Λοιμώξεις αναπνευστικού: Νοσοκομειακή πνευμονία | Πνευμονία σχετιζόμενη με το μηχανικό αερισμό

Κωστής Ποντίκης

What is Ventilator-Associated Pneumonia?

Ventilator-associated pneumonia conceptual definition

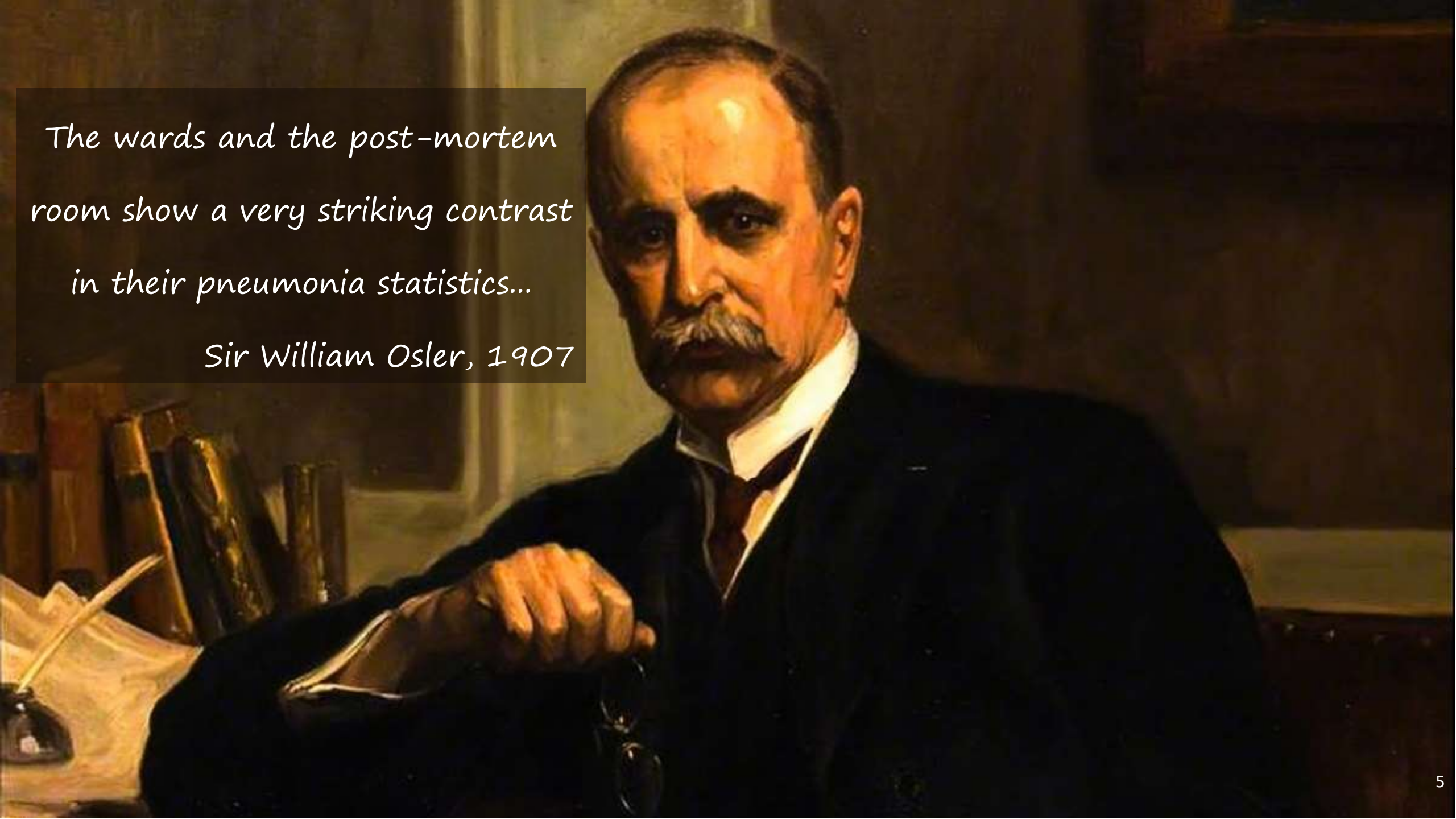
VAP is defined as an inflammation of the lung parenchyma caused by infectious agents not present or incubating at the time mechanical ventilation was started

Chastre and **Fagon** et al. *Am J Resp Crit Care Med* **2002**;165:867

Diagnostic criteria in clinical practice

....if the patient has a **radiographic infiltrate** that is *new or progressive*, along with clinical findings suggesting infection, which include the new onset of **fever**, **purulent sputum**, **leukocytosis**, and **decline in oxygenation**.

ATS and **IDSA**. *Am J Resp Crit Care Med* **2005**;171:388


The wards and the post-mortem room show a very striking contrast in their pneumonia statistics...
Sir William Osler, 1907

THE RATIONAL CLINICAL EXAMINATION

CLINICIAN'S CORNER

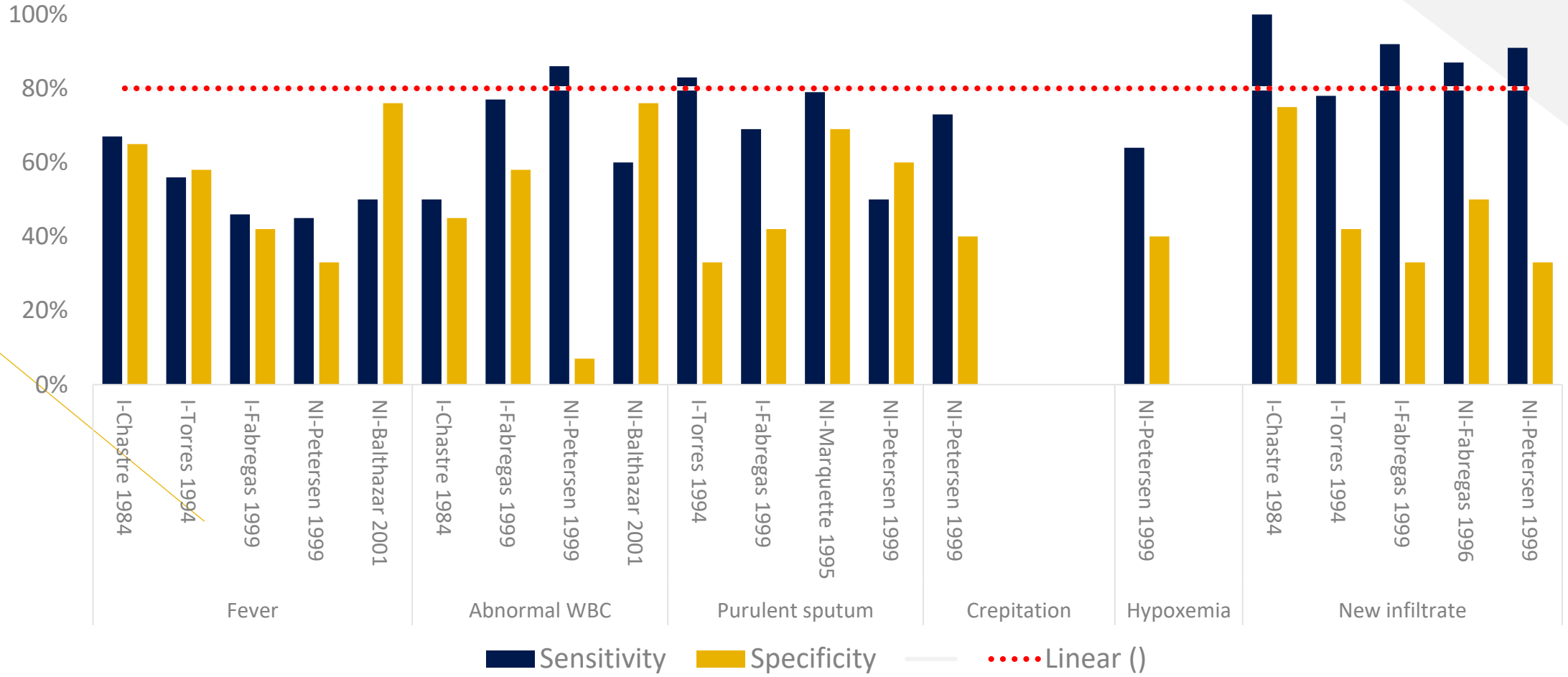
Does This Patient Have Ventilator-Associated Pneumonia?

Michael Klompas, MD

Context Ventilator-associated pneumonia (VAP) is a common and serious nosocomial infection. Accurate, timely diagnosis enables affected patients to receive appro-

Klompas et al. *JAMA* **2007**;297:1583

Accuracy of common features in predicting histological pneumonia



Klompas et al. *JAMA* **2007**;297:1583

Accuracy of common features in predicting histological pneumonia

Independent studies:
patient enrollment the [illegible] examination, without regard to whether there was a clinical suspicion of pneumonia
Which findings should [illegible] consider a diagnosis of pneumonia

Nonindependent studies:
patient enrollment already clinically suspected of having pneumonia
How various clinical clues modify the existing pre-test probability

Positive likelihood ratio:
How much the presence of the feature confirms the diagnosis of VAP

Negative likelihood ratio:
How much the absence of the feature excludes the diagnosis of VAP

95% Confidence Interval:
The certainty about the estimate

Table 3. Sensitivity and Specificity of Clinical Variables for the Diagnosis of Ventilator-Associated Pneumonia

				LR (95% CI)	
	Sensitivity, %	Specificity, %	Positive	Negative
Fever				
Independent				
Chastre et al,[39] 1984 — Histology alone	67	65	1.9 (0.84-4.3)	0.51 (0.16-1.7)
Torres et al,[41] 1994 — Histology alone	56	58	1.3 (0.61-2.9)	0.76 (0.38-1.5)
Fàbregas et al,[45] 1999 — Histology and culture	46	42	0.79 (0.37-1.7)	1.3 (0.56-3.0)
Summary			1.2 (0.76-1.9)	0.86 (0.54-4.1)
Nonindependent				
Petersen et al,[10] 1999 — Histology alone	45	33	0.68 (0.38-1.2)	1.6 (0.73-3.7)
Balthazar et al,[40] 2001 — Histology and culture	50	76	2.1 (0.81-5.6)	0.65 (0.39-1.1)
Abnormal WBC count				
Independent				
Chastre et al,[39] 1984 — Histology alone	50	45	0.91 (0.37-2.2)	1.1 (0.44-2.8)
Fàbregas et al,[45] 1999 — Histology and culture	77	58	1.8 (0.89-3.8)	0.40 (0.13-1.2)
Summary			1.3 (0.76-2.4)	0.74 (0.34-1.6)
Nonindependent				
Petersen et al,[10] 1999 — Histology alone	86	7	0.93 (0.75-1.1)	2.0 (0.23-17.8)
Balthazar et al,[40] 2001 — Histology and culture	60	76	2.6 (1.0-6.5)	52 (0.29-0.95)
Sputum purulence, macroscopic				
Independent				
Torres et al,[41] 1994 — Histology alone	83	33	1.3 (0.80-2.0)	0.50 (0.14-1.8)
Fàbregas et al,[45] 1999 — Histology and culture	69	42	1.2 (0.65-2.2)	0.74 (0.26-2.1)
Summary			1.3 (0.88-1.8)	0.63 (0.28-1.4)
Nonindependent				
Marquette et al,[47] 1995 — Histology alone	79	67	2.4 (0.91-6.1)	0.32 (0.12-0.85)
Petersen et al,[10] 1999 — Histology alone	50	60	1.3 (0.59-2.6)	0.83 (0.46-1.5)
Crepitation on auscultation				
Nonindependent				
Petersen et al,[10] 1999 — Histology alone	73	40	1.2 (0.75-2.0)	0.68 (0.27-1.7)
Hypoxemia				
Nonindependent				
Petersen et al,[10] 1999 — Histology alone	64	40	1.1 (0.63-1.8)	0.91 (0.40-2.1)
New infiltrate on radiograph				
Independent				
Chastre et al,[39] 1984 — Histology alone	100	75	3.5 (1.7-7.5)	(0.01-1.4)
Torres et al,[41] 1994 — Histology alone	78	42	1.3 (0.78-2.3)	0.53 (0.18-1.6)
Fàbregas et al,[45] 1999 — Histology and culture	92	33	1.4 (0.88-2.2)	0.24 (0.03-1.8)
Summary			1.7 (1.1-2.5)	(0.14-0.87)
Nonindependent				
Fàbregas et al,[32] 1996 — Histology alone	87	50	1.7 (0.43-7.0)	0.26 (0.05-1.5)
Petersen et al,[10] 1999 — Histology alone	91	33	1.4 (0.93-2.0)	0.27 (0.06-1.2)

Abbreviations: CI, confidence interval; LR, likelihood ratio; WBC, white blood cell.

- Fever neither confirms, nor excludes pneumonia
- Presence of leukocytosis does not confirm pneumonia
- Macroscopic purulence does not confirm pneumonia
- Crepitation neither confirms, nor excludes pneumonia
- Hypoxemia neither confirms, nor excludes pneumonia
- Absence of new infiltrate on CXR does not exclude pneumonia

Absence of leukocytosis, halves the probability

Absence of macroscopic purulence leads to 1/3 the probability

We should be three times more suspicious of VAP, if a new infiltrate is present

Klompas et al. *JAMA* **2007**;297:1583

Independent studies:
patient enrollment for histological examination, without regard to whether there was a clinical suspicion of pneumonia
Which findings suggest clinicians should consider a diagnosis of pneumonia

Nonindependent studies:
patient enrollment already clinically suspected of having pneumonia
How various clinical clues modify the existing pre-test probability

Positive likelihood ratio:
How much the presence of the feature confirms the diagnosis of VAP

Negative likelihood ratio:
How much the absence of the feature excludes the diagnosis of VAP

95% Confidence Interval:
The certainty about the estimate

Accuracy of radiologic signs in predicting histological pneumonia

Table 5. Sensitivity and Specificity of Radiographic Features*

Radiographic Feature	Sensitivity, %	Specificity, %	LR (95% CI) Positive	LR (95% CI) Negative
Air bronchogram				
Single	17	96	3.8 (0.74-19)	0.87 (0.72-1.1)
Single or multiple	83	58	2.0 (1.3-2.9)	0.29 (0.11-0.73)
Silhouette sign	79	33	1.2 (0.89-1.6)	0.63 (0.26-1.5)
Alveolar infiltrate	88	27	1.2 (0.95-1.5)	0.47 (0.15-1.5)
Fissure abutment	8	96	1.9 (0.3-12.5)	1.0 (0.84-1.1)
Atelectasis	29	62	0.77 (0.37-1.6)	1.1 (0.81-1.6)

Abbreviations: CI, confidence interval; LR, likelihood ratio.
*All data from Wunderink et al.[40]

Best performance for single air-bronchogram, but with not much confidence

Klompas et al. *JAMA* **2007**;297:1583

Independent studies:
patient enrollment for histological examination, without regard to whether there was a clinical suspicion of pneumonia
Which findings suggest clinicians should consider a diagnosis of pneumonia

Nonindependent studies:
patient enrollment already clinically suspected of having pneumonia
How various clinical clues modify the existing pre-test probability

Positive likelihood ratio:
How much the presence of the feature confirms the diagnosis of VAP

Negative likelihood ratio:
How much the absence of the feature excludes the diagnosis of VAP

95% Confidence Interval:
The certainty about the estimate

Accuracy of combinations of signs/symptoms/findings in predicting histological pneumonia

Table 6. Sensitivity and Specificity of Findings in Combination to Diagnose Ventilator-Associated Pneumonia

Source	Combination of Findings	Sensitivity, %	Specificity, %	LR (95% CI) Positive	LR (95% CI) Negative
Independent					
Wunderink et al,[40] 1992	Radiographic infiltrate, positive sputum culture, and either fever or leukocytosis	54	62	1.4 (0.85-2.4)	0.74 (0.45-1.2)
Torres et al,[41] 1994	Purulent secretions and leukocytosis or radiographic infiltrate	72	42	1.2 (0.71-2.2)	0.67 (0.25-1.8)
Fàbregas et al,[45] 1999	Radiographic infiltrate plus dichotomous and ordinal results (below)				
Dichotomous results	≥2 of fever, leukocytosis, and purulent sputum	69	75	2.8 (0.97-7.9)	0.41 (0.17-0.99)
Ordinal results	3 of fever, leukocytosis, and purulent sputum			2.8 (0.33-23)	
	2 of fever, leukocytosis, or purulent sputum			2.8 (0.69-11)	
	1 of fever, leukocytosis, or purulent sputum			0.37 (0.09-1.6)	
	No fever, leukocytosis, or purulent sputum			0.46 (0.10-2.1)	
Nonindependent					
Bregeon et al,[48] 2000	Fever, radiographic infiltrate, purulent sputum, alteration of gas exchange	100	62	2.5 (1.3-4.8)	0.06 (0-0.87)

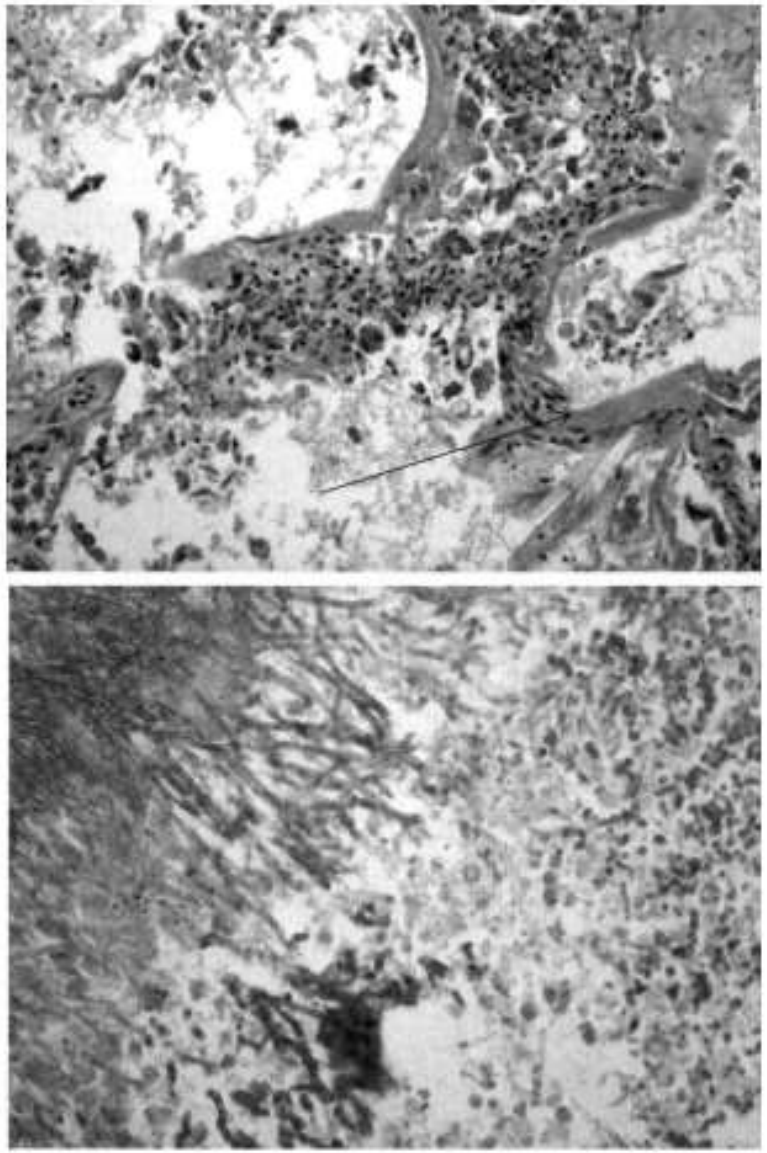
Abbreviations: CI, confidence interval; LR, likelihood ratio.

- Combinations of fever, leukocytosis, infiltrate and purulent secretions at best triple the baseline probability pneumonia
- Absence of combinations, at best, decrease modestly the probability of pneumonia

Klompas et al. *JAMA* **2007**;297:1583

Table 2—*Lung Pathology at Postmortem**

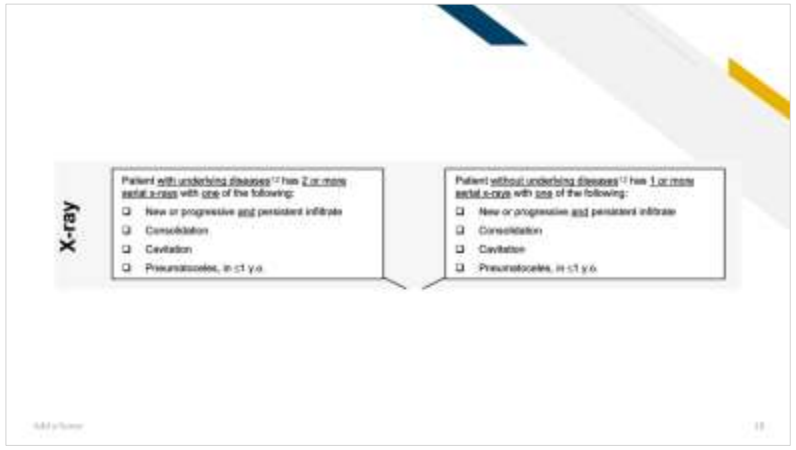
Variables	Values
DAD	
Total	32 (50)
Exudative phase	16 (25)
Organized phase	16 (25)
Isolated	20 (31)
Associated with	12 (19)
Pneumonia/bronchopneumonia	4
Pulmonary invasive aspergillosis	4
Pneumocystis carinii (jiroveci) pneumonia	1
Pulmonary infarct	1
Congestion	1
Lymphangioleiomyomatosis + microthrombi	1
Other pathologic diagnoses (not associated with DAD)	
Pneumonia/bronchopneumonia	16 (25)
Congestion	7 (11)
Pulmonary invasive aspergillosis	4 (6)
Chronic nonspecific inflammatory changes	3
Pulmonary embolism	2
Alveolar hemorrhage	2
Usual interstitial pneumonia	2
P carinii (jiroveci) pneumonia	1
Pulmonary infarct	1
Acute pulmonary graft rejection	1
Inhalation pneumonia	1
Bronchiolitis obliterans organizing pneumonia	1

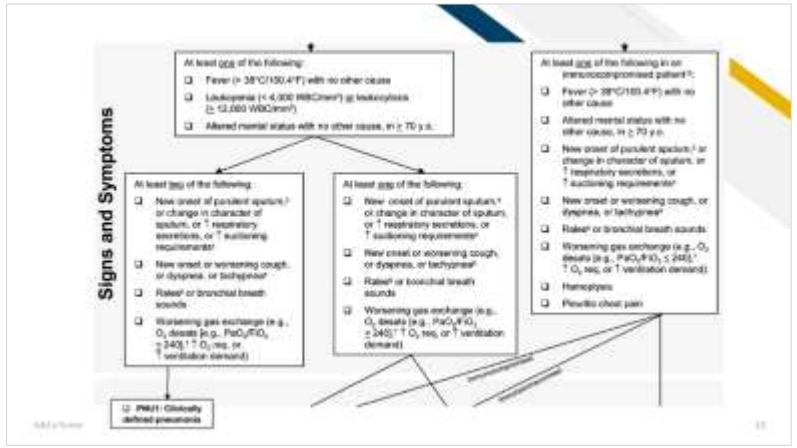


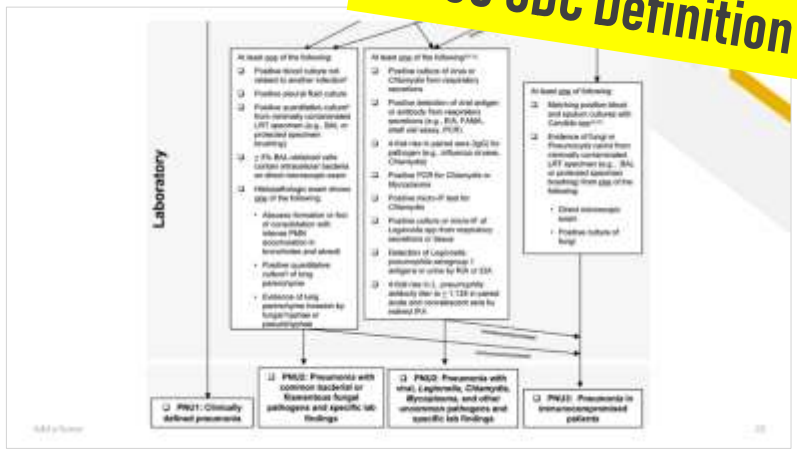
de Hemptinne et al. *Chest* **2009**;135:944

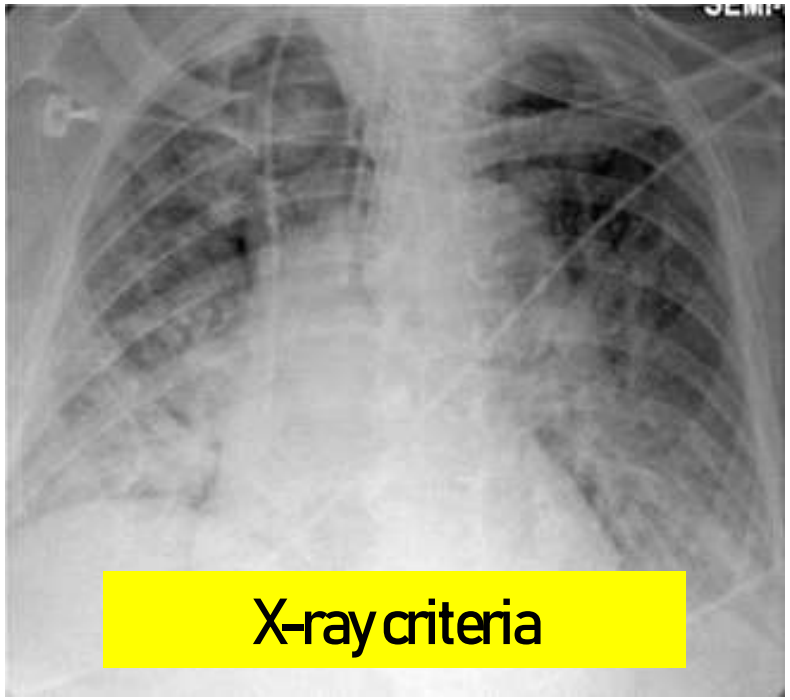
How frequent is Ventilator-Associated Pneumonia?

2008 CDC Definition







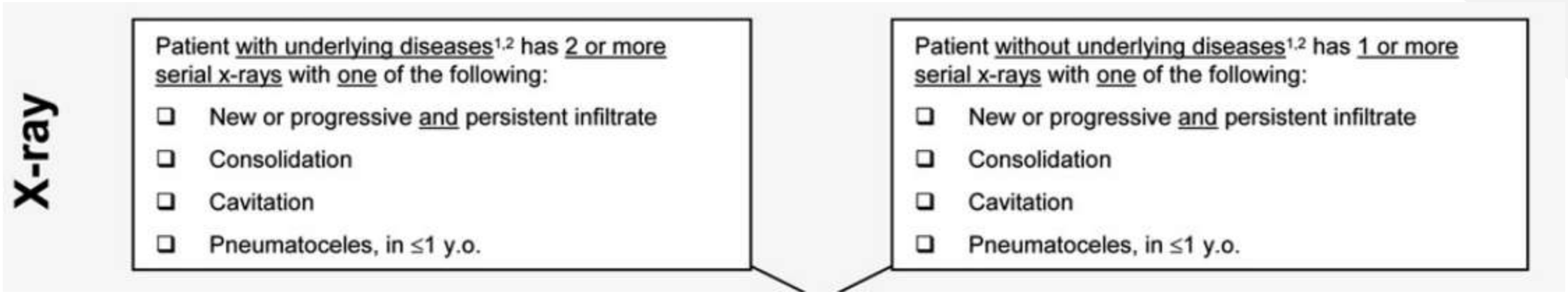


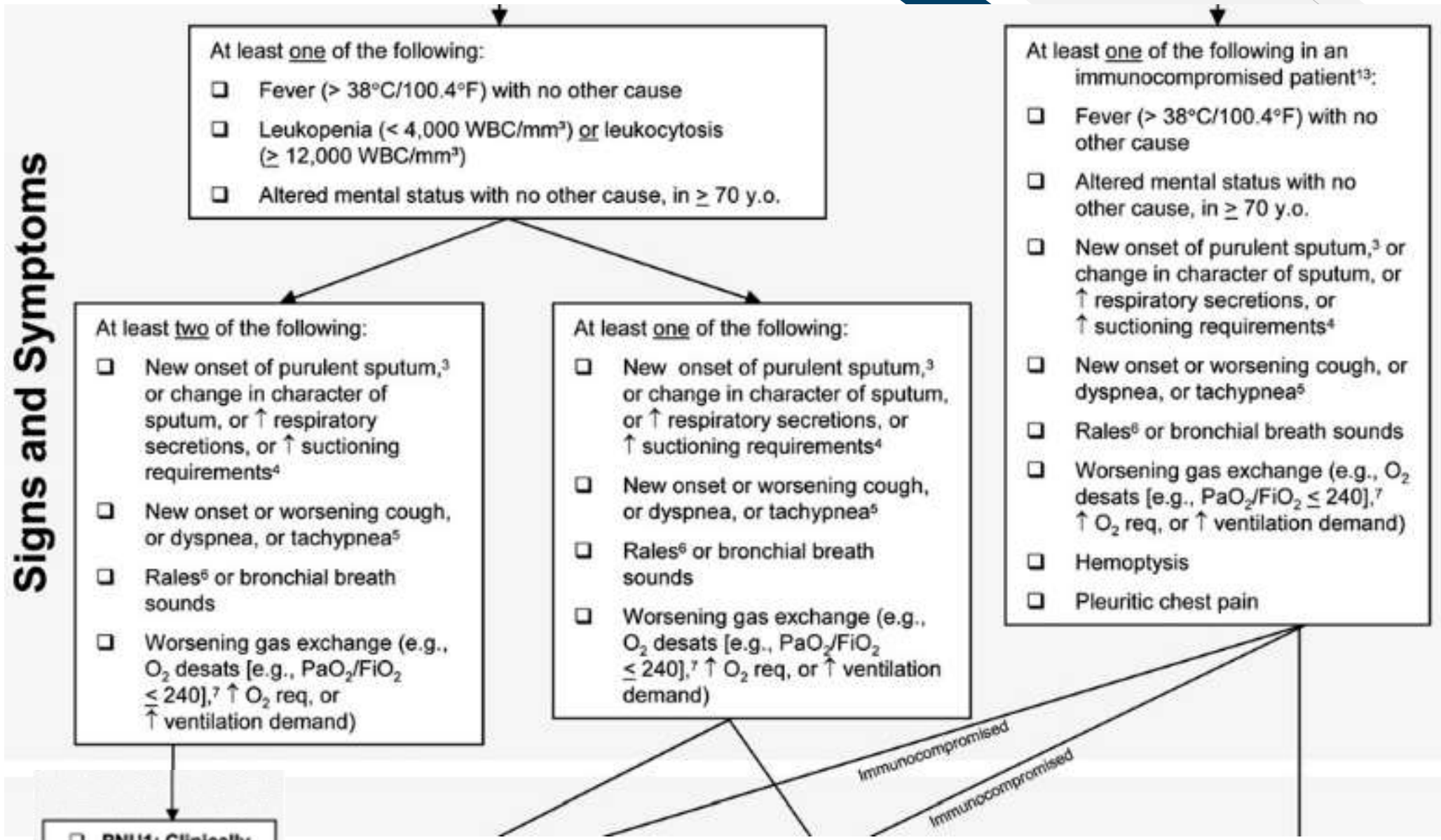
X-ray criteria

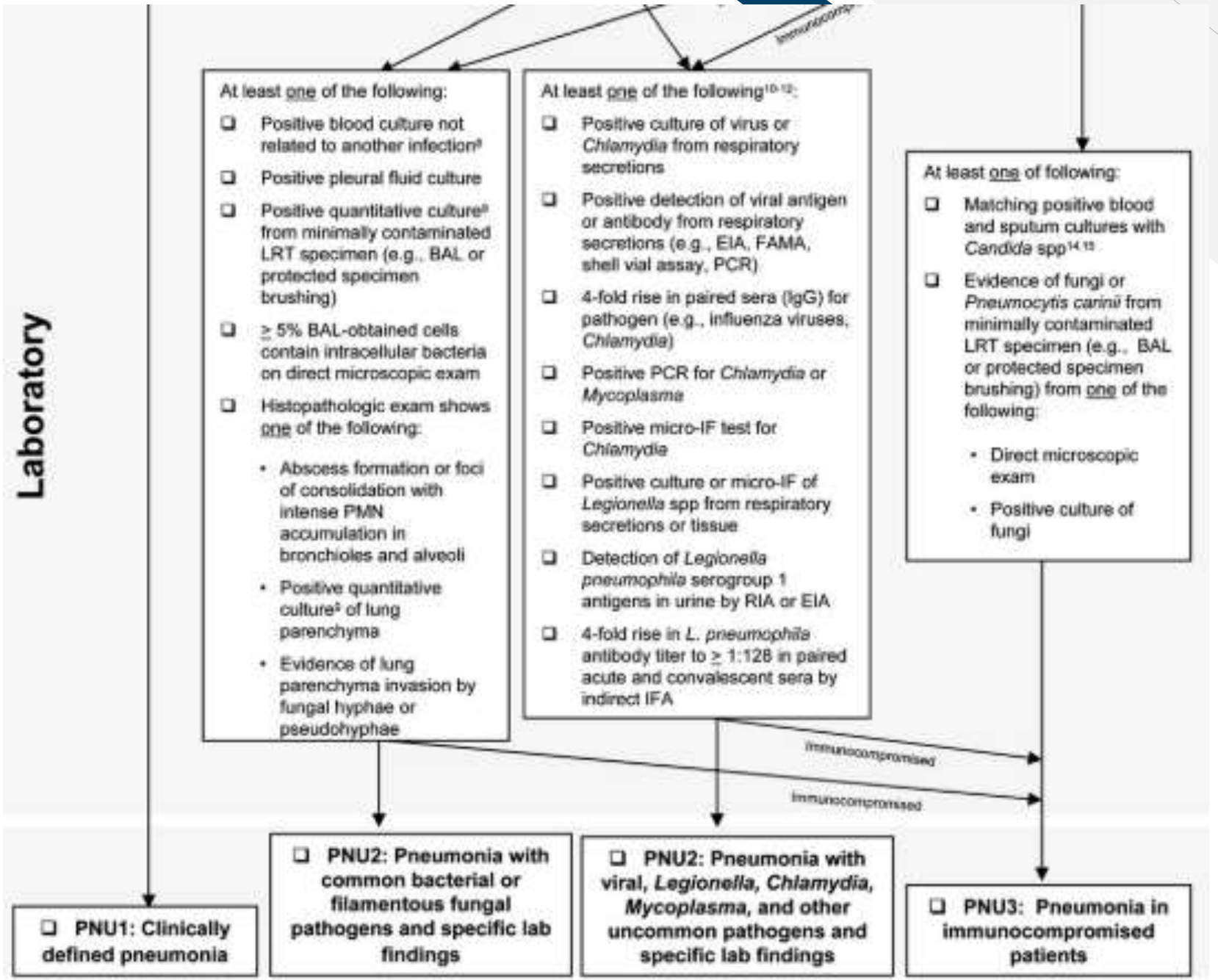
Signs & symptoms

Laboratory

Horan et al. *Am J Infect Control* **2008**;36:309


X-ray
Patient with underlying diseases[1,2] has 2 or more serial x-rays with one of the following:
❑ New or progressive and persistent infiltrate
❑ Consolidation
❑ Cavitation
❑ Pneumatoceles, in ≤1 y.o.
Patient without underlying diseases[1,2] has 1 or more serial x-rays with one of the following:
❑ New or progressive and persistent infiltrate
❑ Consolidation
❑ Cavitation
❑ Pneumatoceles, in ≤1 y.o.


Signs and Symptoms
At least one of the following:
❑ Fever (> 38°C/100.4°F) with no other cause
❑ Leukopenia (< 4,000 WBC/mm³) or leukocytosis (≥ 12,000 WBC/mm³)
❑ Altered mental status with no other cause, in ≥ 70 y.o.
At least two of the following:
❑ New onset of purulent sputum,[3] or change in character of sputum, or ↑ respiratory secretions, or ↑ suctioning requirements[4]
❑ New onset or worsening cough, or dyspnea, or tachypnea[5]
❑ Rales[6] or bronchial breath sounds
❑ Worsening gas exchange (e.g., O_2 desats [e.g., PaO_2/FiO_2 ≤ 240],[7] ↑ O_2 req, or ↑ ventilation demand)
At least one of the following:
❑ New onset of purulent sputum,[3] or change in character of sputum, or ↑ respiratory secretions, or ↑ suctioning requirements[4]
❑ New onset or worsening cough, or dyspnea, or tachypnea[5]
❑ Rales[6] or bronchial breath sounds
❑ Worsening gas exchange (e.g., O_2 desats [e.g., PaO_2/FiO_2 ≤ 240],[7] ↑ O_2 req, or ↑ ventilation demand)
At least one of the following in an immunocompromised patient[13]:
❑ Fever (> 38°C/100.4°F) with no other cause
❑ Altered mental status with no other cause, in ≥ 70 y.o.
❑ New onset of purulent sputum,[3] or change in character of sputum, or ↑ respiratory secretions, or ↑ suctioning requirements[4]
❑ New onset or worsening cough, or dyspnea, or tachypnea[5]
❑ Rales[6] or bronchial breath sounds
❑ Worsening gas exchange (e.g., O_2 desats [e.g., PaO_2/FiO_2 ≤ 240],[7] ↑ O_2 req, or ↑ ventilation demand)
❑ Hemoptysis
❑ Pleuritic chest pain
Immunocompromised
Immunocompromised
❑ PNU1: Clinically defined pneumonia


Laboratory
At least one of the following:
❑ Positive blood culture not related to another infection[9]
❑ Positive pleural fluid culture
❑ Positive quantitative culture[9] from minimally contaminated LRT specimen (e.g., BAL or protected specimen brushing)
❑ ≥ 5% BAL-obtained cells contain intracellular bacteria on direct microscopic exam
❑ Histopathologic exam shows one of the following:
• Abscess formation or foci of consolidation with intense PMN accumulation in bronchioles and alveoli
• Positive quantitative culture[9] of lung parenchyma
• Evidence of lung parenchyma invasion by fungal hyphae or pseudohyphae
At least one of the following[10-12]:
❑ Positive culture of virus or Chlamydia from respiratory secretions
❑ Positive detection of viral antigen or antibody from respiratory secretions (e.g., EIA, FAMA, shell vial assay, PCR)
❑ 4-fold rise in paired sera (IgG) for pathogen (e.g., influenza viruses, Chlamydia)
❑ Positive PCR for Chlamydia or Mycoplasma
❑ Positive micro-IF test for Chlamydia
❑ Positive culture or micro-IF of Legionella spp from respiratory secretions or tissue
❑ Detection of Legionella pneumophila serogroup 1 antigens in urine by RIA or EIA
❑ 4-fold rise in L. pneumophila antibody titer to ≥ 1:128 in paired acute and convalescent sera by indirect IFA
At least one of following:
❑ Matching positive blood and sputum cultures with Candida spp[14,15]
❑ Evidence of fungi or Pneumocytis carinii from minimally contaminated LRT specimen (e.g., BAL or protected specimen brushing) from one of the following:
• Direct microscopic exam
• Positive culture of fungi
immunocompromised
immunocompromised
❑ PNU1: Clinically defined pneumonia
❑ PNU2: Pneumonia with common bacterial or filamentous fungal pathogens and specific lab findings
❑ PNU2: Pneumonia with viral, Legionella, Chlamydia, Mycoplasma, and other uncommon pathogens and specific lab findings
❑ PNU3: Pneumonia in immunocompromised patients

US 2012: Ventilator-associated PNEU rate

Ventilator-associated PNEU rate*					Percentile				
Type of location	No. of locations†	No. of VAP	Ventilator–days	Pooled mean	10%	25%	50% (median)	75%	90%
Acute Care Hospitals									
Critical Care Units									
Burn	36 (34)	86	19,503	4.4	0.0	0.0	1.1	6.7	10.9
Medical									
Major teaching	112 (111)	205	212,392	1.0	0.0	0.0	0.5	1.6	2.9
Medical									
All other	223 (197)	191	206,731	0.9	0.0	0.0	0.0	1.3	3.4
Medical cardiac	178 (170)	135	139,864	1.0	0.0	0.0	0.0	1.5	3.6
Medical/surgical									
Major teaching	152 (145)	372	234,972	1.6	0.0	0.0	0.9	2.2	3.9
Medical/surgical									
All other ≤15 beds	841 (660)	419	383,926	1.1	0.0	0.0	0.0	1.2	3.6
Medical/surgical									
All other >15 beds	405 (400)	666	711,280	0.9	0.0	0.0	0.4	1.3	2.8
Neurologic	23	62	20,859	3.0	0.0	0.0	0.2	2.5	7.0
Neurosurgical	76 (74)	210	98,026	2.1	0.0	0.0	1.5	2.9	3.8
Pediatric cardiothoracic	20	9	36,187	0.2	0.0	0.0	0.0	0.2	0.6
Pediatric medical	16 (9)	2	6,634	0.3					
Pediatric medical/surgical	142 (132)	113	147,441	0.8	0.0	0.0	0.0	0.9	2.4
Pediatric surgical	5 (4)	1	2,328	0.4					
Respiratory	7	4	6,037	0.7					
Surgical									
Major teaching	81 (80)	280	127,251	2.2	0.0	0.6	1.5	3.1	5.6
Surgical									
All other	93 (88)	192	96,388	2.0	0.0	0.0	0.9	2.8	5.9
Surgical cardiothoracic	207 (203)	319	190,785	1.7	0.0	0.0	0.6	2.5	5.1
Trauma	75 (74)	508	141,314	3.6	0.0	0.8	2.6	6.0	9.4

Dudeck et al. *Am J Infect Control* **2013**;41:1148

Europe 2016: Intubation associated pneumonia rates

Pneumonia Case:

- Clinical criteria
  - X-ray
  - Fever > 38°C
  - WBC > 12.000/mm3
  - purulent sputum
- Further subcategorized according to level microbiological confirmation

Table 1. ICU-acquired intubation-associated pneumonia rates by country/network, EU/EEA, 2016

Country/Network	Number of ICUs	Number of patients	Average length of ICU stay (days)	Intubation use (days per 100 patient-days)	Intubation-associated pneumonia rate (episodes per 1 000 intubation-days)			
					Country mean	25th percentile	Median	75th percentile
Belgium	8	1909	8.5	41.0	11.3	5.2	10.2	13.5
Estonia	8	1562	9.9	64.4	6.3	4.3	5.8	9.6
France	200	67899	11.6	51.7	13.9	8.7	13.2	18.1
Italy/GiViTI	73	16275	9.4	58.2	6.1	2.1	4.5	8.3
Italy/SPIN-UTI	26	1478	10.6	67.9	16.4	7.0	15.3	22.7
Hungary	12	1695	8.3	60.7	10.4	6.7	10.2	12.2
Lithuania	32	3321	9.2	38.6	11.5	0.0	4.7	20.9
Luxembourg	9	3142	9.2	27.1	3.0	0.0	2.3	4.6
Poland	9	612	14.6	72.5	17.8	9.3	13.8	29.5
Portugal	41	7729	11.6	63.3	8.2	4.0	6.9	10.5
Slovakia	8	375	8.9	65.2	14.0	1.8	14.4	23.6
Spain	189	36556	8.2	44.7	6.2	2.1	4.8	8.5
United Kingdom – Scotland	21	8449	7.9	60.6	2.8	1.1	2.1	3.2

Source: ECDC, HAI-Net patient-based data 2016. Italy: data from two networks (GiViTI and SPIN-UTI, Table A1)
Percentiles: distribution of incidence per ICU

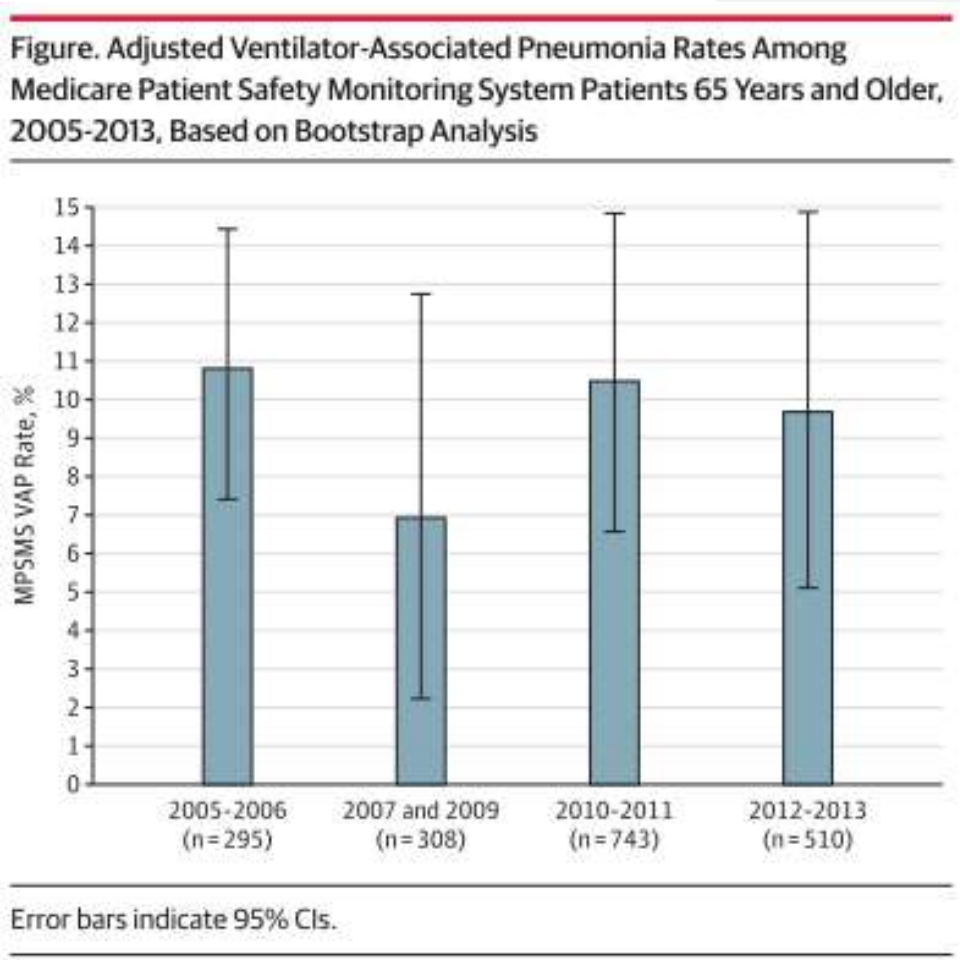
ECDC. Annual Epidemiological Report for 2016. 2018, Stockholm, Sweden

The subjectivity of VAP surveillance

2006-2012
Medical ICUs: 3,1→ 0,9 /1000 ventilator-days
Surgical ICUs: 5,2→2 /1000 ventilator-days

Possible etiology of discordance:

- differences in MPSMS and NHSN measure definitions
- differences in hospitals or patient groups
- changes in characteristics of hospitals reporting to NHSN over time
- preferential decline in VAP rates among hospitals reporting to the NHSN



Ferrer et al. *Curr Opin Crit Care* **2018**;25:325
Metersky et al. *JAMA* **2016**;208:11
Wang et al. *N Engl J Med* **2014**;370:341

Using Ventilator-Associated Pneumonia Rates as a Health Care Quality Indicator: A Contentious Concept

Girish B. Nair, MD FACP, FCCP[1] Michael S. Niederman, MD, MACP, FCCP, FCCM, FERS[2,3]

[1] Department of Medicine, Oakland University William Beaumont School of Medicine, Royal Oak, Michigan
[2] Department of Clinical Medicine, Weill Cornell Medical College, New York
[3] Department of Pulmonary and Critical Care, New York Presbyterian/ Weill Cornell Medical Center, New York

Address for correspondence Michael S. Niederman, MD, MACP, FCCP, FCCM, FERS, Weill Cornell Medical College, 425 East 61st Street, 4th Floor, New York, NY 10065 (e-mail: msn9004@med.cornell.edu).

"...Throughout the United States, there is an increased reporting of hospitals with a 'zero incidence' of VAP, even though the antibiotic prescription and clinical diagnosis remain prevalent..."

Nair & Niederman et al. *Semin Respir Crit Care Med* **2017**;38:237

Special Point of View Article

Developing a New, National Approach to Surveillance for Ventilator-Associated Events*

Shelley S. Magill, MD, PhD[1]; Michael Klompas, MD, MPH[2,3,4]; Robert Balk, MD[5,6];
Suzanne M. Burns, RN, ACNP, MSN, RRT[6];
Daniel Diekema, MD[9,10]; Scott Fridkin, MD
Alice Guh, MD, MPH[1]; David Gutterman, M
David Henderson, MD[15]; Dean Hess, PhD,
Teresa Horan, MPH[1]; Marin Kollef, MD[6,20];
Carole VanAntwerpen, RN, BSN[24,25]; Don W

- Complexity of previous (PNEU) definitions
- Time-consuming and burdensome
  - relative to surveillance definitions for other HAIs
- Concerns about the reliability of VAP surveillance, in the face of:
  - public reporting
  - inclusion of HAI measures in pay-for-reporting and pay-for-performance programs

Magill et al. *Crit Care Med* **2013**;41:2467

Patient has a baseline period of stability or improvement on the ventilator, defined by ≥ 2 calendar days of stable or decreasing daily minimum FiO_2 or PEEP values. The baseline period is defined as the two calendar days immediately preceding the first day of increased daily minimum PEEP or FiO_2.

↓

After a period of stability or improvement on the ventilator, the patient has at least one of the following indicators of worsening oxygenation:

1) Minimum daily FiO_2 values increase ≥ 0.20 (20 points) over the daily minimum FiO_2 in the preceding 2 calendar days (the baseline period), for ≥ 2 calendar days
2) Minimum daily PEEP values increase ≥ 3 cmH_2O over the daily minimum PEEP in the preceding 2 calendar days (the baseline period), for ≥ 2 calendar days

↓

Ventilator-Associated Condition (VAC)

↓

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, the patient meets both of the following criteria:

1) Temperature > 38 °C or < 36°C, **OR** white blood cell count ≥ 12,000 cells/mm^3 or ≤ 4,000 cells/mm^3

AND

2) A new antimicrobial agent(s)* is started, and is continued for ≥ 4 calendar days

*See VAE surveillance protocol (available at: http://www.cdc.gov/nhsn/acute-care-hospital/vae/index.html) for eligible agents

↓

Infection-related Ventilator-Associated Complication (IVAC)

↓

Magill et al. *Crit Care Med* **2013**;41:2467

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:

1) Purulent respiratory secretions (from one or more specimen collections)
   - Defined as secretions from the lungs, bronchi, or trachea that contain ≥25 neutrophils and ≤10 squamous epithelial cells per low power field [lpf, x100] (or corresponding semi-quantitative results)

2) Positive culture (qualitative, semi-quantitative or quantitative) of sputum*, endotracheal aspirate*, bronchoalveolar lavage*, lung tissue, or protected specimen brushing*

**Excludes the following:*
- Normal respiratory/oral flora, mixed respiratory/oral flora or equivalent
- *Candida* species or yeast not otherwise specified
- Coagulase-negative *Staphylococcus* species
- *Enterococcus* species

Magill et al. *Crit Care Med* **2013**;41:2467

Possible Ventilator-Associated Pneumonia

On or after calendar day 3 of mechanical ventilation and within 2 calendar days before or after the onset of worsening oxygenation, ONE of the following criteria is met:

1) Purulent respiratory secretions (from one or more specimen collections—and defined as for possible VAP)
   AND one of the following:
   - Positive culture of endotracheal aspirate*, ≥ 10^5 CFU/ml or equivalent semi-quantitative result
   - Positive culture of bronchoalveolar lavage*, ≥ 10^4 CFU/ml or equivalent semi-quantitative result
   - Positive culture of lung tissue, ≥ 10^4 CFU/g or equivalent semi-quantitative result
   - Positive culture of protected specimen brush*, ≥ 10^3 CFU/ml or equivalent semi-quantitative result

   **Same organism exclusions as noted for Possible VAP.*

2) One of the following (without requirement for purulent respiratory secretions):
   - Positive pleural fluid culture (where specimen was obtained during thoracentesis or initial placement of chest tube and NOT from an indwelling chest tube)
   - Positive lung histopathology
   - Positive diagnostic test for *Legionella* spp.
   - Positive diagnostic test on respiratory secretions for influenza virus, respiratory syncytial virus, adenovirus, parainfluenza viru
     coronavirus

Probable VAP later abandoned

Probable Ventilator-Associated Pneumonia

VAC predicts patient outcomes [more accurately than VAP (?)] and is much faster

OPEN ACCESS Freely available online

PLoS one

Multicenter Evaluation of a Novel Surveillance Paradigm for Complications of Mechanical Ventilation

Michael Klompas[1,2*], Yosef Khan[3], Kenneth Kleinman[1], R. Scott Evans[4,5], James F. Lloyd[5], Kurt Stevenson[3], Matthew Samore[4], Richard Platt[1,2] for the CDC Prevention Epicenters Program

Table 2. Comparison of outcomes for ventilator-associated complication positive and negative patients and ventilator-associated pneumonia positive and negative patients.

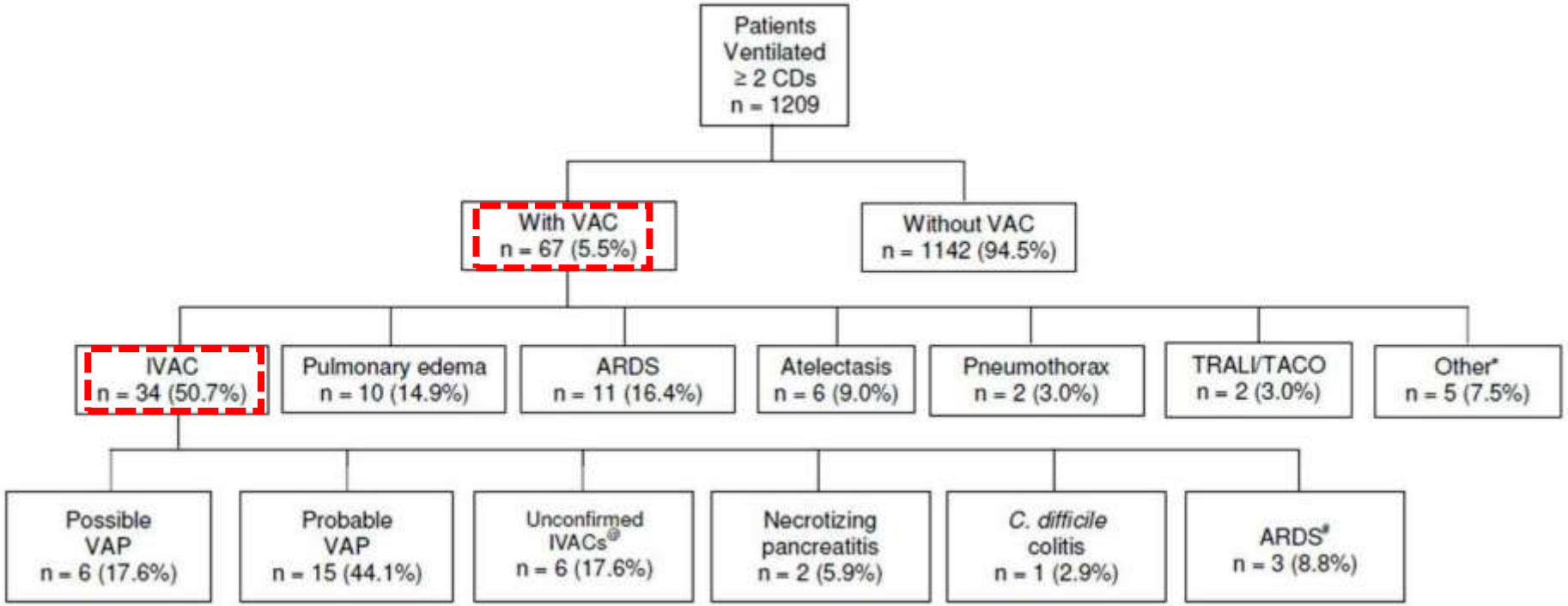
	VAC Positive	VAC Negative	P	VAP Positive	VAP Negative	P
Number of patients	135	462	–	55	542	–
Duration of ventilation (median days)	13.0	6.0	<.001	13.5	7.0	<.001
ICU length of stay (median days)	16.3	8.0	<.001	18.0	9.0	<.001
Hospital length of stay (median days)	21.0	16.0	<.001	24.6	17.0	<.001
Hospital mortality (% of patients)	38%	23%	.001	27%	26%	1.000

Abbreviations:
VAC – ventilator associated complications; VAP – ventilator associated pneumonia.
doi:10.1371/journal.pone.0018062.t002

Mean time for VAP determination
- 39 minutes

Mean time for VAC determination
- 1,8 minutes

Klompas et al. *PLoS One* **2011**;6:e18062



VAEs are infrequent
(in some other places)

- **Only 37,3% of VACs were deemed preventable**
- **Excessive mortality (65,7% vs 14.4%)**
- **Increased length of stay (14,7 vs 7,5 days)**

Boyer et al. *Chest* **2015**;147:68

VAE prospective validation in Europe

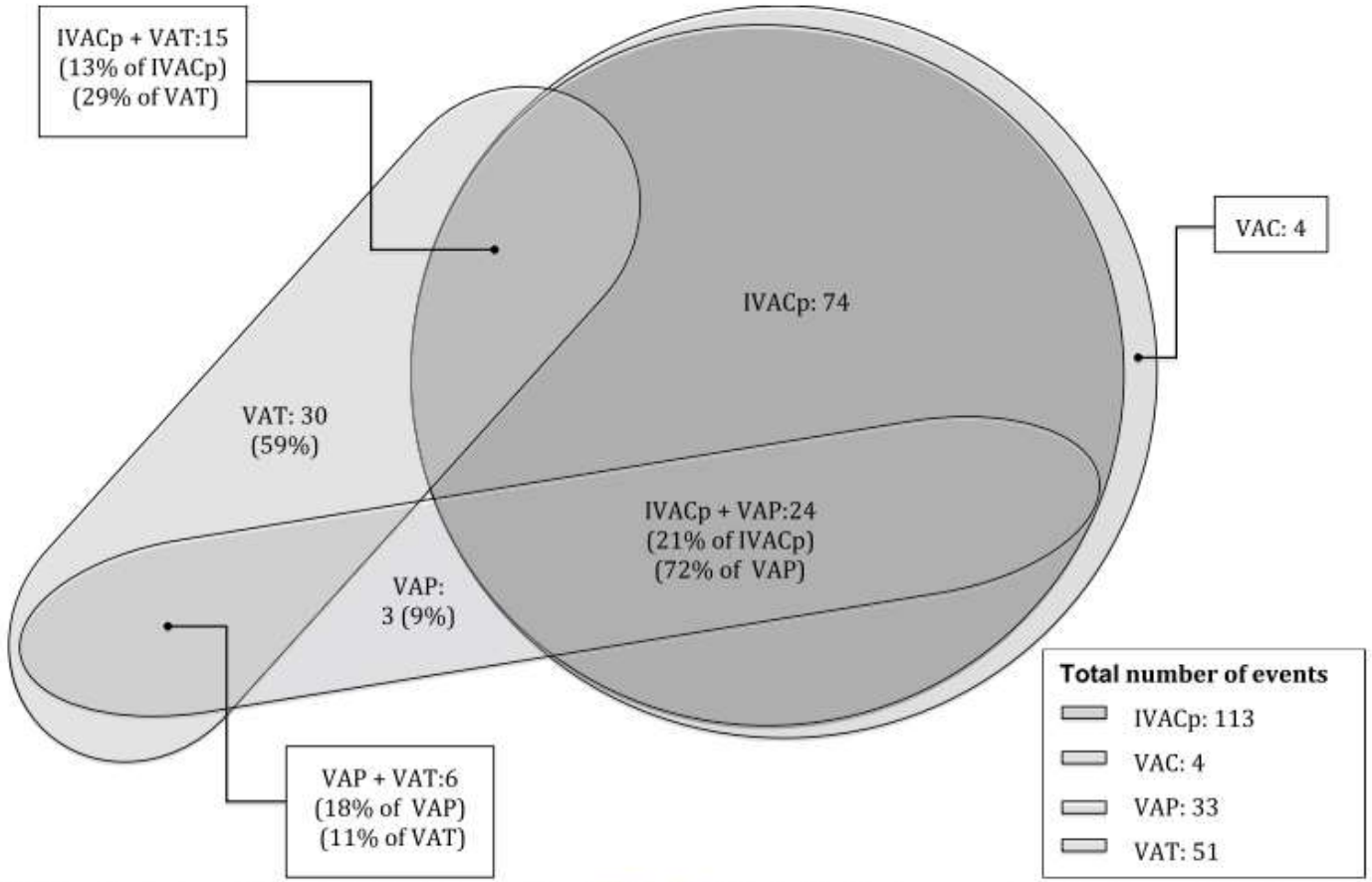


Fig. 3 Relationship between 2008 and 2013 CDC classifications [10, 15, 36]. 2013 classification is represented with circles and 2008 classification with ovals. *VAC* ventilator associated condition, *IVACp* infectious ventilator-associated complication plus, *VAP* ventilator associated pneumonia, *VAT* ventilator associated tracheobronchitis

Ramírez-Estrada et al. *Intensive Care Med* **2018**;44:1212

What is the impact of Ventilator-Associated Pneumonia on patient outcome?

TABLE 1. INCIDENCE AND CRUDE MORTALITY RATES OF VENTILATOR-ASSOCIATED PNEUMONIA

First Author	Ref.	Year of Publication	No. of Patients	Incidence (%)	Diagnostic Criteria	Mortality Rate (%)
Patients in ICU						
Salata	41	1987	51	41	Clinical–autopsy	76
Craven	15	1986	233	21	Clinical	55
Langer	9	1989	724	23	Clinical	44
Fagon	12	1989	567	9	PSB	71
Kerver	43	1987	39	67	Clinical	30
Driks	40	1987	130	18	Clinical	56
Torres	14	1990	322	24	Clinical–PSB	33
Baker	44	1996	514	5	PSB/BAL	24
Kollef	45	1993	277	16	Clinical	37
Fagon	51	1996	1,118	28	PSB/BAL	53
Timsit	46	1996	387	15	PSB/BAL	57
Cook	35	1998	1,014	18	Clinical–PSB/BAL	24
Tejada Artigas	47	2001	103	22	PSB	44
Patients with ARDS						
Sutherland	49	1995	105	15	PSB/BAL	38
Delclaux	17	1997	30	60	PTC/BAL	63
Chastre	16	1998	56	55	PSB/BAL	78
Meduri	50	1998	94	43	PSB/BAL	52
Markowicz	18	2000	134	37	PSB/BAL	57

Definition of abbreviations: ARDS = acute respiratory distress syndrome; BAL = bronchoalveolar lavage; ICU = intensive care unit; PSB = protected specimen brush; PTC = plugged telescoping catheter.

Impact of VAP on patient outcome

- Crude mortality rates of up to 78% have been reported
  - 2-10 increased risk in comparison with pts without pneumonia
- Length of stay (ICU and hospital) and duration of mechanical ventilation increased by several days
- Extra cost up to 40,000 $

Chastre and **Fagon** et al. *Am J Resp Crit Care Med* **2002**;165:867

Do patients die due to VAP or with VAP (1)?

Apart from baseline differences, there were also differences in the evolution of disease since admission

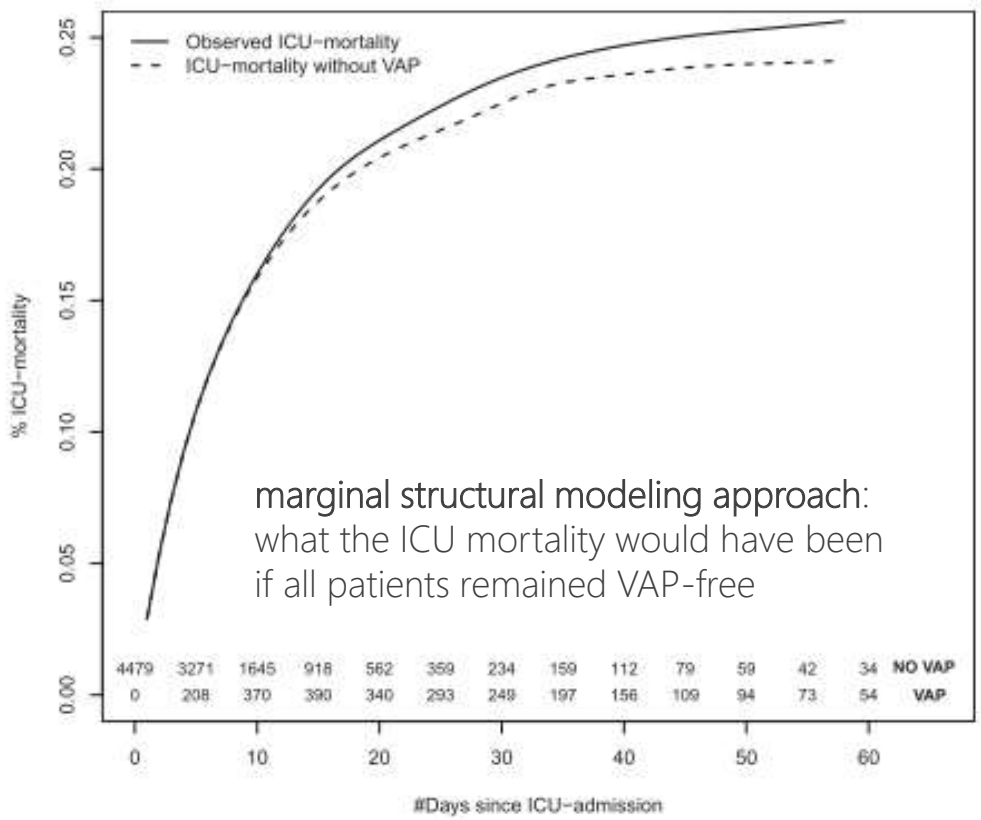
TABLE 2. CHARACTERISTICS AND CRUDE MORTALITY RATES FOR PATIENTS WITH AND WITHOUT VENTILATOR-ASSOCIATED PNEUMONIA

	Patients with VAP (n = 685)	Patients without VAP (n = 3,794)
Male sex, n (%)	493 (72.0)	2,371 (62.5)
Age, mean (SD)	63.2 (15.5)	62.6 (16.8)
ICU length of stay, median (Q1, Q3)	22 (14, 38)	7 (4, 13)
Ventilation days, median (Q1, Q3)	19 (11, 33)	5 (3, 10)
SAPS II, mean (SD)	49.9 (16.2)	48.4 (18.3)
Admission category		
Medicine, n (%)	476 (69.5)	2,317 (62.5)
Emergency surgery, n (%)	114 (16.6)	811 (21.4)
Scheduled surgery, n (%)	93 (13.6)	657 (17.3)
Main symptoms at ICU admission		
Shock, n (%)	185 (27.0)	1,001 (26.4)
Coma, n (%)	143 (20.9)	884 (23.3)
Acute respiratory failure, n (%)	213 (31.1)	846 (22.3)
Other chronic illnesses		
Hepatic, n (%)	53 (7.7)	253 (6.7)
Cardiovascular, n (%)	96 (14.0)	518 (13.7)
Pulmonary, n (%)	139 (20.3)	617 (16.3)
Renal, n (%)	25 (3.6)	147 (3.9)
Immunosuppression, n (%)	83 (12.1)	444 (11.7)
Crude mortality rates		
30-d ICU mortality, n (%)	165 (24.1)	876 (23.1)
60-d ICU mortality, n (%)	226 (33.0)	921 (24.3)
Global ICU mortality, n (%)	237 (34.6)	937 (24.7)

Definition of abbreviations: ICU = intensive care unit; Q1 = first quartile or 25th percentile; Q3 = third quartile or 75th percentile; SAPS II = Simplified Acute Physiology Score II; VAP = ventilator-associated pneumonia.

Bekaert et al. *Am J Respir Crit Care Med* **2011**;184:1133

Do patients die due to VAP or with VAP (2)?



marginal structural modeling approach:
what the ICU mortality would have been
if all patients remained VAP-free

Figure 1. The observed cumulative intensive care unit (ICU) mortality together with the ICU mortality as it would have been observed for the same population if ventilator-associated pneumonia (VAP) were prevented for all.

Bekaert et al. *Am J Respir Crit Care Med* **2011**;184:1133

Do patients die due to VAP or with VAP (3)?

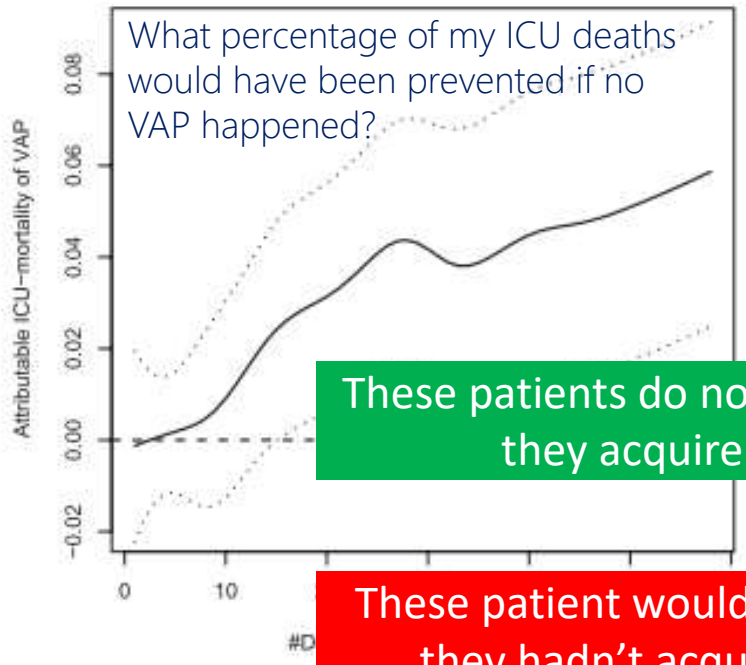


Figure 2. The attributable intensive care unit (ICU) mortality of ventilator-associated pneumonia (VAP) as a function of time, defined as the population-attributable fraction. The *solid line* represents the percentage of ICU mortality that could be attributable to VAP or the percentage of the observed ICU deaths that could be avoided by preventing VAP. The *dashed line* is the corresponding 95% confidence interval.

TABLE 3. HAZARD RATIOS OF INTENSIVE CARE UNIT DEATH PER ADDITIONAL DAY SINCE INFECTION CALCULATED FOR PATIENTS WITH DIFFERENT SAPS II SCORES ON ADMISSION (DIFFERENT PERCENTILES)

SAPS II on Admission	Hazard Ratio of ICU Death per Additional Day Since Infection (95% CI)	*P* Value
15 (5%)	1.023 (0.980–1.068)	0.31
20 (10%)	1.030 (0.997–1.063)	0.07
28 (25%)	1.037 (1.018–1.056)	<0.001
40 (50%)	1.038 (1.025–1.052)	<0.001
53 (75%)	1.027 (1.013–1.041)	<0.001
65 (90%)	1.00 (0.989–1.022)	0.49
73 (95%)	0.990 (0.960–1.010)	0.28
Overall	1.023 (1.011–1.034)	<0.001

Definition of abbreviations: CI = confidence interval; ICU = intensive care unit; SAPS II = Simplified Acute Physiology Score II.

Bekaert et al. *Am J Respir Crit Care Med* **2011**;184:1133

How does Ventilator-Associated Pneumonia happen?

It’s actually tube-associated, not ventilator-associated

Nosocomial pneumonia incidence density among 400 German ICUs (pooled mean)

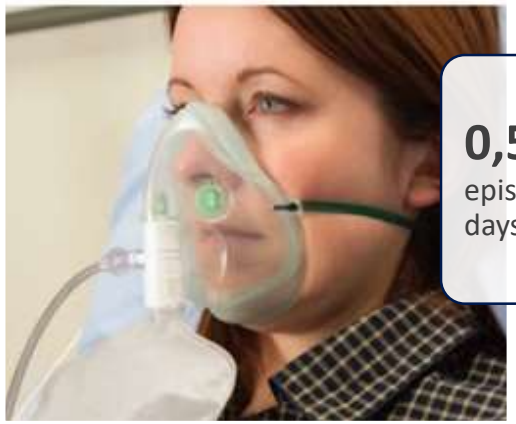
Invasive Mechanical Ventilation

5,44
episodes/1000 days at risk

Non-invasive Ventilation

1,58
episodes/1000 days at risk

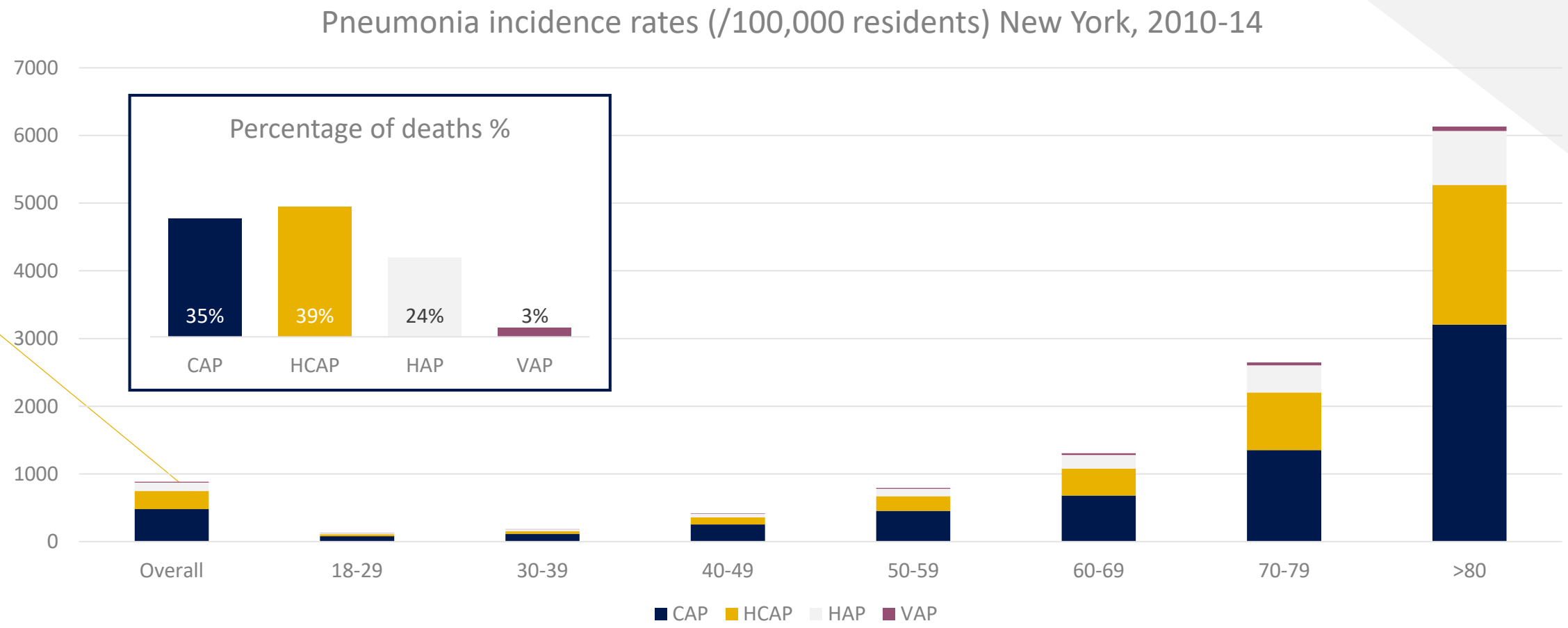
No Mechanical Ventilation



0,58
episodes/1000 days at risk

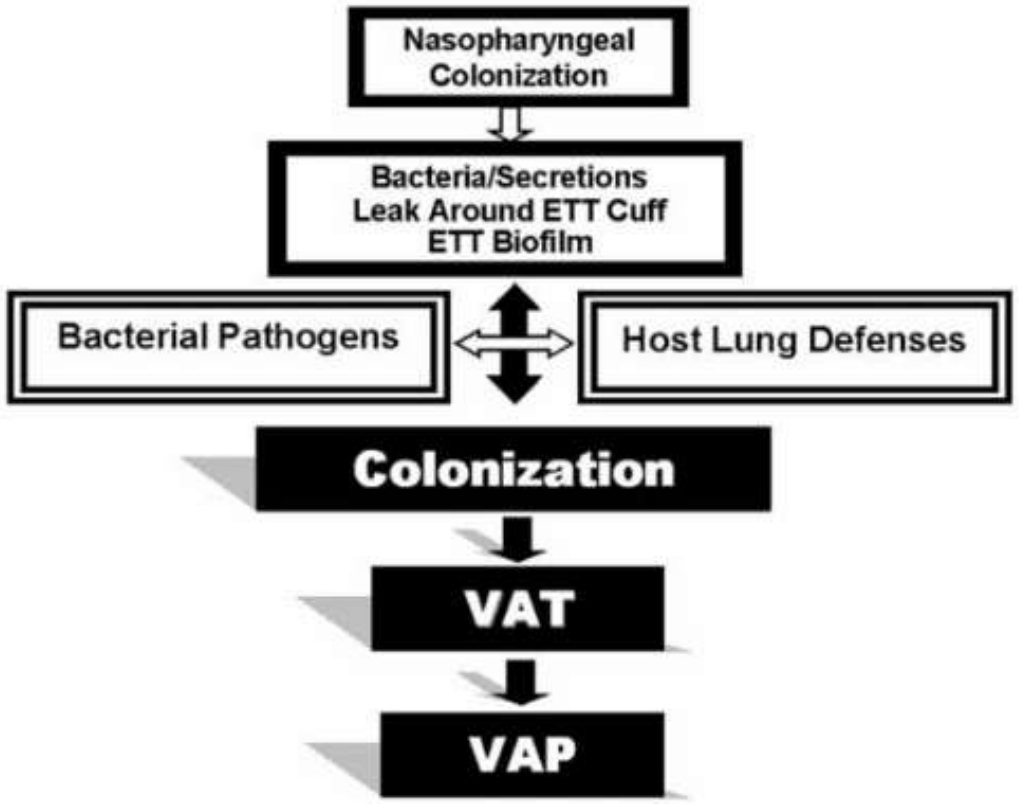
Kohlenberg et al. *Intensive Care Med* **2010**;36:971

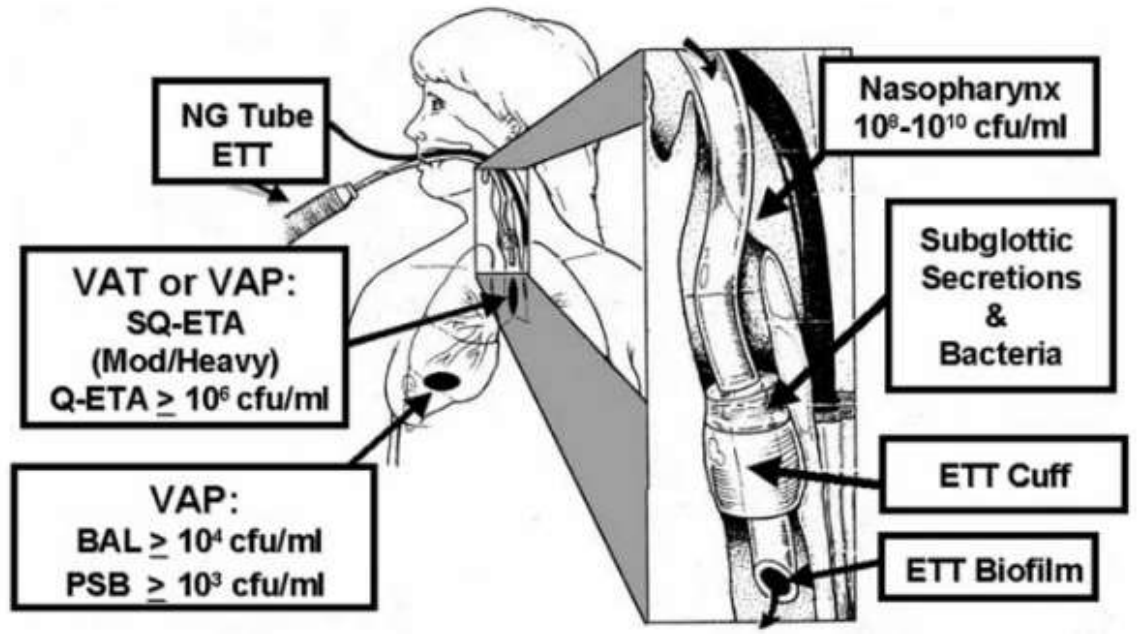
Impact of age on (hospitalized) pneumonia incidence



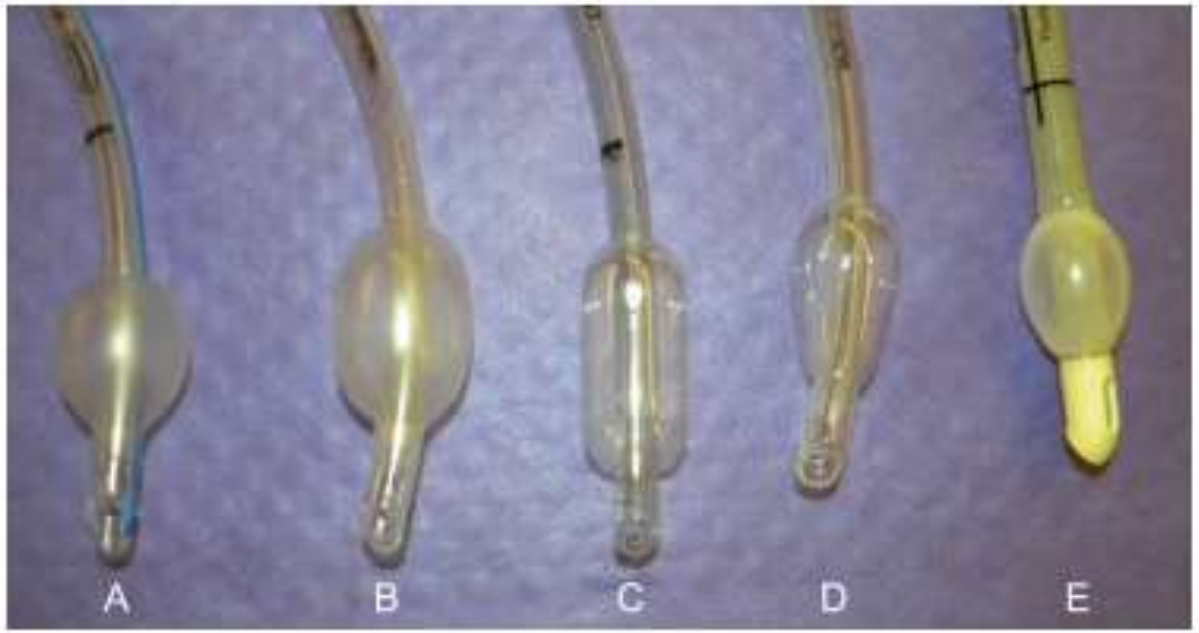
Corrado et al. *Chest* **2017**;152:930

Pathogenesis of VAP





Craven and **Hjalmarson**. *Clin Infect Dis* **2010**;51 Suppl 1:S59



VIEWPOINT

The tracheal tube: gateway to ventilator-associated pneumonia

Parjam S Zolfaghari[1]* and Duncan LA Wyncoll[2]

Figure 2. Photograph of various bench tested tracheal tubes of different designs showing the internal channels created and the leak of liquid material past the cuff. Tube cuffs A and B are made from polyvinyl chloride, and cuffs C and D with thin polyurethane (C has an elongated cylindrical shape and D is a tapered cuff design). Tube E is the LoTrach™ ET tube. (Photograph courtesy of Dr Peter Young, Kings Lynn, UK.)

Zolfaghari and **Wyncoll**. *Crit Care* **2011**;15:310

Biofilm formation on endotracheal tube

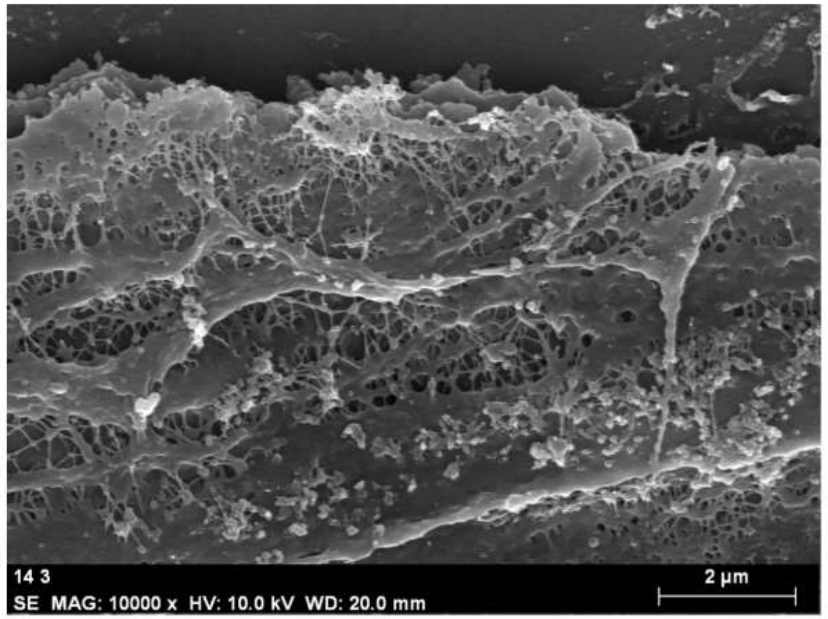


Figure 1 Scanning electron microscopy micrographs of biofilm in the endotracheal tubes. Biofilm at low magnification is composed of a matrix that attaches on the surface of the ETT. Scale bar: 2 µm.

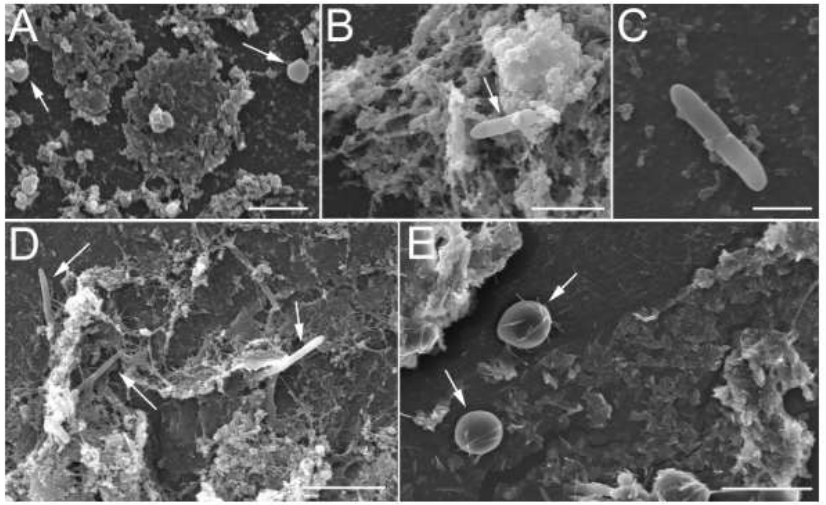


Figure 2 Identification of microorganisms on the surface of biofilm. In certain cases we could identify microorganisms immersed in the biofilm matrix. **A)** Cocci, scale bar: 2 µm, **B-D)** Bacilli, scale bar: 4 µm, 2 µm and 5 µm, respectively, and **E)** yeast. Scale bar: 10 µm.

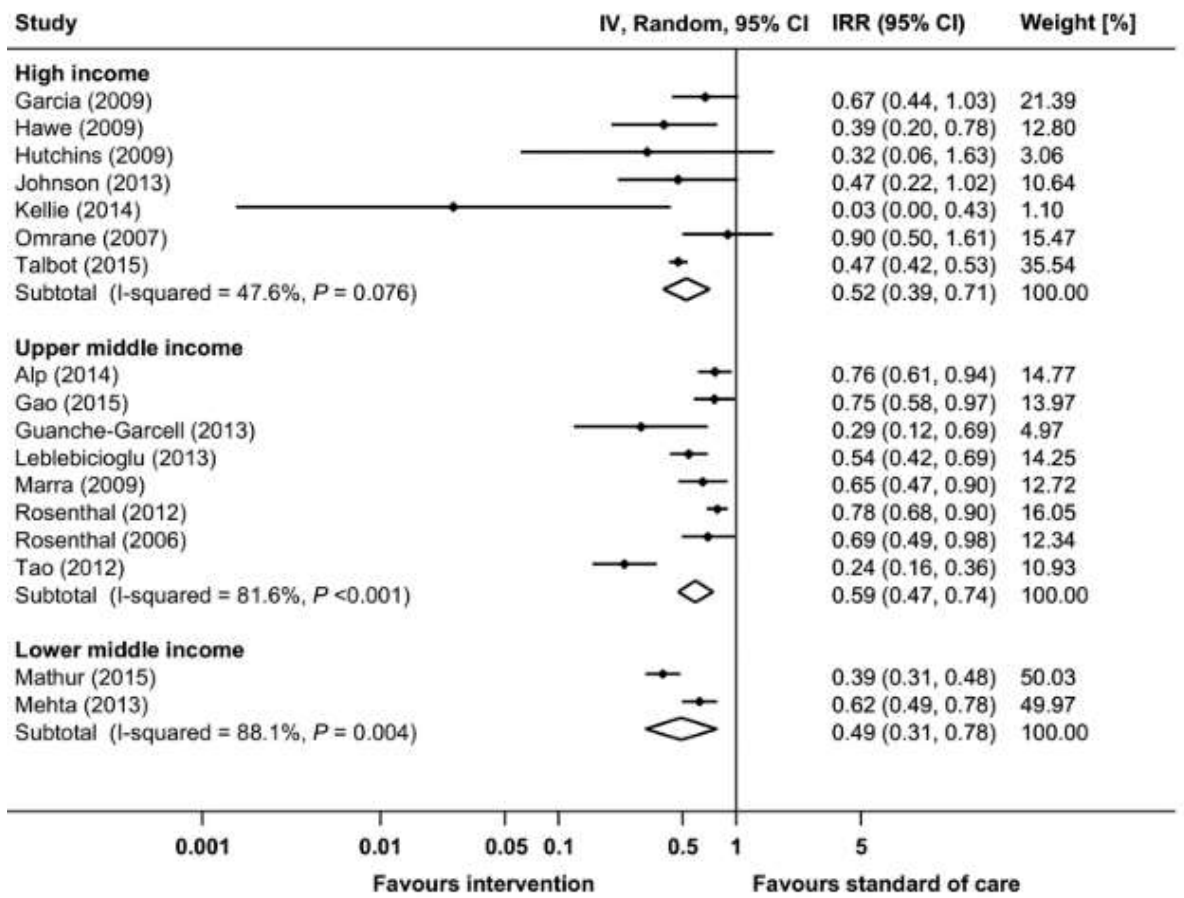
Gil-Perotin et al. *Crit Care* **2012**;16:R93

How can one prevent Ventilator-Associated Pneumonia?

Most of Ventilator-Associated Pneumonias are preventable

- Meta-analysis
- 5,226 screened articles between 2005-16
  - 144 included articles
- Multi-faceted interventions for HAI prevention
- Incidence Rate Ratios:
  - 0.543 (0.435-0.662) for CAUTI
  - 0.459 (0.381-0.554) for CLABSI
  - 0.553 (0.465-0.657) for VAP
- Independent of country economic status (based on World Bank data)
- However, mostly uncontrolled design of studies with high risk of bias

VAP



Schreiber et al. *Infect Control Hosp Epidemiol* **2018**;39:1277

SHEA/IDSA practice recommendation: 2014 update *The Do's*

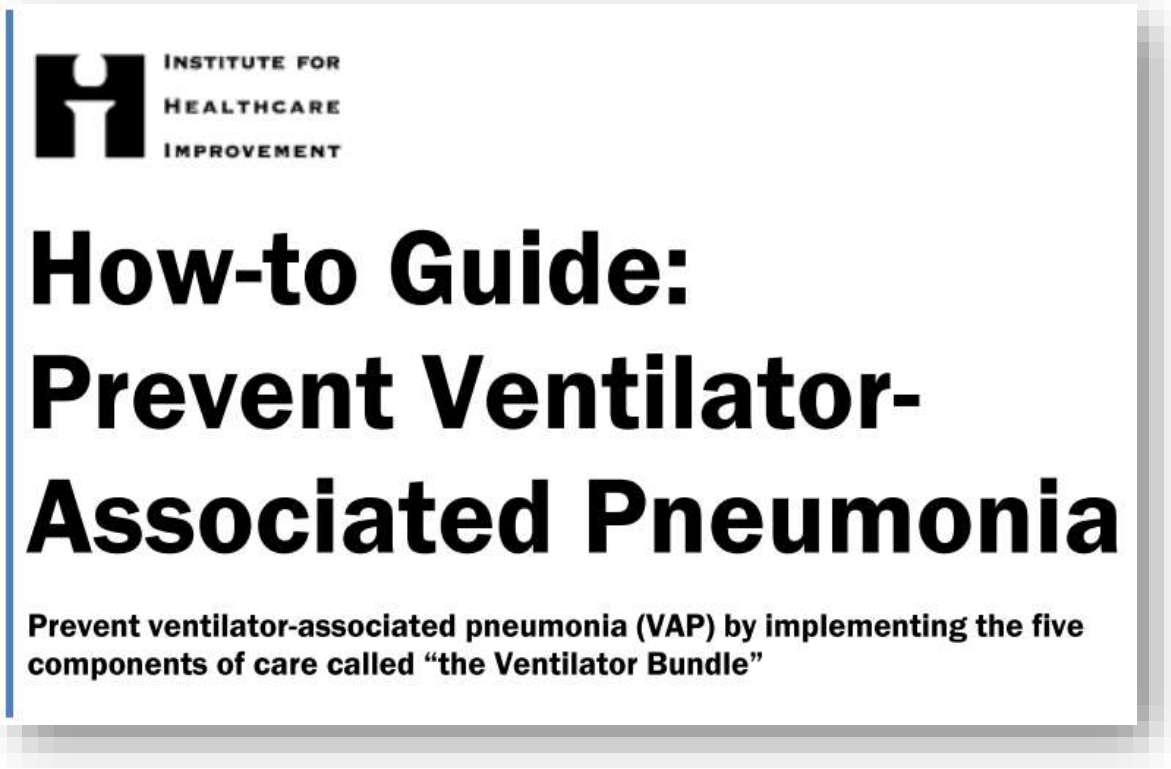
Basic practices	Good evidence that the intervention decreases the average duration of mechanical ventilation, length of stay, mortality, and/or costs; benefits likely outweigh risks	Use noninvasive positive pressure ventilation in selected populations[57,58]	High
		Manage patients without sedation whenever possible[46,61]	Moderate
		Interrupt sedation daily[62]	High
		Assess readiness to extubate daily[47,66-68]	High
		Perform spontaneous breathing trials with sedatives turned off[48]	High
		Facilitate early mobility[49,70-75,78]	Moderate
		Utilize endotracheal tubes with subglottic secretion drainage ports for patients expected to require greater than 48 or 72 hours of mechanical ventilation[50]	Moderate
		Change the ventilator circuit only if visibly soiled or malfunctioning[88-91]	High
		Elevate the head of the bed to 30°–45°[84-86]	Low[a]
Special approaches	Good evidence that the intervention improves outcomes but insufficient data available on possible risks	Selective oral or digestive decontamination[93-96]	High[b]
	May lower VAP rates but insufficient data to determine impact on duration of mechanical ventilation, length of stay, or mortality	Regular oral care with chlorhexidine[98,101-104]	Moderate
		Prophylactic probiotics[111-114]	Moderate
		Ultrathin polyurethane endotracheal tube cuffs[120,121]	Low
		Automated control of endotracheal tube cuff pressure[122,123]	Low
		Saline instillation before tracheal suctioning[124]	Low
		Mechanical tooth brushing[125,126]	Low

Klompas et al. *Infect Control Hosp Epidemiol* **2014**;35:915

SHEA/IDSA practice recommendation: 2014 update
The Do Not's/ Don't Know's

Generally not recommended	Lowers VAP rates but ample data suggest no impact on duration of mechanical ventilation, length of stay, or mortality	Silver-coated endotracheal tubes[127]	Moderate
		Kinetic beds[128]	Moderate
		Prone positioning[87,129-134,c]	Moderate
	No impact on VAP rates, average duration of mechanical ventilation, length of stay, or mortality[c]	Stress ulcer prophylaxis[135,136]	Moderate
		Early tracheotomy[137]	High
		Monitoring residual gastric volumes[138]	Moderate
		Early parenteral nutrition[139]	Moderate
No recommendation	No impact on VAP rates or other patient outcomes, unclear impact on costs	Closed/in-line endotracheal suctioning[141-143]	Moderate

Klompas et al. *Infect Control Hosp Epidemiol* **2014**;35:915



- ✓ Elevation of the head of the bed (HOB) to between 30 and 45 degrees
- ✓ Daily —sedative interruption‖ and daily assessment of readiness to extubate
- ✓ Peptic ulcer disease (PUD) prophylaxis
- ✓ Deep venous thrombosis (DVT) prophylaxis (unless contraindicated)
- ✓ Daily oral care with chlorhexidine

Institute for Healthcare Improvement; 2012. (Available at www.ihi.org)

Table 3. Associations Between Processes of Care and VAEs[a]

Process of Care	HR (95% CI) VAEs	*P* Value	IVACs	*P* Value	Possible VAP	*P* Value
Head-of-bed elevation	1.33 (0.84-2.11)	.23	1.16 (0.59-2.28)	.66	1.60 (0.53-4.88)	.41
Sedative infusion interruptions	0.95 (0.67-1.35)	.76	1.04 (0.61-1.78)	.88	0.82 (0.37-1.82)	.63
Spontaneous breathing trials	0.55 (0.40-0.76)	<.001	0.60 (0.37-1.00)	.05	0.79 (0.39-1.60)	.52
Prophylaxis						
Thromboembolism	0.78 (0.38-1.62)	.51	0.96 (0.26-3.56)	.96	1.13 (0.16-7.78)	.90
Stress ulcer	1.34 (0.87-2.07)	.19	1.62 (0.78-3.35)	.20	7.69 (1.44-41.10)	.02
Oral care with chlorhexidine	0.87 (0.61-1.23)	.42	0.60 (0.36-1.00)	.05	0.55 (0.27-1.14)	.11

Table 4. Associations Between Processes of Care and Patient Outcomes

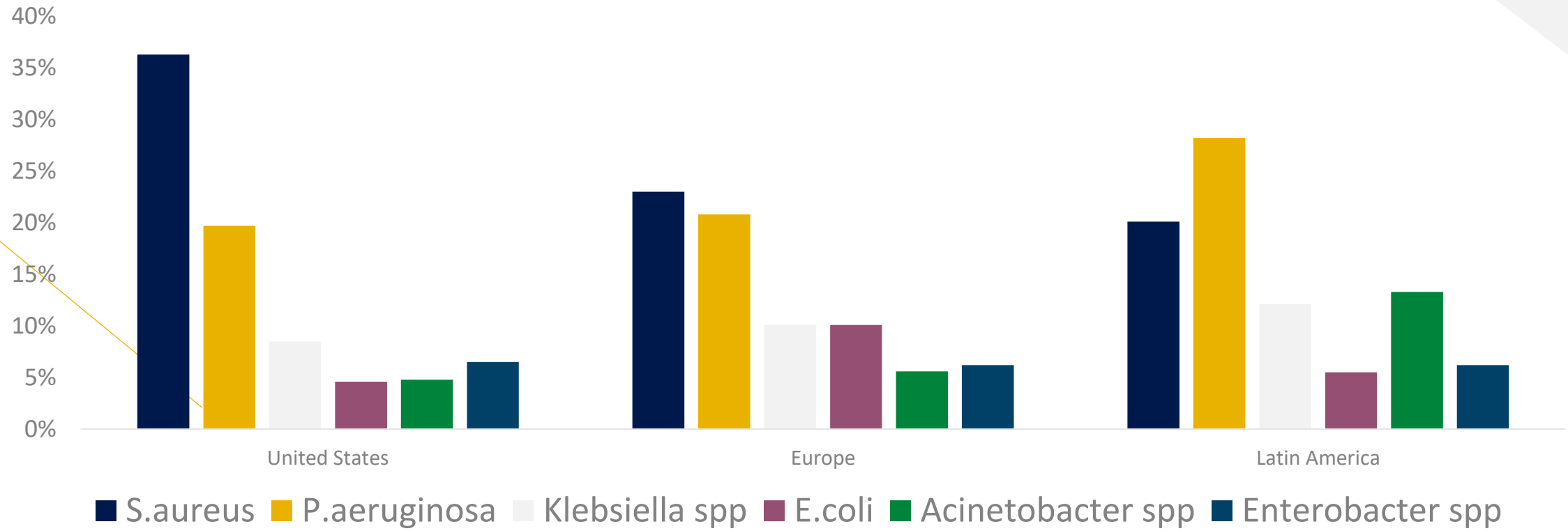
Process of Care	Outcome, HR (95% CI) Time to Extubation Alive	*P* Value	Ventilator Mortality	*P* Value	Time to Hospital Discharge Alive[a]	*P* Value	Hospital Mortality[a]	*P* Value
Head-of-bed elevation	1.38 (1.14-1.68)	.001	0.86 (0.59-1.25)	.42	1.01 (0.96-1.05)	.80	0.98 (0.93-1.03)	.36
Sedative infusion interruptions	1.81 (1.54-2.12)	<.001	0.51 (0.38-0.68)	<.001	1.09 (1.05-1.14)	<.001	0.92 (0.88-0.96)	<.001
Spontaneous breathing trials	2.48 (2.23-2.76)	<.001	0.28 (0.20-0.38)	<.001	1.00 (0.98-1.02)	.92	0.99 (0.96-1.02)	.46
Prophylaxis								
Thromboembolism	2.57 (1.80-3.66)	<.001	1.39 (0.82-2.37)	.23	1.02 (0.97-1.07)	.41	0.97 (0.92-1.02)	.26
Stress ulcer	1.12 (0.95-1.32)	.17	0.91 (0.64-1.31)	.62	1.00 (0.98-1.03)	.89	1.00 (0.96-1.04)	.90
Oral care with chlorhexidine	0.92 (0.80-1.04)	.18	1.63 (1.15-2.31)	.006	0.99 (0.98-1.01)	.26	1.01 (0.98-1.05)	.44

Klompas et al. *JAMA Intern Med* **2016**;176:1277

Which pathogens cause Ventilator-Associated Pneumonia?

Worldwide microbial etiology of HABP

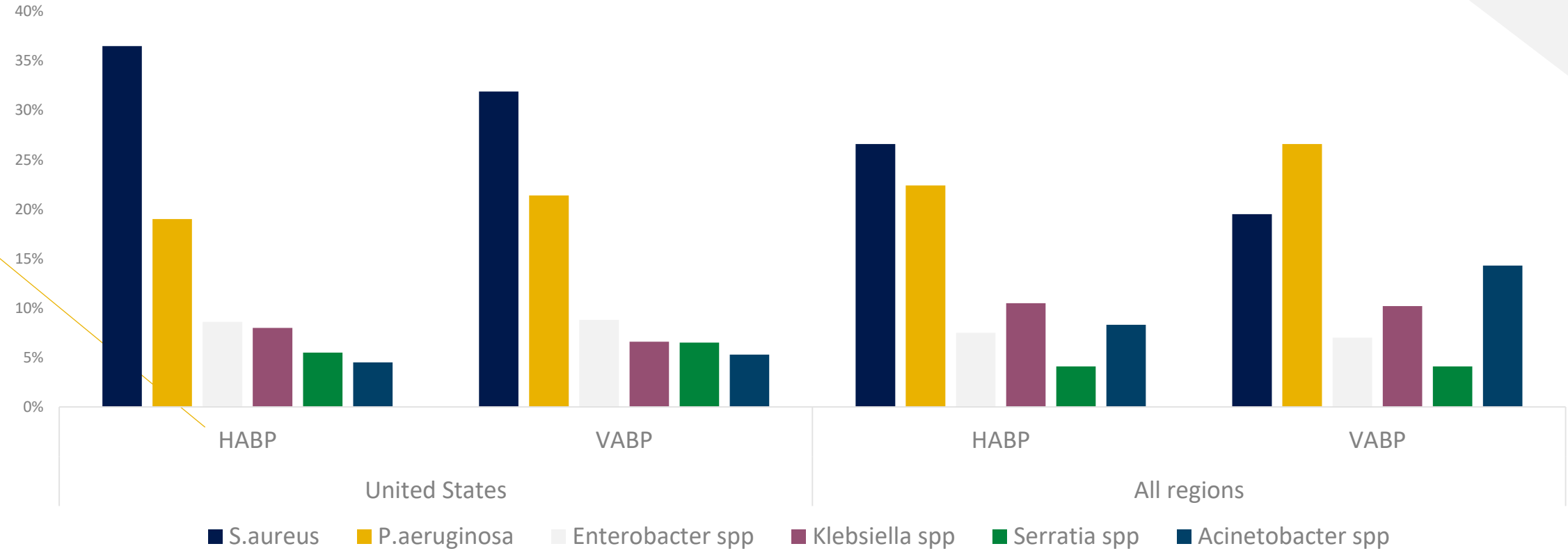
Top 6 pathogens causing hospital acquired bacterial pneumonia. SENTRY antimicrobial resistance surveillance program, 2004-2008



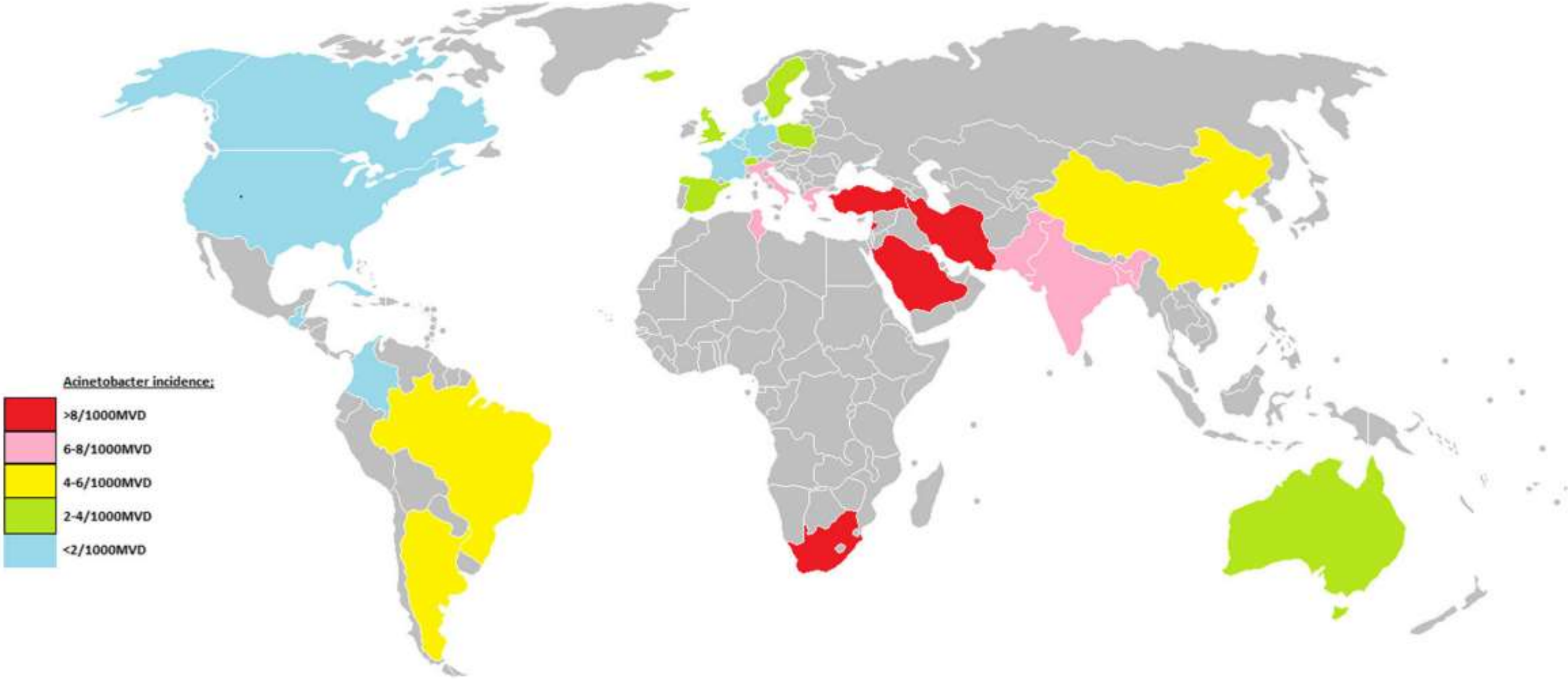
Jones. *Clin Infect Dis* **2010**;51:S81

VABP microbiology

Comparative microbial etiology between HABP and VABP, US and All regions (North America, Europe, Latin America).
SENTRY antimicrobial surveillance program (2004-2008)



Jones. *Clin Infect Dis* **2010**;51:S81



World-wide variation in Acinetobacter etiology among VABP cases

Hurley. *BMC Infect Dis* **2016**;16:577

How to approach the patient with suspected Ventilator-Associated Pneumonia?

Invasive and Noninvasive Strategies for Management of Suspected Ventilator-Associated Pneumonia

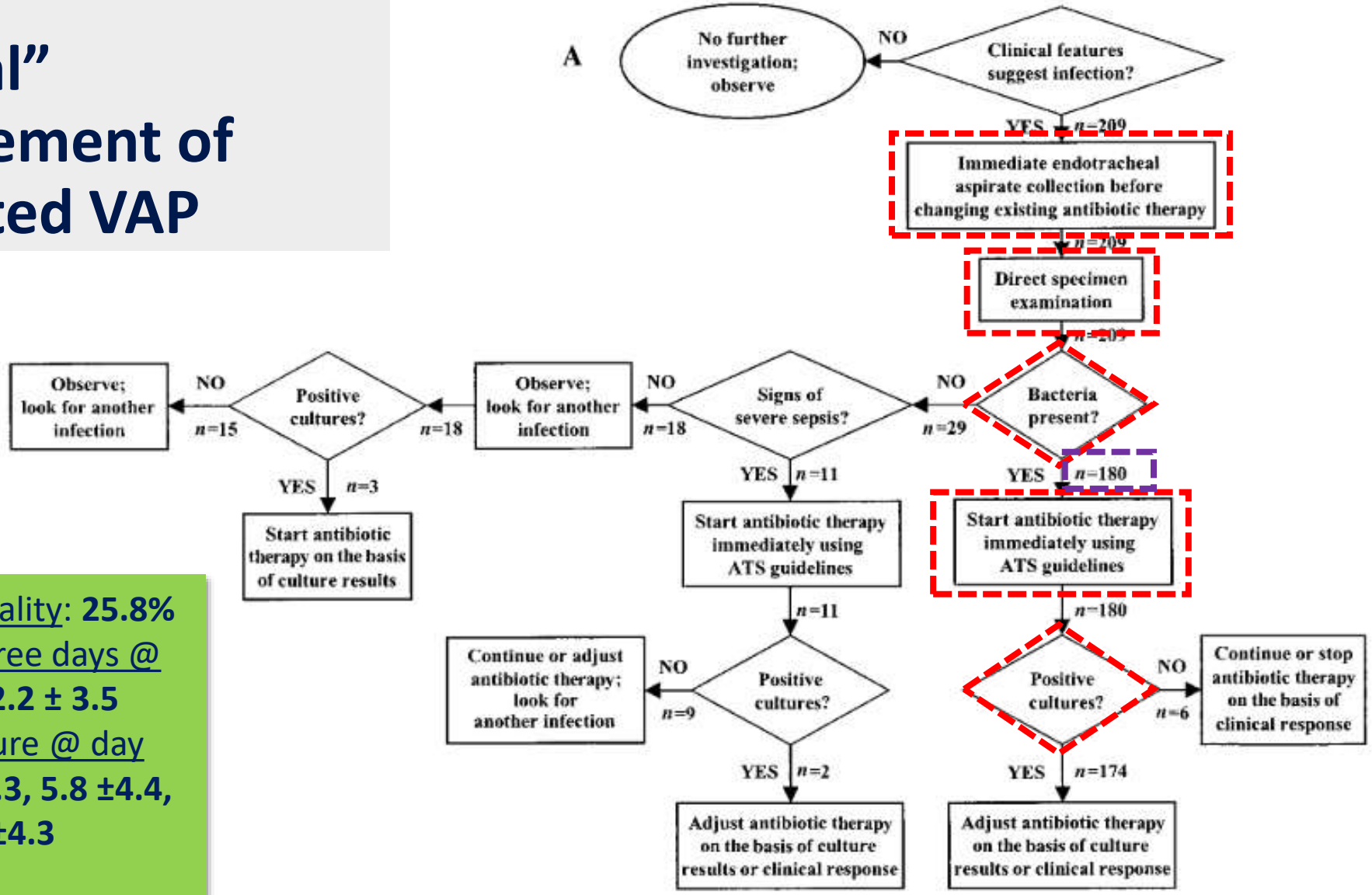
A Randomized Trial

Jean-Yves Fagon, MD; Jean Chastre, MD; Michel Wolff, MD; Claude Gervais, MD; Sylvie Parer-Aubas, MD; François Stéphan, MD; Thomas Similowski, MD; Alain Mercat, MD; Jean-Luc Diehl, MD; Jean-Pierre Sollet, MD; and Alain Tenaillon, MD, for the VAP Trial Group*

- 31 French ICUs
- **Key inclusion criteria**: clinical suspicion of VAP
- **Key exclusion criteria**: recent modification of antibiotics
- **Clinical management** (209 pts) vs **Invasive management** (204 pts)
- **Primary endpoints**:
  - 14-day mortality
  - antibiotic-free days @ day 14
  - organ failure # days 3,7,14 (SOFA & ODIN scores)
- **Secondary endpoints**:
  - 28-day mortality
  - antibiotic-free days @ day 28
  - MV-free days @ day 28
  - LOS (ICU & hospital)
  - Emergence of resistant bacteria
  - Emergence of *Candida* spp
- **Microbiology:**
  - ~20% *P.aeruginosa*
  - ~5% *Acinetobacter* spp
  - ~15% *S.aureus*

Fagon et al. *Ann Intern Med* **2000**;132:621

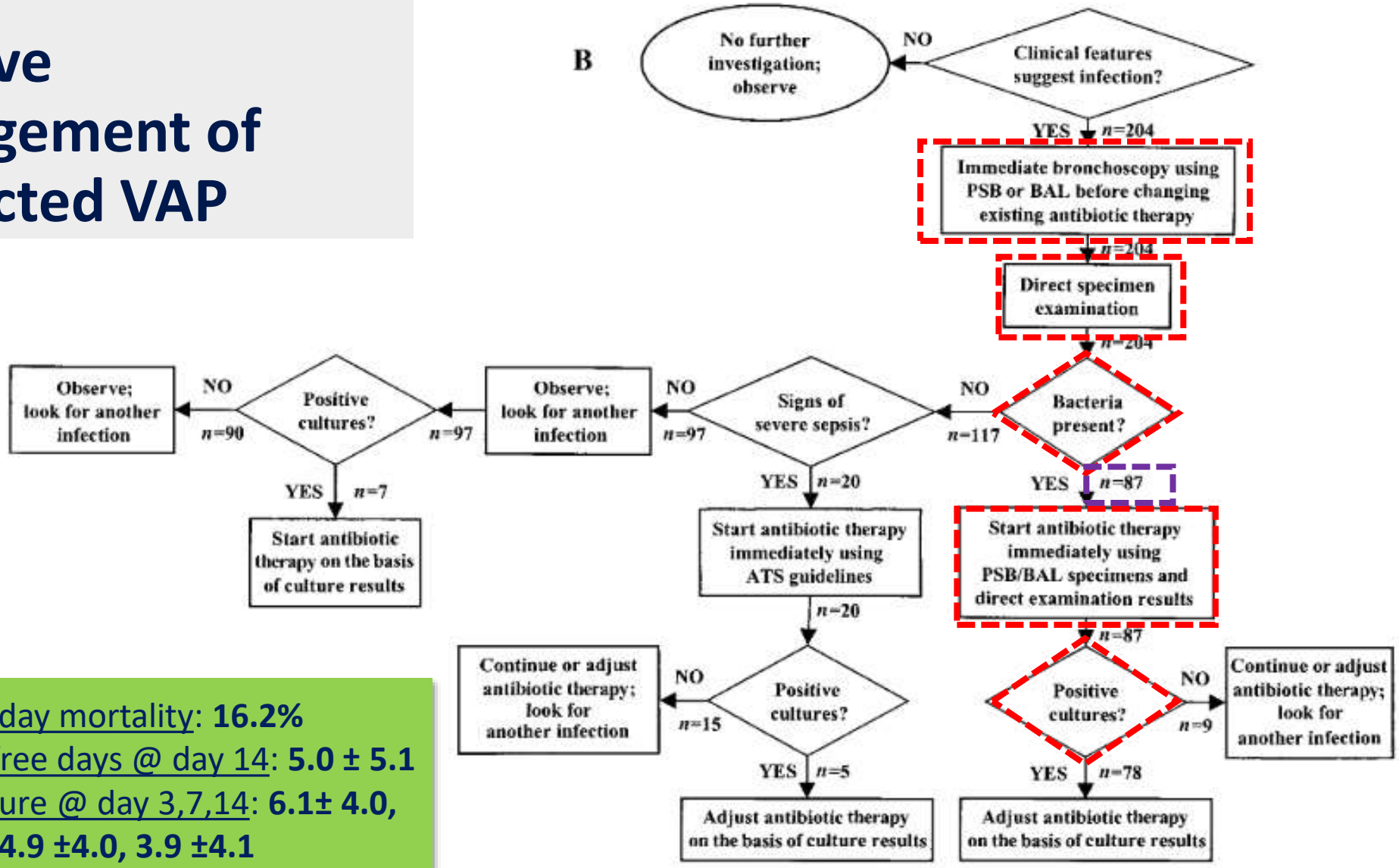
"Clinical" management of suspected VAP



14-day mortality: **25.8%**
Antibiotic free days @ day 14: **2.2 ± 3.5**
Organ failure @ day 3,7,14: **7± 4.3, 5.8 ±4.4, 4.3 ±4.3**

Fagon et al. *Ann Intern Med* **2000**;132:621

Invasive management of suspected VAP



14-day mortality: **16.2%**
Antibiotic free days @ day 14: **5.0 ± 5.1**
Organ failure @ day 3,7,14: **6.1± 4.0, 4.9 ±4.0, 3.9 ±4.1**

Fagon et al. *Ann Intern Med* **2000**;132:621

To BAL or not to BAL?

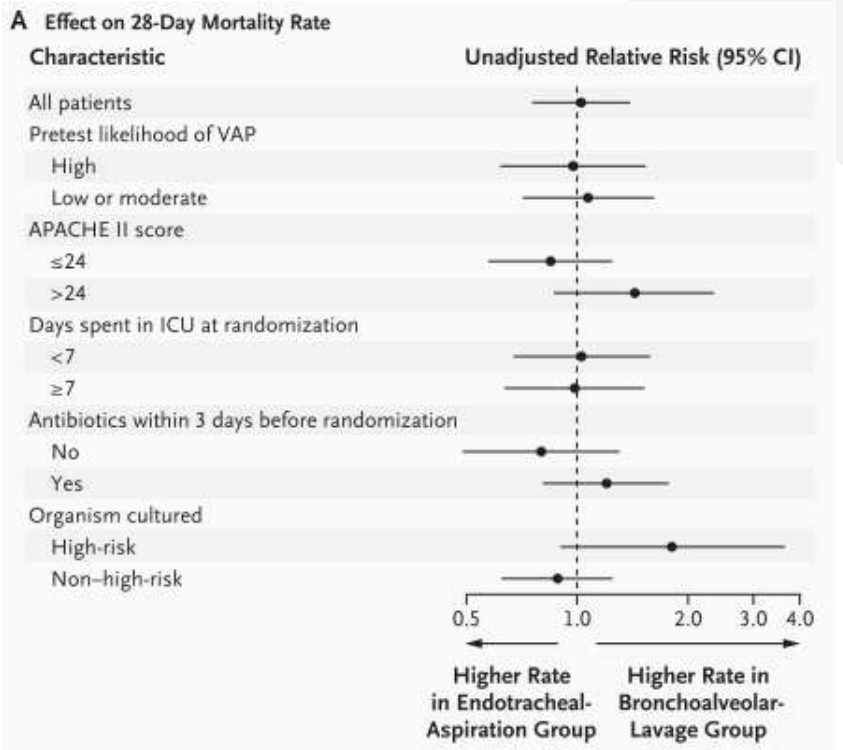
- Multi-center RCT, 2x2 factorial design
- 740 pts, >4 days on ventilator, suspected pneumonia, 28 ICUs (US/Canada)
- BAL with quantitative culture vs standard endotracheal aspiration/culture
  - standardized empiric monotherapy vs empiric combination R_x (Mero vs Mero/Cipro)
- Excluded pts colonized or infected by MRSA or Pseudomonas spp
- Research hypothesis: BAL use would lead to reduced 28-day mortality and increased targeted R_x
- 28-day mortality (95% CI): 18.7% (15.9-21.7%)
  - adjusted RR: 1.01 (0.75-1.37)
  - No signal in subgroup analyses and/or secondary outcomes

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 21, 2006 VOL. 355 NO. 25

A Randomized Trial of Diagnostic Techniques for Ventilator-Associated Pneumonia

The Canadian Critical Care Trials Group*



The Canadian Critical Care Trials Group. *N Engl J Med* **2006**;355:2619

Λήψη καλλιεργειών προ της έναρξης εμπειρικής αγωγής

Η πρόσφατη (<24h) έναρξη αντιμικροβιακής αγωγής, υποδιπλασιάζει την ευαισθησία των καλλιεργειών βρογχοκυψελιδικού εκπλύματος και προστατευόμενης βούρτσας

	ICO Count[a]		BAL Culture[b]		PSB Culture[c]	
	Se	Sp	Se	Sp	Se	Sp
No antibiotic group	0.71	NP	0.71	NP	0.88	1
Current antibiotic group	0.50	1	0.83	0.91	0.77	0.91
Recent antibiotic group	0.67	1	0.38[d]	1	0.40[d,e]	1

cfu, colony-forming units; NP, not performed.
[a]For 5% threshold; [b]for 10^5-cfu/mL threshold; [c]for 10^3-cfu/mL threshold; [d]$p < .05$ between the recent antibiotic group and the no antibiotic and current antibiotic groups combined; [e]$p < .05$ between the recent antibiotic group and the no antibiotic group.

Souweine et al.*Crit Care Med* **1998**;26:236

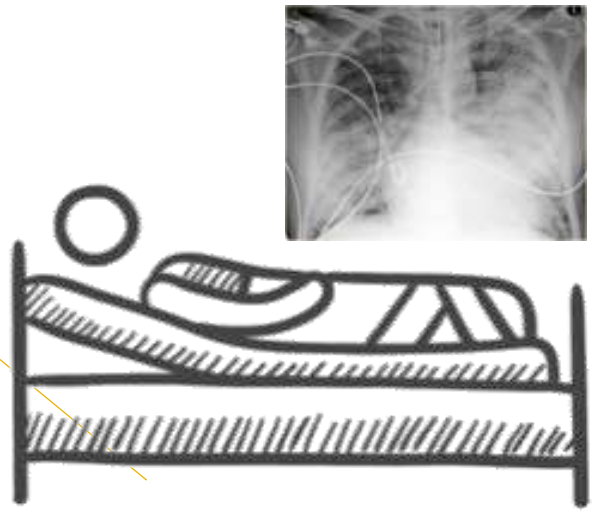
How should Ventilator-Associated Pneumonia be treated?

IDSA GUIDELINE

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

Andre C. Kalil,[1,a] Mark L. Metersky,[2,a] Michael Klompas,[3,4] John Muscedere,[5] Daniel A. Sweeney,[6] Lucy B. Palmer,[7] Lena M. Napolitano,[8] Naomi P. O'Grady,[9] John G. Bartlett,[10] Jordi Carratalà,[11] Ali A. El Solh,[12] Santiago Ewig,[13] Paul D. Fey,[14] Thomas M. File Jr,[15] Marcos I. Restrepo,[16] Jason A. Roberts,[17,18] Grant W. Waterer,[19] Peggy Cruse,[20] Shandra L. Knight,[20] and Jan L. Brozek[21]

Suspected VAP



Do cover for

- *S.aureus*
- *P.aeruginosa*
- Other Gram-negative bacilli

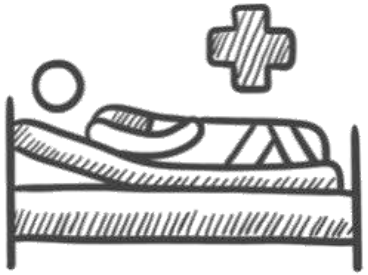
VAP: Ventilator-Associated Pneumonia
AMG: Aminoglycoside
COL: Colistin

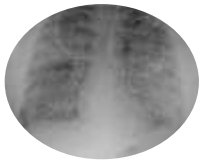
Kalil et al. *Clin Infect Dis* **2016**;63:e61

IDSA GUIDELINE

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

Andre C. Kalil,[1,a] Mark L. Metersky,[2,a] Michael Klompas,[3,4] John Muscedere,[5] Daniel A. Sweeney,[6] Lucy B. Palmer,[7] Lena M. Napolitano,[8] Naomi P. O'Grady,[9] John G. Bartlett,[10] Jordi Carratalà,[11] Ali A. El Solh,[12] Santiago Ewig,[13] Paul D. Fey,[14] Thomas M. File Jr,[15] Marcos I. Restrepo,[16] Jason A. Roberts,[17,18] Grant W. Waterer,[19] Peggy Cruse,[20] Shandra L. Knight,[20] and Jan L. Brozek[21]





MRSA>10–20%

Suspected VAP
Staphylococcal coverage

- Do cover *S.aureus*
- **MRSA if risk factors present**
  (see left, *weak recommendation*)
  - Vancomycin or linezolid
    - *strong recommendation*
- **Otherwise, MSSA**
  - Pip-tazo, cefepime, levo, imi-mero
- Anti-staphylococcal β-lactam
  - In proven MSSA

Kalil et al. *Clin Infect Dis* **2016**;63:e61

VAP: Ventilator-Associated Pneumonia
MRSA: Methicillin-Resistant *Staphylococcus aureus*
MSSA: Methicillin-susceptible *Staphylococcus aureus*

IDSA GUIDELINE

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

Andre C. Kalil,[1,a] Mark L. Metersky,[2,a] Michael Klompas,[3,4] John Muscedere,[5] Daniel A. Sweeney,[6] Lucy B. Palmer,[7] Lena M. Napolitano,[8] Naomi P. O'Grady,[9] John G. Bartlett,[10] Jordi Carratalà,[11] Ali A. El Solh,[12] Santiago Ewig,[13] Paul D. Fey,[14] Thomas M. File Jr,[15] Marcos I. Restrepo,[16] Jason A. Roberts,[17,18] Grant W. Waterer,[19] Peggy Cruse,[20] Shandra L. Knight,[20] and Jan L. Brozek[21]

Suspected VAP

- Do cover Pseudomonas
- **two antipseudomonals**
  - *weak recommendation, low-quality evidence*
- different classes
- avoid AMG, COL if alternative agents are available
- **otherwise, one antipseudomonal**

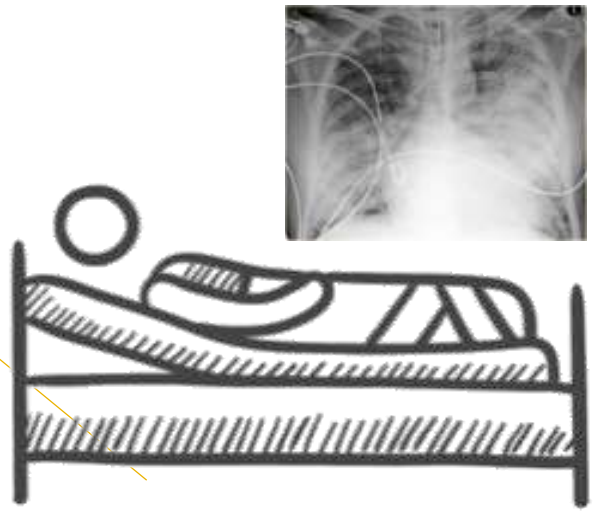
VAP: Ventilator-Associated Pneumonia
AMG: Aminoglycoside
COL: Colistin

Kalil et al. *Clin Infect Dis* **2016**;63:e61

IDSA GUIDELINE

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

Andre C. Kalil,[1,a] Mark L. Metersky,[2,a] Michael Klompas,[3,4] John Muscedere,[5] Daniel A. Sweeney,[6] Lucy B. Palmer,[7] Lena M. Napolitano,[8] Naomi P. O'Grady,[9] John G. Bartlett,[10] Jordi Carratalà,[11] Ali A. El Solh,[12] Santiago Ewig,[13] Paul D. Fey,[14] Thomas M. File Jr,[15] Marcos I. Restrepo,[16] Jason A. Roberts,[17,18] Grant W. Waterer,[19] Peggy Cruse,[20] Shandra L. Knight,[20] and Jan L. Brozek[21]



Suspected HAP

- Do cover for *S.aureus*
  - MRSA if :
    - Risk factors for MRSA
    - Risk factors for mortality
      - Septic shock
      - Ventilated HAP
- Conditionally cover for *P.aeruginosa* or other Gram-negative bacteria
  - Risk factors present
  - Risk factors for mortality present
    - Do so with 2 agents

VAP: Ventilator-Associated Pneumonia
AMG: Aminoglycoside
COL: Colistin

Kalil et al. *Clin Infect Dis* **2016**;63:e61

Dosages & PK/PD considerations

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	

'.. antibiotic dosing be determined using PK/PD data, rather than the manufacturer's prescribing information...'

Kalil et al. *Clin Infect Dis* **2016**;63:e61

Κατευθυντήριες γραμμές ΕΕΧ

Πίνακας 5. Αρχική εμπειρική αντιμικροβιακή αγωγή για ασθενείς με HAP/VAP

Ασθενείς με κλινική υποψία HAP, χωρίς σηπτική καταπληξία και χωρίς παράγοντες κινδύνου για πολυανθεκτικά παθογόνα → Μονοθεραπεία[1,2]
Πιπερακιλλίνη-ταζομπακτάμη: 4,5g x 4
Κεφεπίμη: 2g x 3
Μεροπενέμη[3,6]: 2g x 3
Ιμιπενέμη/σιλαστατίνη[3]: 1g x 3

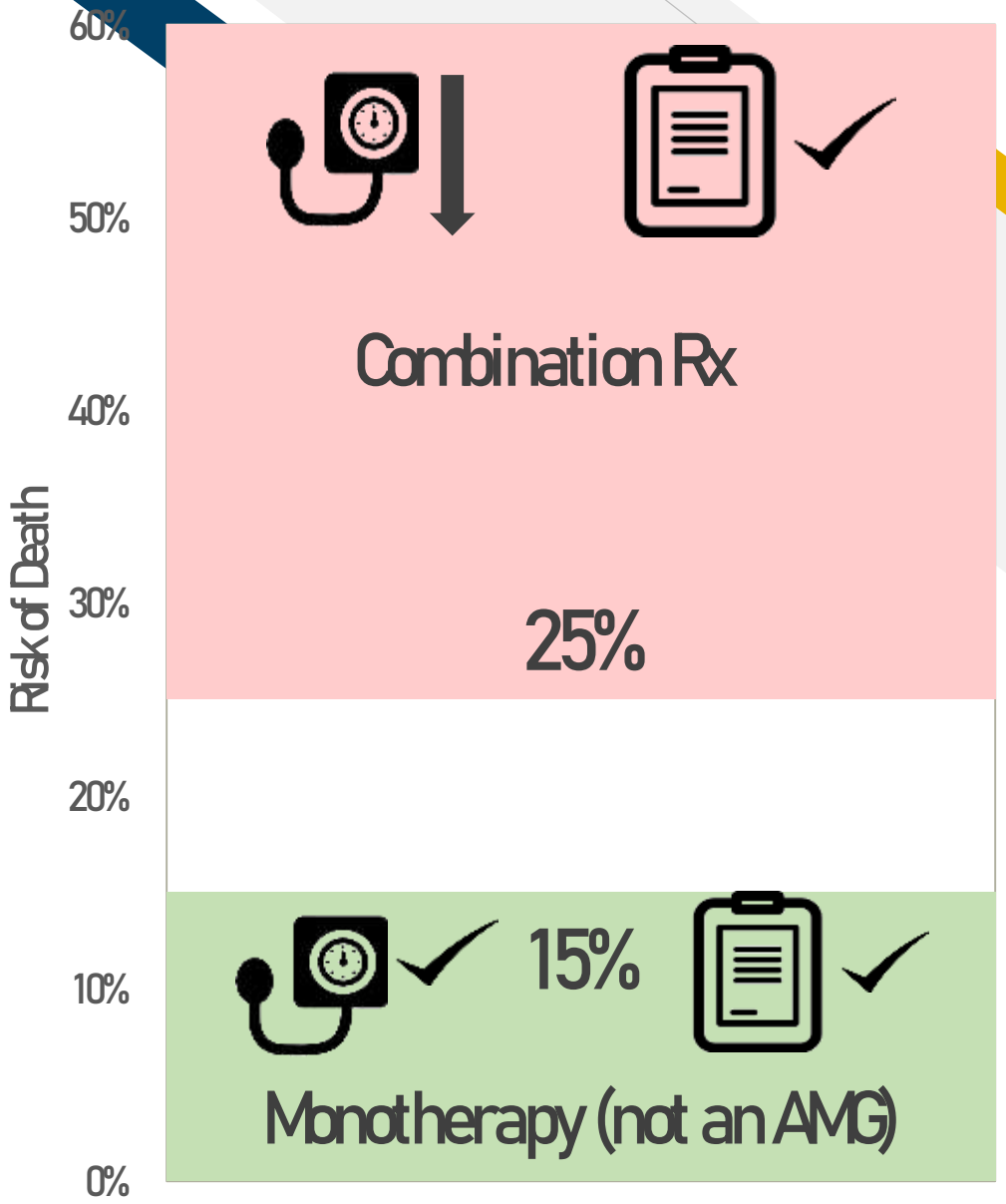
Ασθενείς με κλινική υποψία HAP/VAP σε σηπτική καταπληξία ή με παράγοντες κινδύνου για πολυανθεκτικά παθογόνα → Συνδυασμοί αντιβιοτικών[1,2,4]
Ένα από τα παρακάτω
Πιπερακιλλίνη-ταζομπακτάμη: 4,5g x 4
Κεφεπίμη ή Κεφταζιντίμη[5]: 2 g x 3
Ιμιπενέμη/σιλαστατίνη[3]: 1g x 3
Μεροπενέμη[3,6]: 2g x 3
Ντοριπενέμη[3]: 1g x 3
Αζτρεονάμη: 2g x 3
ΚΑΙ ένα από τα παρακάτω
Αμικασίνη[7]: 20mg/kg x 1
Γενταμικίνη[7]: 5-7mg/kg x 1
Τομπραμυκίνη[7]: 5-7mg/kg x 1
Σιπροφλοξασίνη[8]: 400mg x 3 ή 600mg x 2
Σε υποψία παθογόνου με αντοχή στις καρβαπενέμες,[9,10] προσθήκη τουλάχιστον ενός από τα κάτωθι
Κολιστίνη: 9 IU, φόρτιση, ακολούθως 4,5 IU x 2
Τιγεκυκλίνη: 200 mg φόρτιση, ακολούθως 100mg x 2

Proven, microbiologically documented Pseudomonas VAP

IDSA GUIDELINE

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

Andre C. Kalil,[1,a] Mark L. Metersky,[2,a] Michael Klompas,[3,4] John Muscedere,[5] Daniel A. Sweeney,[6] Lucy B. Palmer,[7] Lena M. Napolitano,[8] Naomi P. O'Grady,[9] John G. Bartlett,[10] Jordi Carratalà,[11] Ali A. El Solh,[12] Santiago Ewig,[13] Paul D. Fey,[14] Thomas M. File Jr,[15] Marcos I. Restrepo,[16] Jason A. Roberts,[17,18] Grant W. Waterer,[19] Peggy Cruse,[20] Shandra L. Knight,[20] and Jan L. Brozek[21]



Addition of inhaled antibiotics in pathogens only susceptible to colistin and/or polymyxins

VAP: Ventilator-Associated Pneumonia
AMG: Aminoglycoside

Kalil et al. *Clin Infect Dis* **2016**;63:e61

HAP/VAP definitive R_x

- ESBL-producing Gram-negative pathogens
  - *based upon AST results & patient-specific factors*
    - *strong recommendation, very-low quality evidence*
- *Acinetobacter spp*
  - Carba CR A/S (susceptible isolate)
    - *weak recommendation, low quality evidence*
  - Polymyxin (CR pathogen) iv + neb
    - *strong recommendation, low-quality evidence/weak recommendation, low-quality evidence*
  - Rifampin (*suggestion not to use*), Tigecycline (*recommendation against use*)
- Carbapenem-resistant pathogens
  - Polymyxin (CR pathogen) iv + neb
    - *strong recommendation, low-quality evidence/weak recommendation, low-quality evidence*

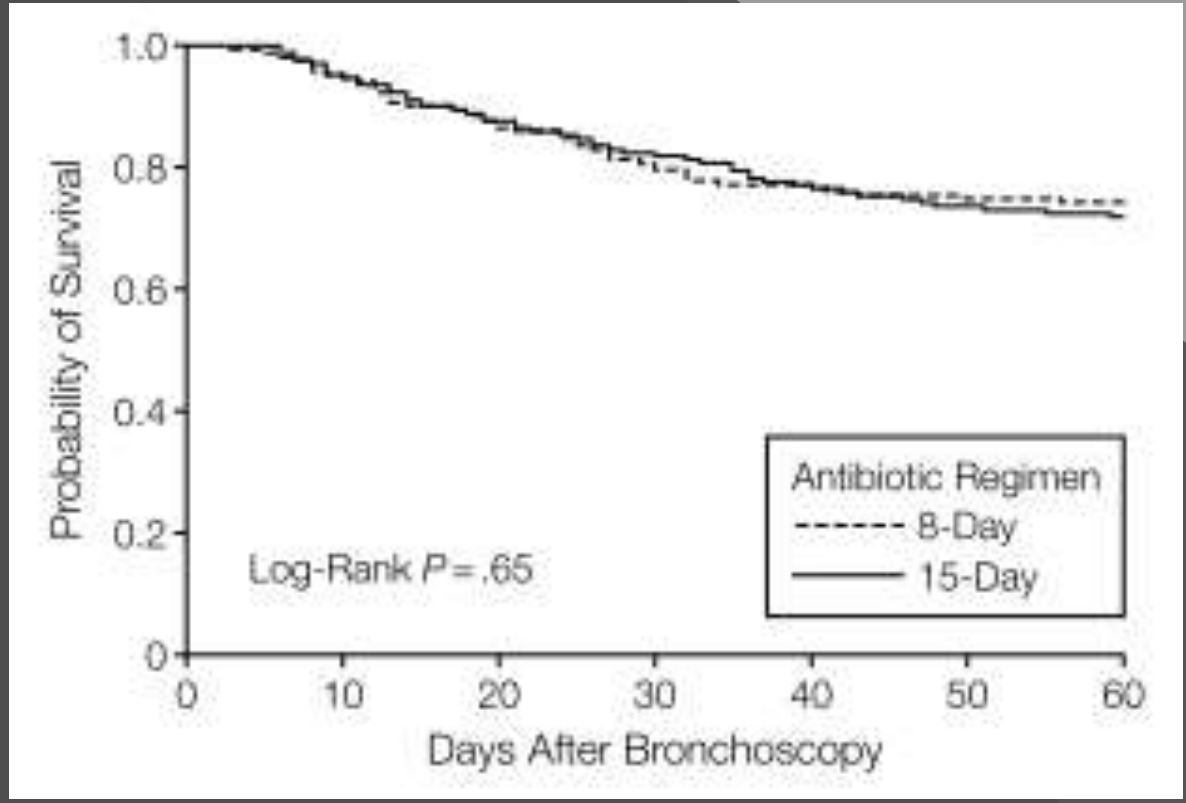
HAP: Hospital-acquired pneumonia
VAP: Ventilator-Associated Pneumonia
ESBL: Extended-spectrum beta-lactamases
AST: Antimicrobial Susceptibility Testing
A/S: Ampicillin/sulbactam
CR: Carbapenem-resistant

Kalil et al. *Clin Infect Dis* **2016**;63:e61

How long to treat VAP for?

- Most experts recommended that treatment of VAP last 14 to 21 days
- Randomize, double blind, parallel group, non-inferiority clinical trial
- 51 French ICUs; 197 pts (8-day) vs 204 pts (15-day)
- ~ 30% non-fermenters, ~10% MRSA
- **Key inclusion criteria**
  - VAP suspicion (fever, leukocytosis etc)
  - Positive distal quantitative cultures
  - In vitro active, not delayed antibiotic R_x
- **Key exclusion criteria**
  - Immunosuppression
  - Concurrent extrapulmonary infection
  - presumed antibiotic-sensitive infection
- **Primary endpoints**
  - Death from any cause
  - microbiologically documented recurrence
  - antibiotic-free days

Chastre et al. *JAMA* **2003**;290:2588



Recurrence rate : 28,9% vs 26% (NS) ☺
Antibiotic-free days: 13,1 vs 8,7 days (p<0,001) ☺
BUT Higher recurrence rate in *non-fermenters* (40,6 vs 25,4%) ☹
More *MDR recurrent infections* in 15-day group (62,3 vs 42,1%) ☺

What is the optimum duration of treatment?

- Systematic review & meta-analysis
- 6 studies; 1088 pts
  - most conclusions based on 2 or 3 studies
- Comparison of fixed treatment durations (7-8d vs 10-15d)
- Low to moderate quality of evidence
- Short course is safe, in the absence of NFGNB, reducing antibiotic exposure & recurrence with MDR bacteria

Pugh et al. *Cochrane Database Syst Rev* **2015**; Aug 24;(8):CD007577

Should short-course antibiotic therapy versus prolonged-course antibiotic therapy be used in critically ill patients with hospital-acquired pneumonia?

Patient or population: hospital-acquired pneumonia
Settings: intensive care
Intervention: short-course antibiotic therapy
Comparison: prolonged-course antibiotic therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Prolonged-course antibiotic therapy	Short-course antibiotic therapy				
Mortality Follow-up: 28 days	175 per 1000	201 per 1000 (141 to 277)	OR 1.18 (0.77 to 1.8)	598 (3 studies)	⊕⊕⊕○ **moderate**[1]	-
Mortality NF-GNB Follow-up: 28 days	265 per 1000	255 per 1000 (123 to 450)	OR 0.95 (0.39 to 2.27)	179 (2 studies)	⊕⊕○○ **low**[1,2]	-
Mortality MRSA Follow-up: 28 days	238 per 1000	286 per 1000 (91 to 614)	OR 1.28 (0.32 to 5.09)	42 (1 study)	⊕⊕⊕○ **moderate**[1]	-
Recurrence of pneumonia Clinical and/or microbiological criteria	180 per 1000	237 per 1000 (171 to 318)	OR 1.41 (0.94 to 2.12)	733 (19 studies)	⊕⊕○○ **low**[1,3]	-
Recurrence of pneumonia NF-GNB Clinical and/or microbiological criteria	247 per 1000	417 per 1000 (272 to 577)	OR 2.18 (1.14 to 4.16)	176 (2 studies)	⊕⊕⊕○ **moderate**[1]	-
Recurrence of pneumonia MRSA Clinical and/or microbiological criteria	370 per 1000	479 per 1000 (66 to 920)	OR 1.56 (0.12 to 19.61)	49 (2 studies)	⊕⊕⊕○ **moderate**[1]	-
28-day antibiotic-free days Follow-up: 28 days	The mean 28-day antibiotic free days in the intervention groups was **4.02 higher** (2.26 to 5.78 higher)			431 (2 studies)	⊕⊕○○ **low**[1,4]	-

Recommended treatment duration

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

- For patients with VAP, we recommend a 7-day course of antimicrobial therapy rather than a longer duration
  - *strong recommendation, moderate quality evidence*
- *The panel agreed that a different recommendation was not indicated for NFGNB VAP*
  - based on the absence of an impact on mortality and low quality of existing evidence
- For patients with HAP, we recommend a 7-day course of antimicrobial therapy
  - *strong recommendation, very low quality evidence*

Kalil et al. *Clin Infect Dis* **2016**;63:e61
Torres et al. *Eur Respir J* **2017**;50:1

International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia

- We suggest using a 7–8-day course of antibiotic therapy in patients with VAP without immunodeficiency, cystic fibrosis, empyema, lung abscess, cavitation or necrotising pneumonia and with a good clinical response to therapy
  - *Weak recommendation, moderate quality of evidence*
- This recommendation also includes patients with nonfermenting Gram-negatives, Acinetobacter spp. and MRSA with a good clinical response
- The panel believes that applying the rationale and recommendations used for VAP in nonventilated patients with HAP represents good practice
  - *Good practice statement*

Take home messages

- VAP is defined as an inflammation of the lung parenchyma caused by infectious agents not present or incubating at the time mechanical ventilation was started
- The concordance between clinical diagnostic criteria and histological pneumonia is poor
- There seems to be a decline in incidence of VAP, using simple measures
- The surveillance of VAP has shifted away from clinical pneumonia
- VAP is associated with increased mortality and leads to prolongation of mechanical ventilation, ICU & hospital stay
- Colonization of the upper airways and stomach, are believed to be the first steps for the development of pneumonia

a few more…

- Most episodes of VAP are deemed preventable with measures targeting the pathogenesis
  - colonization of upper airways/ stomach
  - aspiration
- The microbiology of HAP/VAP consists of S.aureus, non-fermenting Gram negative bacilli and *Enterobacteriaceae,* with regional differences
- Invasive diagnostic methods do not, reliably, alter patient outcomes
- Currently, relatively short courses of antimicrobial treatment are recommended, occasionally with combinations of antimicrobials