

# Ventilator Associated Pneumonia: Prevention and Treatment

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# Ventilator Associated Pneumonia (VAP)

- Causes significant morbidity/mortality in ICUs
- Accurate diagnosis is a major challenge
  - Affects treatment, prevention, study
- Prevention focuses primarily on limiting risk of aspiration of pathogens into LRT
- Empiric therapy increasingly broad as antimicrobial resistance advances
  - Obtain micro sample, reassess response at 48-72 hours, reduce duration of therapy

# Ventilator Associated Pneumonia

- Most common nosocomial infection in the ICU
  - 25% of all NI reported from Med-Surg ICUs
  - Affects between 9-27% of intubated patients
- Increased morbidity, mortality and LOS
  - Increases LOS by 7-9 days
  - Increases hospital costs by \$11- 40K
  - Attributable mortality from 0-50%!

Hidron AI, et al. Infect Cont Hosp Epidemiol 2008;29:996.

Safdar N, et al. Crit Care Med 2005;33:2184-93.

Rello J, et al. Chest 2002;122:2115-2121.

Rello J, et al. Chest 1991;100:439-444.



# CDC Definition of VAP

## Radiologic signs

≥2 serial chest radiograph<sup>†</sup> with at least 1 of the following:

- New or progressive *and* persistent infiltrate
- Consolidation
- Cavitation

## Clinical signs

At least 1 of the following:

- Fever (temperature >38 °C) with no other recognized cause
- Leukopenia ( $<4.0 \times 10^9$  cells/L) or leukocytosis ( $>12.0 \times 10^9$  cells/L)
- For adults ≥70 y of age, altered mental status with no other recognized cause

And ≥2 of the following:

New onset of purulent sputum, change in character of sputum, increased respiratory secretions, or increased suctioning requirements

New-onset or worsening cough, or dyspnea, or tachypnea

Rales or bronchial breath sounds

Worsening gas exchange (e.g., oxygen desaturation ratio [ $P_{aO_2}-F_{iO_2}$ ] ≤240, increased oxygen requirement, or increased ventilation demand)

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\* Data from the Centers for Disease Control and Prevention

† In patients without underlying pulmonary or cardiac disease (e.g., respiratory distress syndrome, bronchopulmonary dysplasia, pulmonary edema, or chronic obstructive pulmonary disease), 1 definitive chest radiograph is acceptable.

# Limitations of VAP Definitions

“The wards and the post-mortem room show a very striking contrast in their pneumonia statistics...”

Sir William Osler, 1907

- One third with VAP have no autopsy evidence
- One fourth without VAP have autopsy evidence
- Aspects of definition are subjective
- Conditions with similar clinical findings:
  - atelectasis, pulmonary edema, thromboembolic dz, ARDS, alveolar hemorrhage, hypersensitivity pneumonitis, pulmonary contusion, combinations of disorders (e.g. BSI + pulmonary edema)

# Ventilator Associated Pneumonia

## Organism Distribution: NHSN data


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Organism	% of all
<i>Staphylococcus aureus</i>	24.4
<i>Pseudomonas aeruginosa</i>	16.3
<i>Acinetobacter baumannii</i>	8.4
<i>Enterobacter</i> spp.	8.4
<i>Klebsiella pneumoniae</i>	7.5

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Hidron AI, et al. Infect Control Hosp Epidemiol 2008;29:996-1011.

## Ventilator Associated Pneumonia: Risk Factors (partial list)

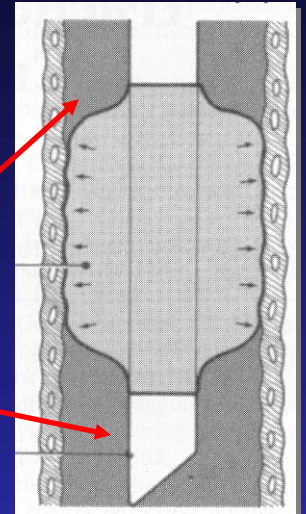
- *Mechanical ventilation*
  - Recumbent position
  - Increased gastric pH
  - Enteral feeding
  - ↓ level of consciousness
  - Advanced age
  - Male sex
  - Pre-existing pulmonary disease
- 
- aspiration

<http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5303a1.htm>

Niederman et al. Am J Resp Crit Care Med 2005;171:388-416.

# Pathogenesis of VAP

- Entry of pathogens into lower respiratory tract → colonization → infection
  - Leakage/aspiration around ET tube
  - Biofilm adherent to ET tube
- Inhalation of contaminated aerosols
- Direct inoculation
- Hematogenous spread
- Infection often multifocal
  - Sampling issues?



Niederman, Craven, et al. Am J Resp Crit Care Med 2005;171:388-416.



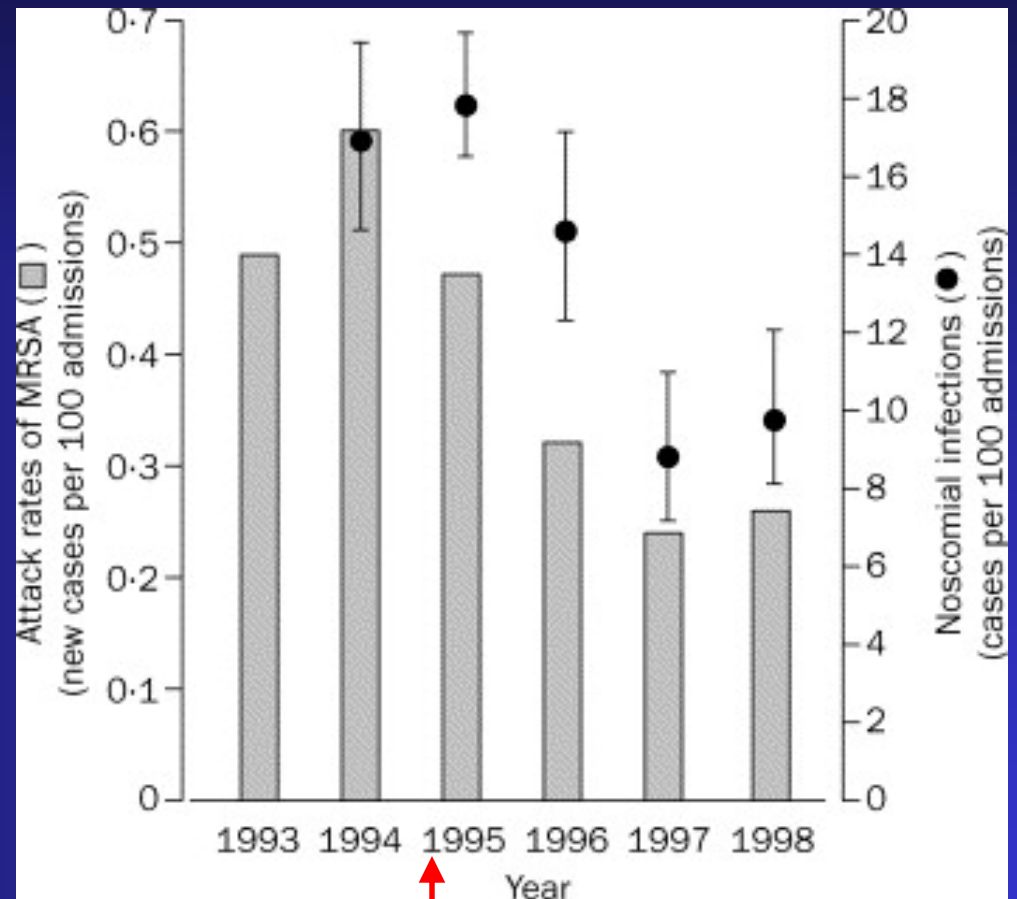
# Preventing VAP:

## ↓ use of mechanical ventilation

- Facilitate/accelerate weaning
  - Protocols require adequate staffing
  - Reintubation also increases VAP risk
- Use non-invasive ventilation when possible
  - Positive pressure ventilation/facemask
  - COPD exacerbations, acute hypoxemic respiratory failure, immunocompromise with infiltrates and respiratory failure

# Preventing VAP: Reducing pathogen transmission

- Hand hygiene
  - Hospital-wide hand hygiene campaign with alcohol product led to ↓ in overall nosocomial infection rate



Pittet D, et al. Lancet 2000;356:1307.

# Preventing VAP: Reducing aspiration risk

- Head of bed elevation (30-45 degrees):

- Torres et al, *Annals of Int Med* 1992;116:540-543
- Ibanez et al. *JPEN* 1992;16:419-422
- Orozco-Levi et al. *Am J Respir Crit Care Med* 1995;152:1387.
- Drakulovic et al. *Lancet* 1999;354:1851-1858
- Davis et al. *Crit Care* 2001;5:81-87
- Grap et al. *Am J of Crit Care* 2005 14:325-332

- Subglottic suctioning:

- Mahul et al. *Int Care Med* 1992;18:20-25
- Valles et al. *Ann Int Med* 1995;122:179-186
- Kollef et al. *Chest* 1999;116:1339-1346
- Smulders et al. *Chest* 2002;121:858-862
- Dezfulian et al. *Am J Med* 2005;118:11-18

# Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: A randomized study\*

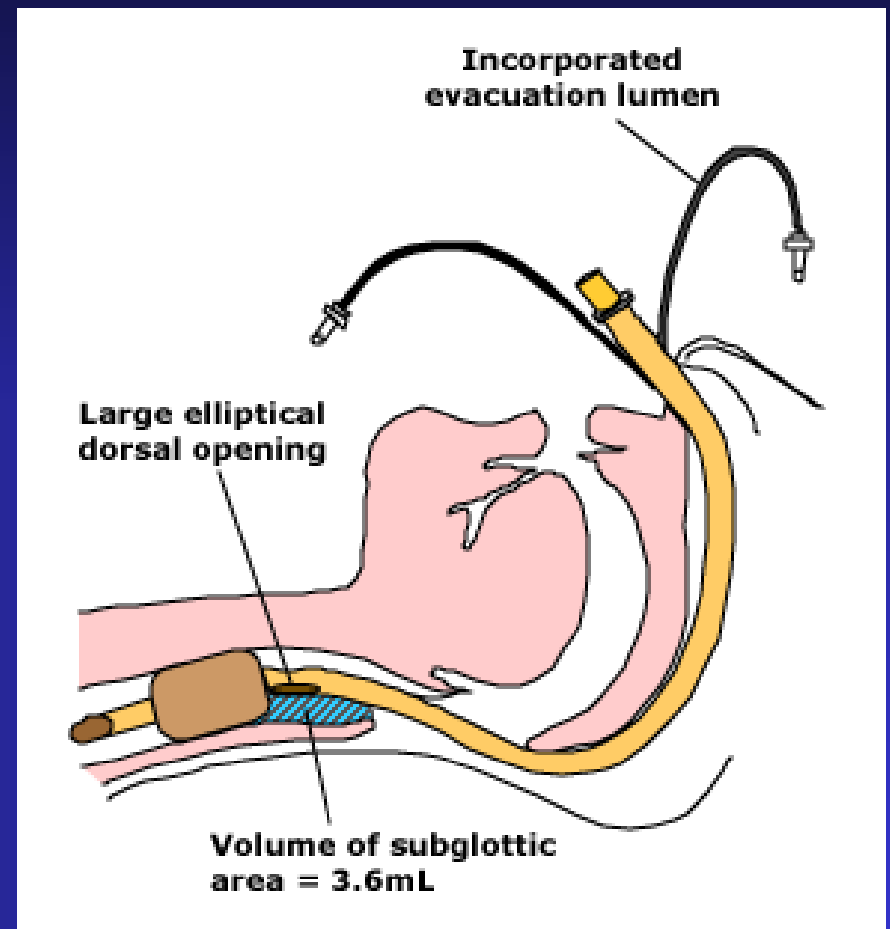
Christianne A. van Nieuwenhoven, MD; Christine Vandenbroucke-Grauls, PhD; Frank H. van Tiel, PhD; Hans C. A. Joore, MD; Rob J. M. Strack van Schijndel, MD; Ingeborg van der Tweel, PhD; Graham Ramsay, PhD; Marc J. M. Bonten, PhD

Crit Care Med 2006;34:396

- Pts randomized to target HOB of 45° (n=112) vs standard care (10°) (n=109)
- Achieved difference was 28% vs. 10%, with no significant difference in VAP rate
- Generalizability (can HOB elevation be maintained? Are any patients tx at 0°?)

# Preventing VAP: Continuous subglottic suctioning

- Meta-analysis,  
5 studies, 896 pts
  - VAP RR = 0.51;  
95% CI 0.37-0.71
  - Greatest effect in  
those intubated  
>72 hrs



Dezfulian et al. Am J Med 2005;118:11-18

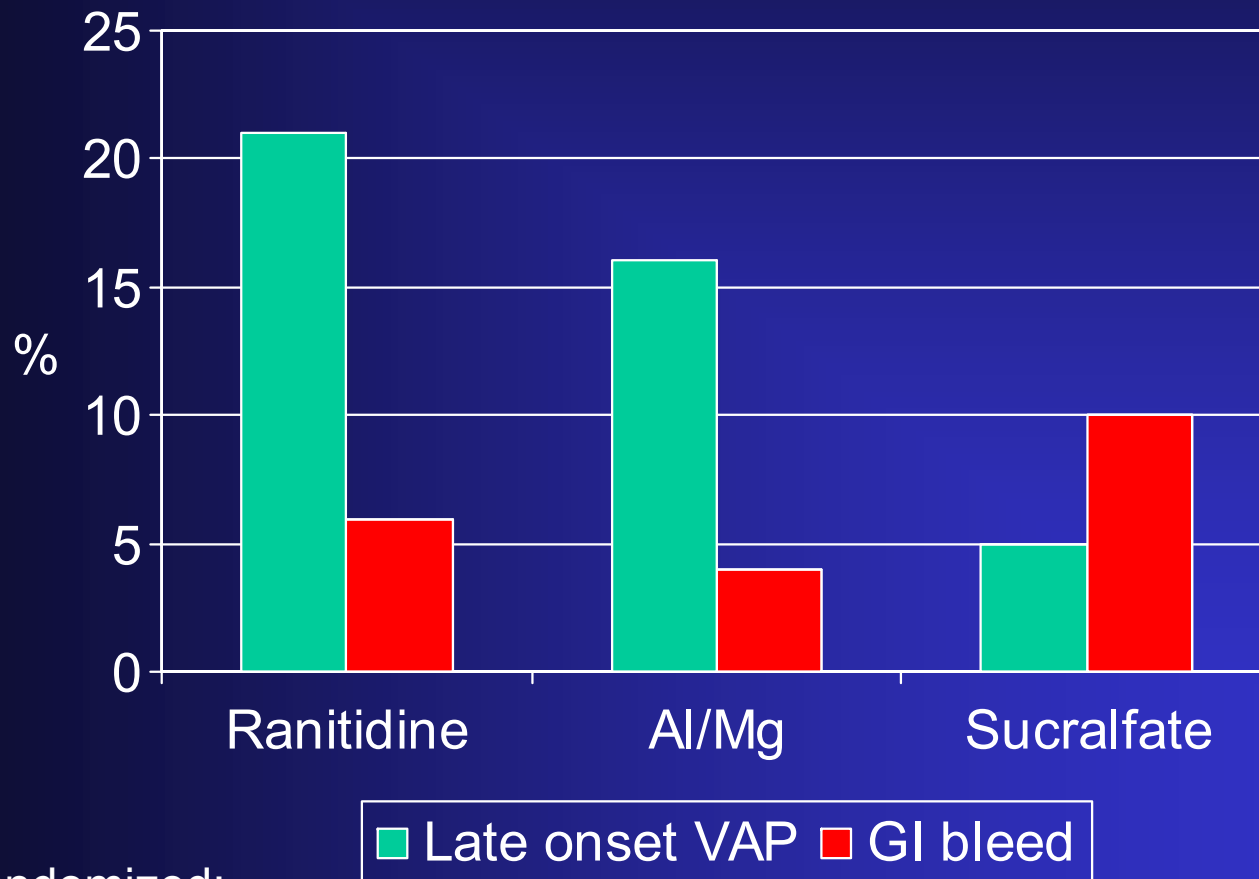
# Preventing VAP: The “sedation vacation”

- Daily interruption of sedation:
  - 128 patients on mechanical ventilation randomized to daily interruption of sedation until awake
  - Duration of ventilation 4.9 vs. 7.3 days (p=0.004)

Kress JP et al. N Engl J Med 2000;342:1471-77.

# Preventing VAP: Choice of ulcer prophylaxis

- Ranitidine vs. Al/MgOH vs. sucralfate

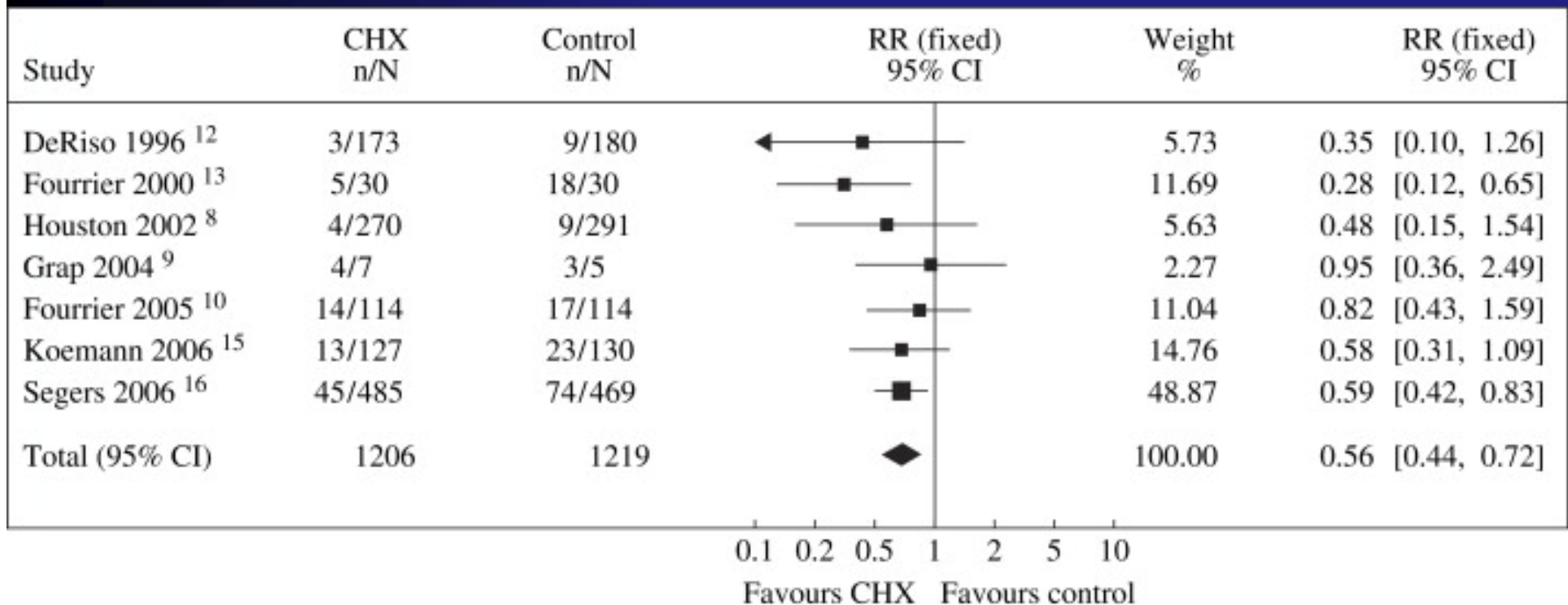


N = 244 randomized;  
213 observed > 4 days

Prodhom et al. Ann Intern Med 1994;120:653.

# Preventing VAP: Chlorhexidine oral care

- 2 meta-analyses published in 2007:
  - 11 RCTs → RR 0.56 [95% CI, 0.39-0.81]<sup>1</sup>
  - 7 RCTs → RR 0.58 [95% CI, 0.44-0.72]<sup>2</sup>



(1) Chan et al. BMJ 2007;334:889. (2) Kola et al. J Hosp Infect 2007;66:207.



# Preventing VAP:

## Antibiotic Use: Selective DD +/- systemic

- Complex literature, variety of regimens used, definitions for outcome measure, etc.
  - 16 RCTs, 3361 patients<sup>1</sup>
    - OR 0.35 [95% CI, 0.29-0.41] for VAP
    - OR 0.8 [95% CI, 0.69-0.93] for mortality
  - 54 RCTs, 9473 patients<sup>2</sup>
    - OR 0.11 [95% CI, 0.06-0.2] for Gram negative LRTI
    - OR 0.52 [95% CI, 0.34-0.78] for Gram positive LRTI

(1) D'Amico et al. BMJ 1998;316:1275.

(2) Silvestri et al. Anaesth Intensive Care 2008;36:324.

# Digestive or Oropharyngeal Decontamination?

- Cluster randomized, crossover trial in 13 Dutch ICUs, S-DD v. S-OD v. standard care
- All regimens used over 6 months in each ICU
- S-DD: IV cefotaxime + tobra-colistin-ampho B
- S-OD: oropharyngeal application only (T-C-A)
- Only those with expected ICU stay > 72 hrs
- 5939 enrolled, 28 day mortality = 27.5%
- MLR model compared to standard care:
  - S-OD: OR 0.86 [0.74-0.99] for 28 d mortality
  - S-DD: OR 0.83 [0.72-0.97] for 28 d mortality

De Smet et al. N Engl J Med 2009;360:20.

# S-DD for VAP Prevention

- Pro:

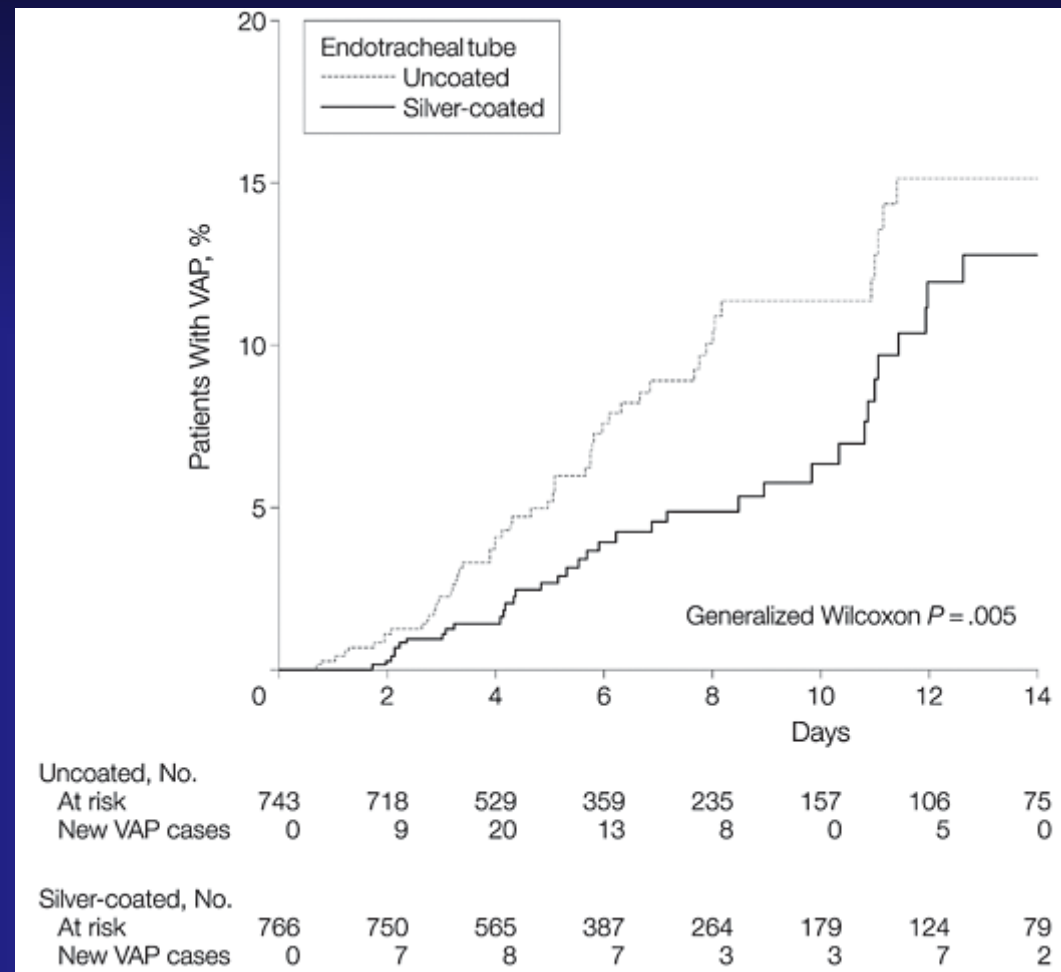
- Accumulated trials data support efficacy in reducing VAP and mortality

- Cons:

- Impact of systemic + oral antimicrobials on resistance emergence
- Can oral decontamination with chlorhexidine provide similar benefit?

# Preventing VAP: Antimicrobial (silver) coated ET tubes

- 2003 pts randomized
- Among those intubated > 24 hrs:
  - 4.8 vs. 7.5% micro-confirmed VAP,  $p=0.03$
  - No differences in intubation time, LOS, mortality



Kollef et al. N Engl J Med 2008;300:805.

# Multifactorial Interventions: The “ventilator bundle”

- Implementation of those interventions with the supporting evidence/feasibility
  - Hand Hygiene
  - Elevation of HOB
  - “Sedation vacation” each day
  - Assessment of readiness to wean
  - PUD and DVT prophylaxis

# The IHI Ventilator Bundle: Meta-analysis

- Only four studies met inclusion criteria
  - All had methodologic problems
    - All were “before-after” study designs
    - Little information re diagnostic approach before and after
    - Selection/publication bias, confounding?
  - **38-60% reduction in VAP post-intervention**
    - Resar et al. Jt Comm J Qual Pt Saf 2005;31:243.
    - Berriel-Cass et al. Jt Comm J Qual Pt Saf 2006;32:612.
    - Youngquist et al. Jt Comm J Qual Pt Saf 2007;33:219.
    - Unahalekhaka et al. Jt Comm J Qual Pt Saf 2007;33:387.
- Is the bundle cost-effective? Which aspects are most important? Should new elements be added?

Zilberberg et al. Crit Care Med 2009;37:305.

# Ventilator-Associated Pneumonia—The Wrong Quality Measure for Benchmarking

Michael Klompas, MD, MPH, and Richard Platt, MD, MSc

- Drive to reduce VAP rates to “zero”
- But “zero”, or lower rates, could mean:
  - Excellent care, improved processes
  - Narrowing application of definition  
e.g. “defining your way to zero”
- Better to follow process measures

Klompas M, Platt R. Ann Intern Med 2007;147:803-805.

*VAP prevention: Do we really know what we are doing?*

# Clinical Diagnosis

Findings	SENS	SPEC	Likelihood ratio (+/-)
Infiltrate, + sputum cx, fever or leukocytosis	54	62	1.4/0.7
Purulent secretions and leukocytosis or infiltrate	72	42	1.2/0.7
Infiltrate plus at least 2 of: fever, leukocytosis, or purulent sputum	69	75	2.8/0.4
Clinical Pulmonary Infection Score > 6	72-77	42-85	2.1/0.4

Adapted from Klompas M. JAMA 2007;297:1583-93.

Wunderink et al. Chest 1992;101:458-463.

Torres et al. Am J Respir Crit Care Med 1994;149:324-331.

Fabregas et al. Thorax 1999;54:867-873.

Papazian et al. Am J Resp Crit Care Med 1995;152:1982.



# Microbiological Diagnosis

Finding	Source	SENS	SPEC	Likelihood ratio (+)
Gram stain	Blind aspirate	56	74	2.1
Gram stain	BAL	44-85	88-100	3.8-18
Culture ( $>10^4$ )	BAL	50-77	42-95	0.9-10
Culture ( $>10^5$ )	Blind aspirate	56-69	75-95	2.4-11

Adapted from Klompas M. JAMA 2007;297:1583-93.

Torres et al. Am J Respir Crit Care Med 1994;149:324-331.

Fabregas et al. Thorax 1999;54:867-873.

Papazian et al. Anesthesiology 1997;87:268.

Papazian et al. Am J Resp Crit Care Med 1995;152:1982.

Marquette et al. Am J Resp Crit Care Med 1995;151:1878.

VAP suspected: new/progressive infiltrate + at least 2 of 3:  
(1)  $T > 38$ , (2) leukocytosis or leukopenia, (3) purulent secretions

Consider empiric  
antimicrobial regimen

Obtain LRT sample for culture  
and microscopy

Risk for MDR?

Low

High

Ceftriax  
FQ  
Amp/Sul  
Erta

Multiple,  
know  
own flora!

Check cultures, assess  
clinical response at 48-72h

Adjust or stop abx, consider search  
for other pathogens or diagnoses

Am J Resp Crit Care Med 2005;171:388-416.

Antimicrobials in preceding 90 days, hospitalized  $\geq 5$  days, high frequency of AMR in community or unit, hospitalized 2 days or more in prior 90 days, LTCF, home infusion, chronic dialysis, family member with MDR pathogen, immunosuppressed

NO

*S. pneumoniae*, *H. flu*,  
MSSA, susceptible GNRs

ceftriaxone, or  
FQ, or  
ampicillin-sulbactam, or  
ertapenem

YES

*P. aeruginosa*, ESBL,  
*Acinetobacter*, MRSA

Cefepime/ceftazadime, or  
Imipenem/meropenem, or  
Piperacillin-tazobactam  
*plus*  
FQ or aminoglycoside  
*plus*  
Linezolid or vancomycin

*Local patterns of AMR  
should be incorporated into  
empiric regimens*

# Important Treatment Considerations

- Tailor regimen to local epidemiology/AMR:
  - e.g. KPC-KPN, MDR-Acinetobacter
- Use appropriate dosing:
  - e.g. Adequate vanco dosing for MRSA
- 48-72 hour assessment:
  - Clinical response & culture data
- Duration of therapy:
  - Consider shorter course (e.g. 7-8 days) if pt improving, and bug not *P. aeruginosa*
    - Chastre et al. JAMA 2003;290:2588.

# Re-assessment at 48-72 hours

- Responders

- Pathogen isolated?
  - Directed therapy
  - Duration of therapy?
- No pathogen, and no recent abx  $\Delta$ ?
  - Narrow regimen if no *Pseudomonas* or MRSA
  - Consider d/c abx?
  - Duration of therapy?

- Nonresponders

- Wrong bug?
  - Resistant? Not bacterial?
  - Antibiotic dosing inadequate?
- Wrong diagnosis?
  - PE, ARDS, bleed, neoplasm, etc.
- Complication of infection?
  - Empyema, lung abscess, C. diff, drug fever, etc.

# Ventilator Associated Pneumonia: Summary (1)

- VAP is common, and increases LOS, hospital costs, and (probably) mortality
- Better diagnostics for VAP are needed to reduce misclassification
- VAP prevention literature is murky, but:
  - IHI bundle + oral care with chlorhexidine
  - CSS if expect to be on vent >72 hrs
  - Other approaches (silver coated ET tubes, selective DD, etc.) if rate remains high

# Ventilator Associated Pneumonia: Summary (2)

- Treatment should be based upon risk for MDR, microbiology, and clinical response
  - Broad (combination) therapy initially
  - Use appropriate dosing
  - Obtain LRT sample for Gram stain and culture
  - 48-72 hour re-assessment is critical
  - Narrow therapy and shorten course when able