-110; BP-130/90; Lungs-bilat rhonchi.
- ET aspirate-moderately purulent secretions.
- **Does this patient have Pneumonia?**
- **Diagnostic studies?**
- **Therapy?**

# HAP/VAP-Clinical trials Issues

- Need for individualization: Specific De-escalation associated with lower mortality

Table 3
Mortality rates in relation to de-escalation status

| Study (Reference Number) | De-Escalation | No De-Escalation | Escalation | *P* Value |
|---|---|---|---|---|
| 1. SooHoo et al,[10] 2005 | | | | |
| • Mortality at 14 d, guided group | 6.6% | 13% | — | — |
| • Mortality at 30 d, guided group | 20% | 32% | — | — |
| 2. Leone et al,[18] 2007 | | | | |
| • Mortality | 18% | 11% | — | 0.15 |
| 3. Alvarez-Lerma et al,[19] 2006 | | | | |
| • Mortality | 14.6% | 20.4 | 33.3% | — |
| 4. Giantsou et al,[17] 2007 | | | | |
| • Mortality at 15 d, all pts | 5.1% | 31.7% | — | <0.05 |
| • Mortality at 28 d, all pts | 12% | 43.5% | — | <0.05 |
| 5. Joffe et al,[16] 2008 | | | | |
| • Mortality at 28 d in pts with | | | | |
| Negative cultures | 22.2% | 19.6% | — | 0.66 |
| Positive cultures | 17.2% | 14.1% | — | 0.53 |
| • Hospital mortality in pts with | | | | |
| Negative cultures | 26.5% | 33% | — | 0.28 |
| Positive cultures | 22.8% | 17.4% | — | 0.32 |
| 6. Kollef et al,[12] 2006 | | | | |
| • Mortality at 30 d | 17% | 23.7% | 42.6% | 0.001 |
| 7. Eachempati et al,[22] 2009 | 33.8% | 42.1% | — | 0.324 |
| 8. Stolz et al,[21] 2009 | | | | |
| • Mortality at 28 d | 16% with PCT protocol | 24% without PCT protocol | — | 0.327 |

Niederman et al. Clinics in Chest Med. 2011; 32: 517-34

# HAP/VAP-Clinical trials Issues

"Although randomized controlled trials are ideal, logistic considerations for such a study are almost insurmountable. The obstacles include the large number of patients required to attain statistical power and the difficulty in establishing a definitive diagnosis."

Sun et al. Chest 2011;139;1172-11

# NOSOCOMIAL PNEUMONIA Diagnostic Dilemma

- "The diagnosis of HAP is difficult…the specificity of the diagnosis undefined
  - ATS/IDSA, 2005
- "The diagnosis of HAP and VAP is a challenge, and….controversial"
  - Canadian Guidelines, 2008
- "The diagnosis of pneumonia, HAP, VAP is difficult and there are no universally accepted 'gold' standard diagnostic criteria
  - British Society for Antimicrobial Chemotherapy, 2008
- "Debate continues about the appropriate standard for the diagnosis of VAP. Clinical criteria alone are generally nonspecific"
  - Shorr et al. Crit Care Med 2005
- "VAP represents a great challenge to clinical practice and has triggered numerous discussions regarding the best diagnostic approach
  - The Cochrane Collaboration, 2009

# Review of key points for Treatment Guidelines for HAP and VAP: basis for recommendations

Among various Guidelines, there is relatively consistent recommendations regarding diagnosis and treatment

- DX:
  - Clinical: Infiltrate + 2 of Fever, Leukocytosis, Purulence
  - Microbiological: Obtain LRT sample
    - ETA or BAL but need + culture
- Therapy: Stratify by risk factors
  - Combination for high risk patients
  - Duration based on clinical response (?CPIS; biomarkers)
    - 7-15 days

File T. Clin Infect Dis. 2010; 51 (Suppl 1): S42-47

# AIDAC--Considerations

- Primary efficacy endpoint of all-cause mortality, expected mortality, and timing of mortality
- Number Phase 3 trials
- Use of prior antibacterial agents
- MITT as primary population

# Mortality: How much?

- Empiric Antibiotic Therapy of VAP: systematic review and meta-analysis
  - 41 trials, 7015 patients
  - **Overall mortalilty 20.3%;** treatment failure 37.4%
  - Overall No mortality differences observed for monotherapy vs combination therapy (one study showed comb ceftazidime/aminogly inferior to meropenem monotherapy)

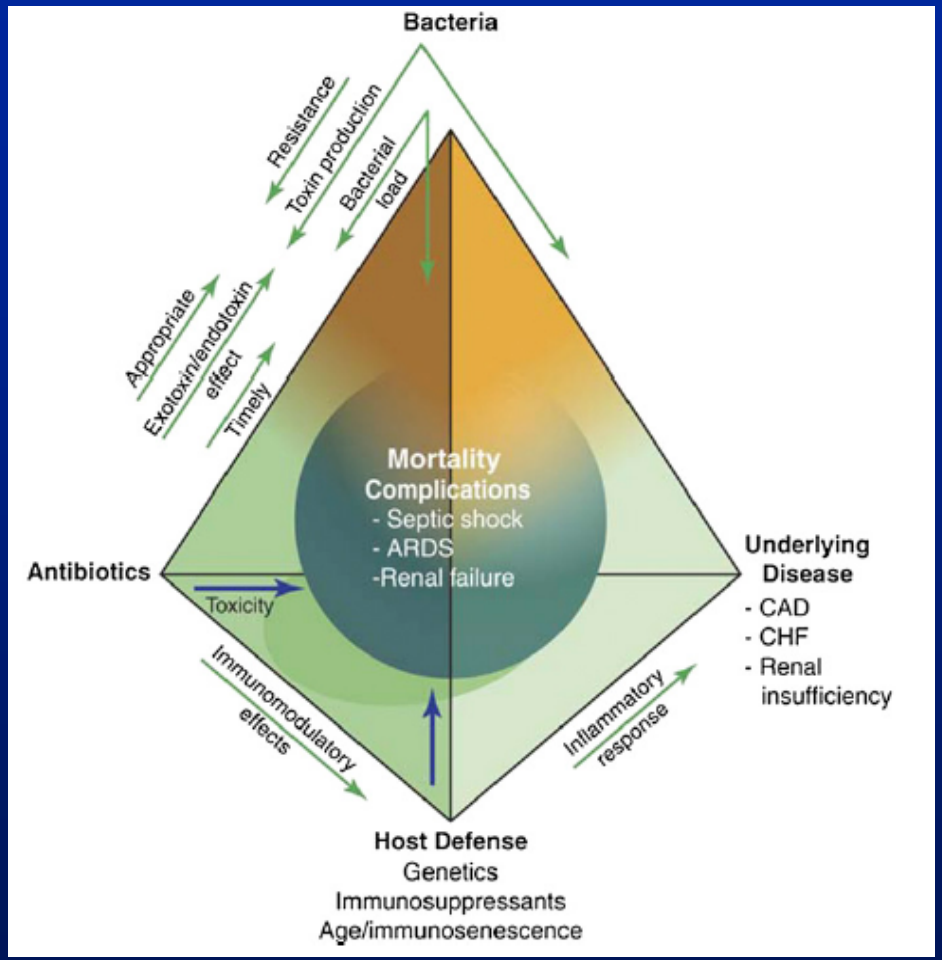
Aarts et al. Crit Care Med. 2008; 36: 108-17

# Mortality: RCTs Studies

- Doripenem vs Imipenem (VAP)[1]
  - "We found the 28-day mortality rate to be substantially lower (**10.8%** in the doripenem arm and **9.5%** in the imipenem arm), and this may be due to the impact of the stringent inclusion/exclusion criteria that excluded unstable patients with acute respiratory distress syndrome, septic shock, severe renal disease or dialysis, or immediately life threatening"
- Linezolid vs Vancomycin (VAP)[2]
  - **8.8%** of ITT population (14-day All-cause Mortality; **13.6%** 28-day ACM))
  - APACHE II and IBMP-10 scores may not be the ideal tools to adjust for severity of disease….age was significantly associated with all-cause mortality at day 14.
- Tigecycline vs Imipenem (VAP)[3]
  - Tigecycline **19.1%**; Imipenem **11.5%**
- Televancin vs. Vancomycin (HAP & VAP; All Treated)[4]
  - Televancin 20**%**; Vanc 18.6**%**

1. Chastre et al. Crit Care Med 2008 Vol. 36, No. 4; 2. Peyrani et al. Abstract 362 IDSA 2011;
3. Tygacil ™ PI; 4. Rubenstien et al. Clin Infect Dis. 2011;52(1):31–40

# MORTALITY: Multifactorial

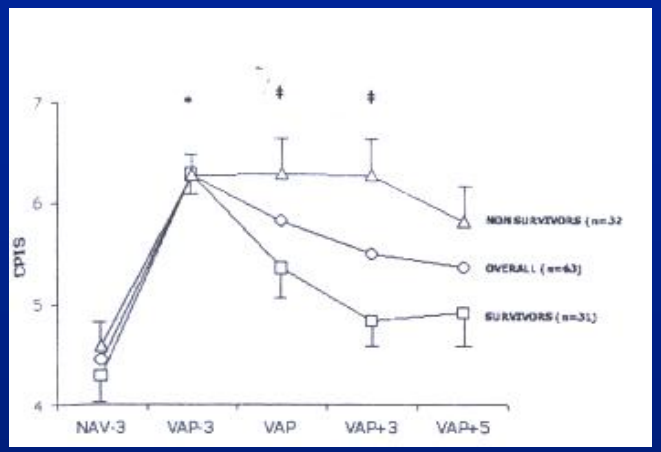


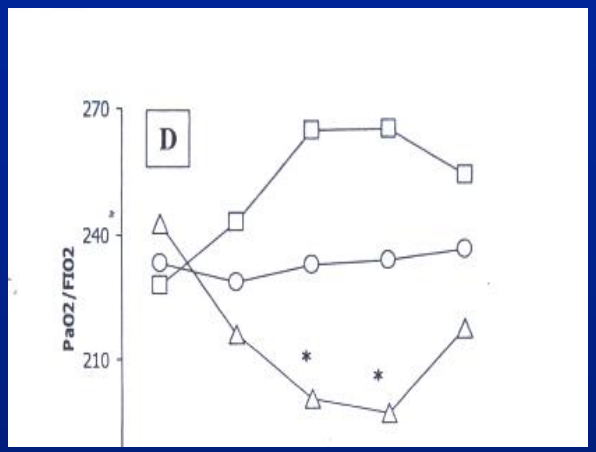

Waterer , Rello, Wunderink Am J Respir Crit Care Med Vol 183. pp 157–164, 2011

- Multifactorial (Antimicrobial just one factor)
- Most ICU patients don't die directly of sepsis; often from withdrawal of care
- "We have become very good at keeping patients alive in the ICU..early mortality will never even approach 15%...late assessment, disconnect between antibiotic treatment and mortality"
  (Wunderink R personal communication)

# Clinical Outcomes

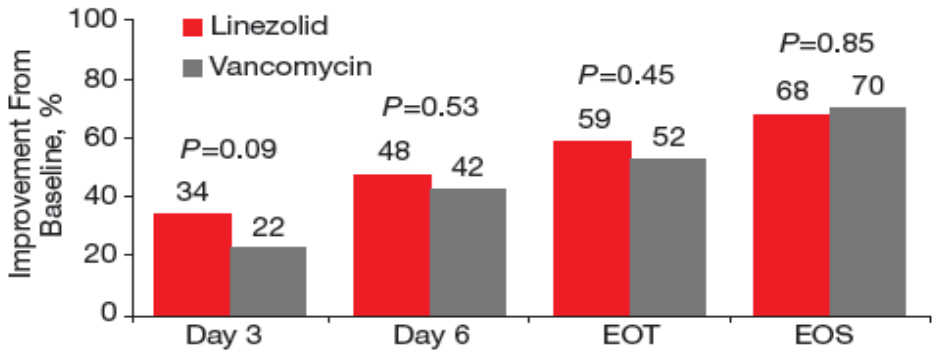
- CPIS Luna et al. Crit Care Med. 2003; 31: 676-82




- Rubenstein et al. Abstract 572 IDSA 2011

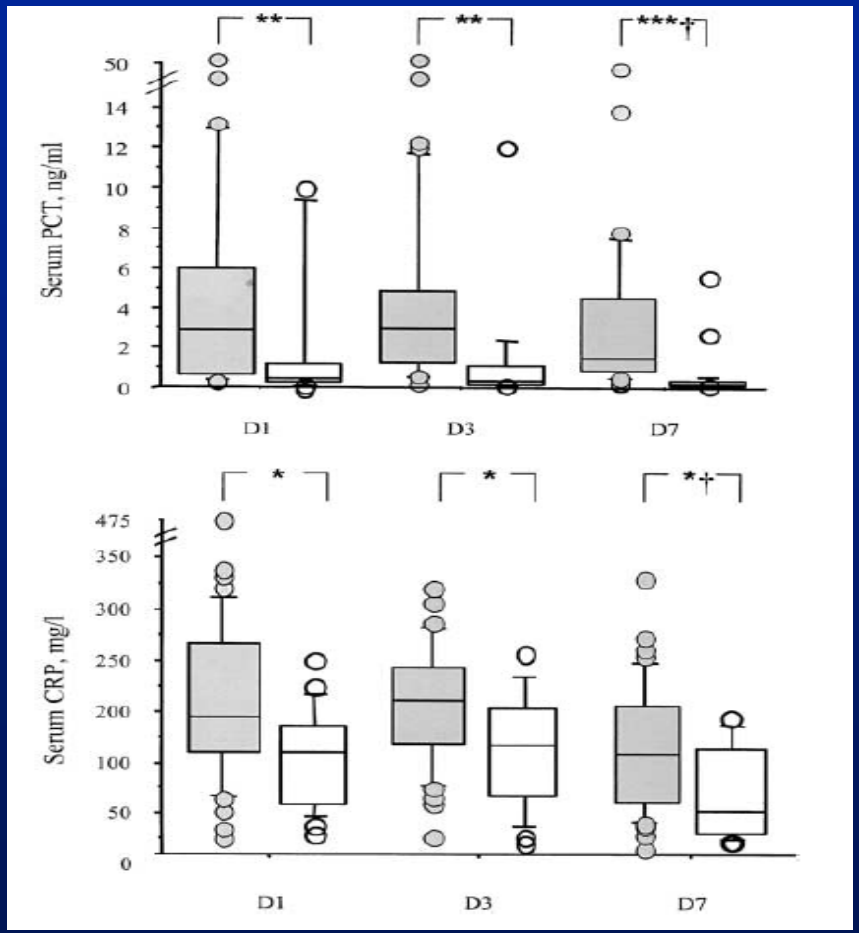
**Figure 3.** Effect of Treatment on Hypoxemia Among Ventilated Patients With MRSA-NP Treated With Linezolid Versus Vancomycin in the Per-Protocol Population.




MRSA, methicillin-resistant *Staphylococcus aureus*; NP, nosocomial pneumonia; EOT, end of treatment; EOS, end of study.
Missing values were excluded from the analyses.

# Outcomes in VAP-Procalcitonin

Kinetics of serum procalcitonin (*top)*
*and C-reactive protein (bottom) in VAP*



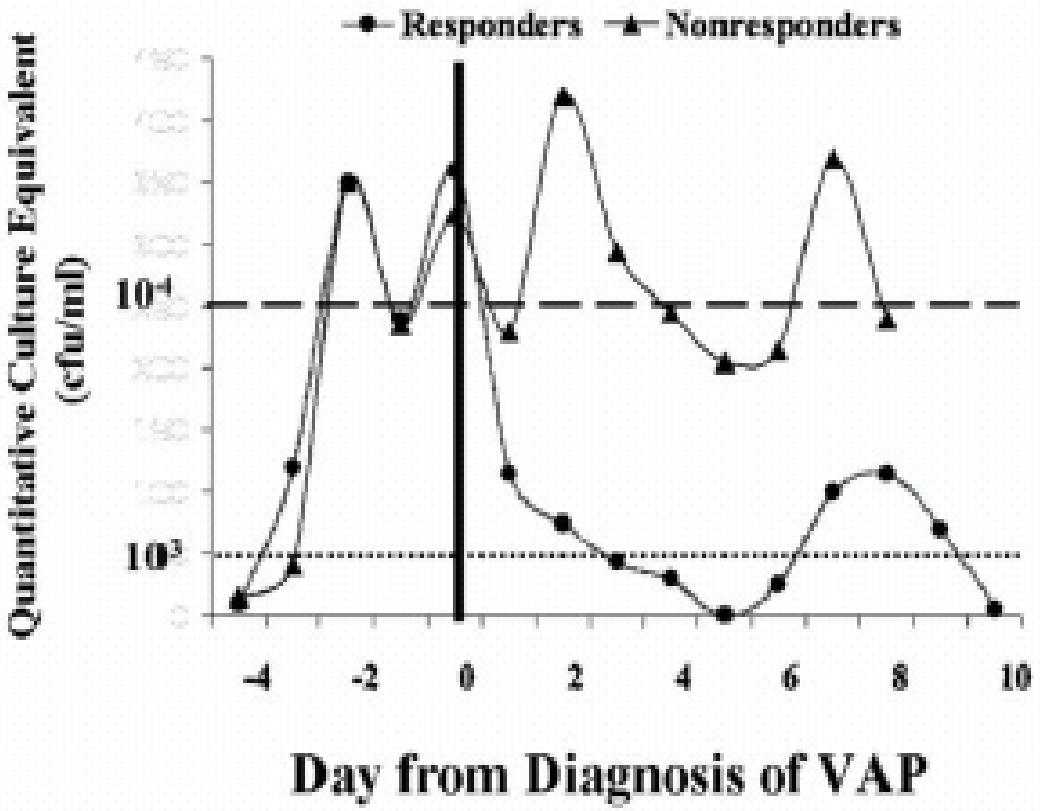

*horizontal line showing the median*
and *T bars the 10th and 90th percentiles. Circles represent outliers.* *p 0.05, **p 0.001, and ***p 0.0001 for comparisons between

- Serum procalcitonin levels decreased during the clinical course of VAP but were significantly higher from Day 1 to Day 7 in patients with unfavorable outcomes. Multivariate analyses retained serum procalcitonin levels on Days 1, 3, and 7 as strong predictors of unfavorable outcome.

- Conclusion: Based on these data, procalcitonin could be a prognostic marker of outcome during VAP.

Luyt et al. Am J Resp Crit Care Med. 2005; 171: 48-53

# Microbiological Response




- 64 patient requiring MV for pneumonia (CAP and NP)
- "NBLs yielded only $10^3$ cfu/ml, or were sterile…exceptions were with *S. auerus* or *P. aeruginosa*

From Wunderink R. Clin Infect Dis. 2010 51(S1):S126–S130; modified from A'Court CH et al. Quart J Med 1993; 86:635–648.

# Prior Antimicrobials

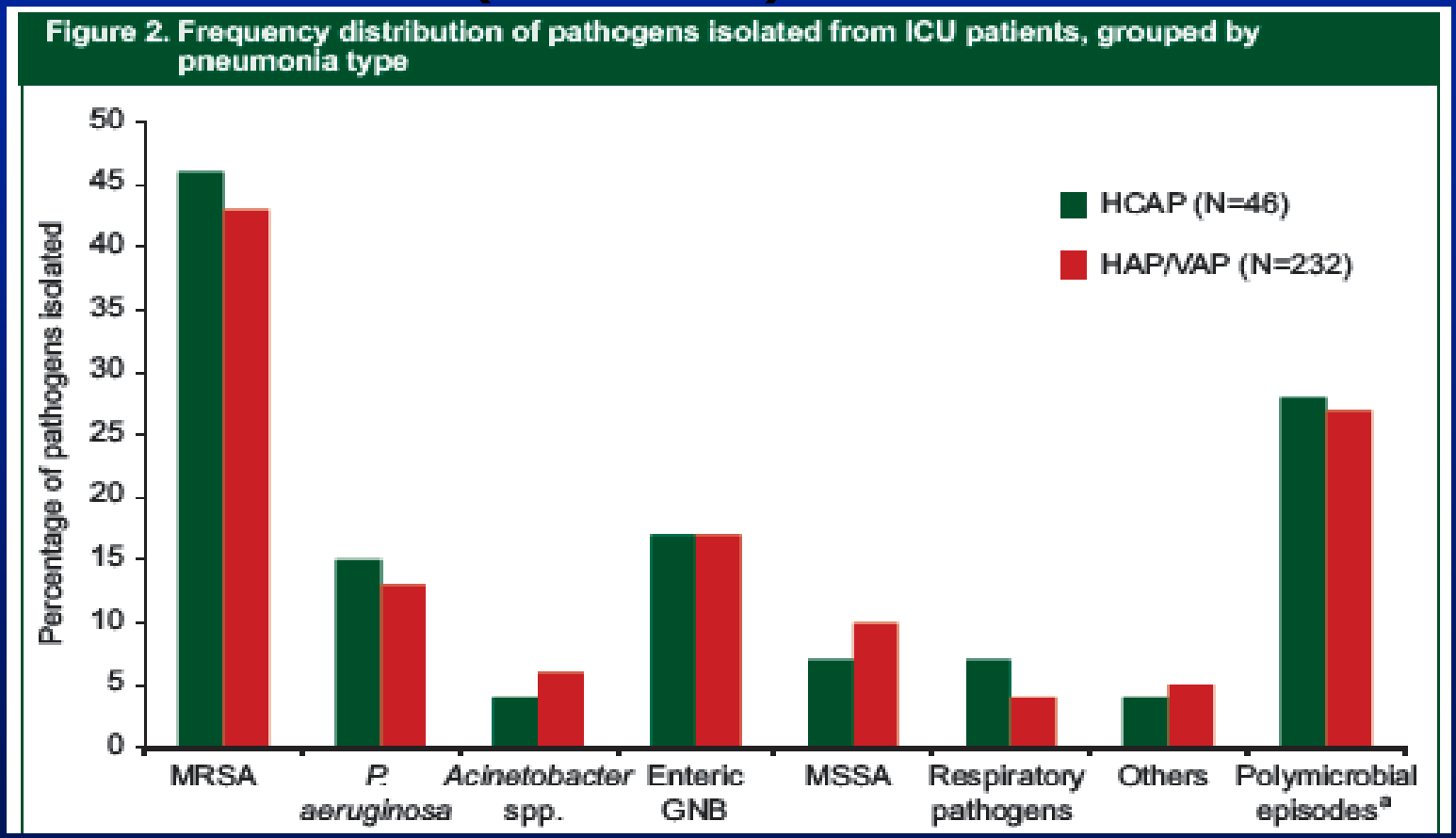
- Allow
  - Patient outcomes affected
    - » Early therapy associated with decreased mortality
    - » Sepsis studies: 1 hour delay increases mortality by 7%
  - Most patients in ICU on prior antimicrobials
  - Significant pathogens not eradicated early
    - » MRSA [1]
    - » GNR [2]
  - Mortality may be higher in patients on prior therapy[3]

1. Wunderink R et al. Chest 2008; 134; 1200-7; 2. Dennesen PJ, et al. *Am J Resp Crit Care Med*. 2001;163:1371-1375; 3. Rello J et al. Chest 2009; 136 (Suppl 5): e30.

# Number of Trials

- Must be feasible
- If too restricted, will never be able to acrue number to provide meaningful results
- Consider one VAP trial with support from PK/PD data and other indications
- Include HCAP admitted to ICU on ventilator
  - Microbiology similar to VAP (File et al. Abstract 368 IDSA 2011)

# Evaluating Healthcare-Associated Pneumonia (HCAP) in Intensive Care




- Retrospective analysis of 278 patients
- MDR Pseudomonas similar in HCAP and HAP/VAP
- HCAP requiring ICU has similar etiology as HAP/VAP

File et al. Abstract 368 IDSA 2011 Boston

# Trial Design-Comparator

- Doubt can use one regimen
  - Variable MDR patterns at different sites
- Consider Individual Optimal Baseline Therapy
  - Specify after ID of pathogen(s)
  - Some of newer anti-GNR agents have some selective antimicrobial spectrum (may be good for Acinetobacter sp or KPC but not Pseudomonas and visa versa)

# Clinical Trials: Barriers

| Barrier | Response |
|---|---|
| Prior ABX; Early therapy associated with decrease mortality | Allow ABX therapy prior to enrollment (most in ICU will have prior ABX) |
| Consent Forms (Intimidating), time consuming; Pts too sick and family too concerned | Well trained Study staff; Allow prior ABX while obtaining Consent |
| Study agents not active against all relevant pathogens | Allow adjuctive therapy initially; specify after ID of pathogen(s); May require non traditional dosing: extended or continuous infusion, Alternative agents: Combinations, Colistin |
| Regimens limited by international availability | Allow “State of Art” Comparison; Use “optimized baseline therapy” initially, then specific after ID of pathogen |
| VAP bundles=Reduced incidence VAP | Will prolong enrollment; consider fewer cases before preliminary, restricted approval |

Source: File T. Personal Experience; Talbot G Clin Infect Dis. 2010; 51 (Suppl 1): S144-49

# Endpoints and Clinical Trial Issues in Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia--Considerations

- Feasible studies
  - Achievable by industry and optimal care of patients
  - 20% mortality too high for RCTs
  - Allow prior Antibacterials (early therapy)
  - Use molecular tests
  - Endpoints
    - » Early and 28 day time periods; Morality and Clinical; Microbiological; Procalcitonin?
  - Include HCAP (especially admitted to ICU)

# Endpoints and Clinical Trial Issues in Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia--Considerations

- Feasible studies
  - Smaller VAP studies supported by other indications
  - Recognize Barriers
  - Optimize Care
    - Broad spectrum then DE-ESCALATION
    - Consider Optimal comparator then De-escalate
    - Difficult to use fixed comparator
    - IRB issues
  - Clinical Trials Networks
    - NIH; CAPO; IMPACT-VAP; EPIC; Other groups

PhRMA

# Development of Drugs for HABP-VABP

**Robert A. Fromtling, PhD**

**Merck & Co, Inc.**

**FDA AIDAC, Nov 4, 2011**

# Question 1

- **Please discuss the merits and limitations of the single trial plus supportive information proposal for HABP/VABP. Please discuss the types of supportive evidence that would be considered acceptable if only a single trial is conducted.**
  - PhRMA consensus view: We agree with FDA that one trial can be sufficient when paired with data from another indication
  - We even think that one trial alone could suffice in some cases
  - Here's why…

# How many trials for *any* indication?

- **Core requirement: 21 CFR 314.126**
  - "Reports of adequate and well-controlled [clinical][1] investigations provide the primary basis for determining whether there is 'substantial evidence' to support the claims of effectiveness for new drugs."
- **Important implications**
  - Preclinical data are usually insufficient alone[2]
  - Adequate & well-controlled clinical data are required
  - Confirmation via more than 1 trial is desired: thus the word investigations in the CFR above
  - FDA has flexibility:[3] Other confirmatory evidence may be acceptable at FDA's discretion in support of an adequate and well-controlled trial

[1]The word "clinical" is not actually in this sentence but is clearly stated elsewhere in the same paragraph. [2]The animal rule suggests that preclinical data alone can be used in some specific high-risk unmet need medical situations (e.g., approval of ciprofloxacin for anthrax). [3]Both 21 CFR 314.105 and 21 CFR 312.80 speak of FDA having broad flexibility in applying statutory standards.

# The particular case of antibiotics

- **What might this mean for antibiotics? For example,**
- **Do we really need two trials in every indication?**
  - Infection is unusually rich in non-clinical confirmatory data
- **…..or, can we can we approach this differently by**
  - Allowing for the uniquely powerful preclinical estimates[1] of antibiotic efficacy?
  - Allowing for the fact that the way antibiotics work (i.e., their 'pharmacological effect')[2] is identical across all settings?
  - Allowing for our ability to show exposure-response correlations from human studies that reproduce the exposure-response effects proven in animals?

[1]We can determine the critical exposure required for efficacy in a test tube and in a mouse. If this exposure is achieved in man, the likelihood of efficacy is very high. [2]That effect is, of course, the drug's effect on bacteria. The "receptor" for all current antibiotics is some aspect of microbial physiology. Ultimately, the patient's improved symptoms are an "off target" consequence of bacterial clearance.

# The goal: Independent substantiation

- **Let's look at this again – Guidance for Industry ***
  - "The usual requirement for more than one adequate & well-controlled investigation reflects the need for independent substantiation of experimental results.
  - A single clinical experimental finding of efficacy, unsupported by other independent evidence, has not usually been considered adequate scientific support."
- **Interestingly, the requirement is not replication**
  - FDA 1998: There are other possible paths
  - Related diseases, related endpoints

*Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. CDER/CBER, May 1998.

# Independent Substantiation

- **Two trials: Trials in related diseases where the general purpose of therapy is similar[1]**
  - A reasonable start. *One trial in each of two indications should be seen as a very strong registration package*
- **One trial? Multiple endpoints from different events[2]**
  - Combining pharmacological/pathophysiological endpoints[3] with clinical endpoints is permitted…
  - … (when) pathophysiology of disease and mechanism of action of therapy are very well understood and…
  - … (when) the linkage between the pharmacological effect[4] and the clinical outcome is strong
  - *This has precedent and fits antibiotics very nicely[5]*

[1]Sections C.2.e and C.2.f, Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products. CDER/CBER, May 1998.. [2]Ibid, C.3.d. [3]Ibid, C.2.h. [4]e.g., effect on bacterial load. [5]Use of a single study is permitted by the US Food, Drug, and Cosmetic Act, Section 505(d): "If the Secretary determines, based on relevant science, that data from one adequate and well-controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness, the Secretary may consider such data and evidence to constitute substantial evidence for purposes of the preceding sentence."

# Other issues
## HABP & VABP vs. each alone

- **The proposed separation of HABP from VABP**
  - Will reduce program feasibility – it's hard enough to enroll one patient group, much less each separately
  - Separate studies approach is artificial – both are bacterial infections of the lung, both are managed in the same way
- **We group other infections**
  - Appendicitis and colon perforation are both part of cIAI
  - Pyelonephritis and lower UTI are both part of cUTI
- **An appropriate balance would be**
  - Permit both in the same study
  - Require a minimum percentage with VABP – consult with FDA
  - We would suggest requiring at least 25% VABP in a HABP-VABP study as the requirement for "Nosocomial bacterial pneumonia, including ventilator-associated pneumonia"

# Single trial and single trial/indication approaches are needed to permit flexible development

- **Medically relevant package *for a label making limited claims* could consist of:**
  - One adequate & well-controlled study in one indication,
  - Plus consistent microbiological effect data in that indication,
  - Plus consistent exploratory micro/clinical data in other indications,
  - Plus supportive preclinical and clinical pharmacologic predictions.
  - *Other indications would require single additional studies*
- **Labeling *would note approval data set* and also discuss**
  - Potential for activity against important types of resistant pathogens
  - Current understanding of the likelihood of activity beyond the current indication(s). Many disease settings are not feasible to study. Physicians are often forced to make educated guesses – let's help them by making the label as informative as possible

# Question 3 (yes, this is out of order)

- **Please discuss the preferred timing for the all cause mortality endpoint. Would an assessment at an earlier time point be preferred to the 28-day assessment?**
  - PhRMA consensus view: If mortality is to be used, we think 28-days makes as much sense as anything else
  - But, this begs the question – Is mortality a good endpoint?
  - Here's our thinking…

# What is the most relevant and informative endpoint?

- **Issue: All-cause mortality (ACM) has many limitations**
  - A recent position paper endorsed by four societies (IDSA, ATS, ACCP, SCCM) emphasizes that "limiting trials to a mortality-only primary efficacy end point is not consistent with standard clinical practice." [1]
  - ACM is reduced by supportive care and increased by underlying disease[1,2]
  - Fever, oxygenation, etc. are routinely assessed. "Failure to consider (these) decreases clinical relevance and creates a risk that results of registrational studies will not extrapolate well to postapproval use". [1]

- **Suggestion: While ACM is a possible endpoint, clinical response based on clinical stabilization (with survival) may be more appropriate and relevant:**
  - Better reflect current medical practice and treatment scenarios
  - Clinical stabilization based on parameters similar to those used to evaluate ceftaroline for CABP[3] would be biologically & medically sound
  - Supporting example: $PaO_2/FiO_2$ changes are linked to mortality[4]

*[1]Spellberg et al. Clin Infect Dis 51:S150-70 2010; [2]Wenzel AAC 54:4956-60, 2010; [3]Temperature, heart rate, respiratory rate, blood pressure, oxygen saturation, and mental status; [4]Combes et al, Crit Care Med 2007; 35:146-54*

# Thus, we suggest “mortality+”

- **“Mortality+”: Clinical stabilization with survival**
  - Require survival to 28 days
  - Require physiological improvement without a change in antibiotics
  - This really is what physicians want to know
- **This should give a success rate around 70%**
- **With this as the success rate, we would now think of an Odds Ratio-based margin of 1.714 (same as 10% margin at 80% success)**
  - Now let’s examine Question 2….

# Question 2

- **Please discuss if a noninferiority margin of 10% will be acceptable if the active control mortality rate is less than 20%. Please discuss if the odds ratio or risk difference metric is preferred when the control mortality rate is less than 20%.**
  - PhRMA consensus view: At our preferred endpoint ("mortality+"), we would select an Odds Ratio (OR) margin of 1.714
  - If we must stay with the less informative endpoint of mortality, we think that agreed designs must tolerate a mortality rate of as low as 15%
  - In that case, we believe the risk difference metric with a margin of 10% still applies at a mortality rate of 15%

# With “mortality+” as the endpoint…

- **Odds Ratio margin of 1.714**
- **We the think the trial design should be similar to CABP**
  - OR margin of 1.714 (~10% at 80%) in ITT population
  - OR margin of 2.15 (~15% at 80%) in micro-proven ITT
- **Resulting study at 90% power**
  - 336/arm (672 total) for ITT population
  - At 70% evaluable, need to enroll 214/arm to have enough for the micro-proven ITT at 90% power (so, this has sufficient power and is a reasonable patient enrollment goal)

# But if you really must use the endpoint of mortality (1 of 2)

- **At a 20% mortality rate…**
- **We still believe the design should be similar to CABP**
  - Margin of 10% for ITT population
  - Margin of 15% for micro-proven ITT population
- **We would power assuming 20% mortality**
  - Using Risk Difference (RD) for margin, gives a larger n/arm than 15% mortality
  - We believe this requires 336/arm or 672 for the ITT analysis
  - We believe this might be feasible
- **With this study size and a 20% mortality rate**
  - At worst case, point estimate is -3.6%, or 1.18-fold increase
  - ≤ 2.5% probability of a ≥ 1.5-fold increase (at 10% margin)

# But if you really must use the endpoint of mortality (2 of 2)

- **And at a 15% mortality rate…**
- **And with the study size on the previous slide…**
  - At worst case, point estimate is -4.2%, or 1.28-fold increase
  - ≤ 2.5% probability of a ≥ 1.67-fold[1] increase (at 10% margin)
- **For the micro-proven ITT confirmatory analysis**
  - At 70% micro-proven, study is over-powered for 15% margin
  - Current N is adequate for 12% margin at 90% power
- **Must take all the data together**
  - Within the bounds of all the other approximations we've used, this hypothetical 17% difference is well within the overall error of the method
  - The micro-proven ITT provides further support
  - As do all the other supportive data / other trials

[1]NI boundary allows 25% test v 15% control mortality → 1.67-fold increase

# The elephant in the room

- **FDA has assumed 70% rates of microbiology proof**
  - True (perhaps) for Gram-negatives
- **But, two important narrow-spectrum cases are now rendered inaccessible**
  - *S. aureus*
  - *P. aeruginosa*
- **At rates of 25% (*S. aureus*) and 10% (*P. aeruginosa*), agents limited to these pathogens would require trial sizes 3- to 7-fold larger than those already discussed**
  - The sample sizes are staggering: A *P. aeruginosa*-focused program would require 2900/arm to prove non-inferiority at an OR margin of 1.71

# Questions 4a and 4b

a. **Should a patient who develops HABP/VABP while receiving antibacterial drugs for other infections be enrolled in a HABP/VABP trial? If so, please discuss some scenarios where this will be acceptable.**

b. **If empiric antibacterial treatment for HABP/VABP has begun prior to enrollment in the trial, what duration of therapy would be acceptable and unlikely to confound interpretation of the treatment effect of the study drug? Please describe your rationale. Please discuss what other information might be useful to address this question.**

# Prior antibiotics

- **Prior antibiotics for other infections**
  - If the patient develops an HABP/VABP while on something else, the prior "something else" can be ignored
- **Brief courses of other empirical therapy**
  - We believe that permitting 24 hr of other empirical therapy is essential to successful recruitment. Without this proviso, we believe that the regulatory and clinical hurdles would be so high that antibiotics for HABP-VABP may not be developed
  - We also think that such patients are part of the standard usage patterns for any new drug
  - If you exclude those with prior empirical therapy, you will likely exclude critical subsets (e.g., the most seriously ill)
  - Futhermore, prior therapy would be expected to have uniform effect in all treatment arms, thus the clinical trial should still yield conclusive results

# Other issues
## Microbiology and Safety Database

- **Microbiology and breakpoints**
  - Although the focused programs being discussed today will enable progression of drug candidates, the smaller programs will lead to lesser numbers of micro-proven cases
  - There will likely be few (or no) cases at the population MIC90
  - This must not lead to setting the breakpoint at the MIC50
  - As discussed yesterday, it is critical to use clinical data, population MIC distributions, and PK-PD to set breakpoints
- **Safety database**
  - All prior comments have focused just on efficacy
  - It is a given that the overall program must accrue sufficient experience to give a reasonable view of the safety profile
  - This is not a specific number but depends on the AE pattern

# Other issues
## Diagnostic Clinical Criteria

The criteria proposed in the draft guidance will reduce trial feasibility and lead to enrollment of non-representative study populations

| Guidance Requirement | Issues | Recommendation |
|---|---|---|
| • Requirement of ≥ 3 clinical criteria for diagnosis of HABP/VABP: i.e.,<br>• Documented fever<br>• ↑↑ or ↓↓wbc count ; or bandemia ≥15%<br>• New onset purulent sputum or tracheal secretions | • Highly specific but poorly sensitive<br>• Patients > 65y are often normothermic despite serious infection<br>• Substantial proportion of potentially eligible patients may be excluded | • Require ≥ 2 clinical criteria with a positive CXR for diagnosis of HABP/VABP<br>• This has the best combination of sensitivity/specificity |

*Fabergas et al* Thorax. 1999 Oct;54(10):867-73.

| Variables | Sensitivity % (n) | Specificity % (n) | PPV % (n) | NPV % (n) |
|---|---|---|---|---|
| CXR + 2 criteria[1] | 69 (9/13) | 75 (9/12) | 75 (9/12) | 69 (9/13) |
| CXR + 3 criteria | 23 (3/13) | 92 (11/12) | 75 (3/4) | 52 (11/21) |

[1]Clinical criteria were fever, purulent secretions ,and leukocytosis

# Other issues:
## CPIS

The CPIS score requires data not available at enrollment. Its use to guide enrollment is not possible.

| Guidance Requirement | Issues | Recommendation |
|---|---|---|
| • CPIS > 6 required for eligibility | • Not validated as a prospective baseline diagnostic tool<br>• Pugin[1] calculated the score ***retrospectively*** & included results of tracheal aspirate culture (rarely available at baseline)<br>• Studies have shown diagnostic sensitivity and specificity is sub-optimal<br>• Current data suggests best use is as a prognostic tool[2] | • Do NOT require CPIS as a baseline entry criteria<br>• Collect CPIS and use for assessment of clinical progress |

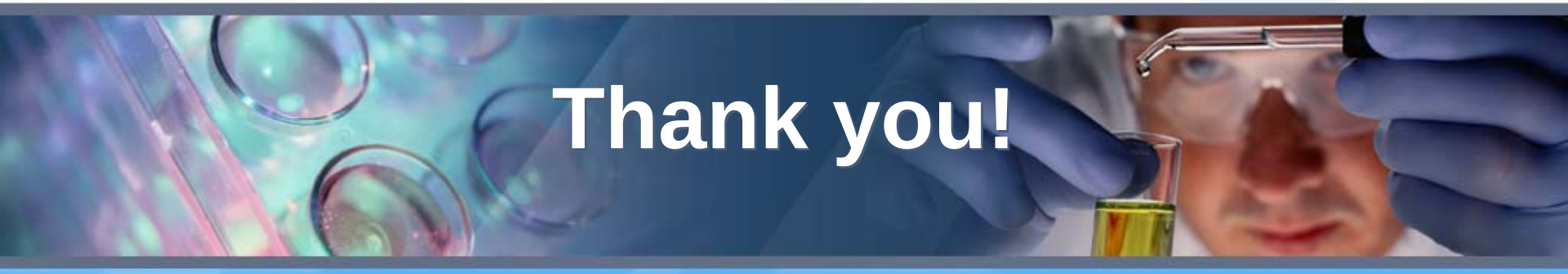
[1]Pugin J. Minerva Anestesiol 2002 Apr;68(4):261-5.

[2]Singh et al. Am J Respir Crit Care Med. 2000 Aug;162(2 Pt 1):505-11.

# Summary

- **One trial is enough when another indication is studied**
  - One trial by itself could be enough for a specific labeled indication
    - Labeling would include a summary of the studies
  - A sponsor might choose to do more
- **A mortality+ endpoint makes the most sense**
  - With an Odds Ratio-based margin, it also helps with sample size
- **We still have problems with**
  - Prior antibiotics: if not accommodated, we will be faced with significantly higher clinical trial barriers
  - Less common pathogens: staggering trial sizes required
  - Setting of breakpoints: clinical data must not be the only factor
  - Entry criteria: CPIS is inappropriate, simple rules are needed

PhRMA



# Thank you!

***Our head is round so that our thinking can change direction***

***(Francis Picabia)***