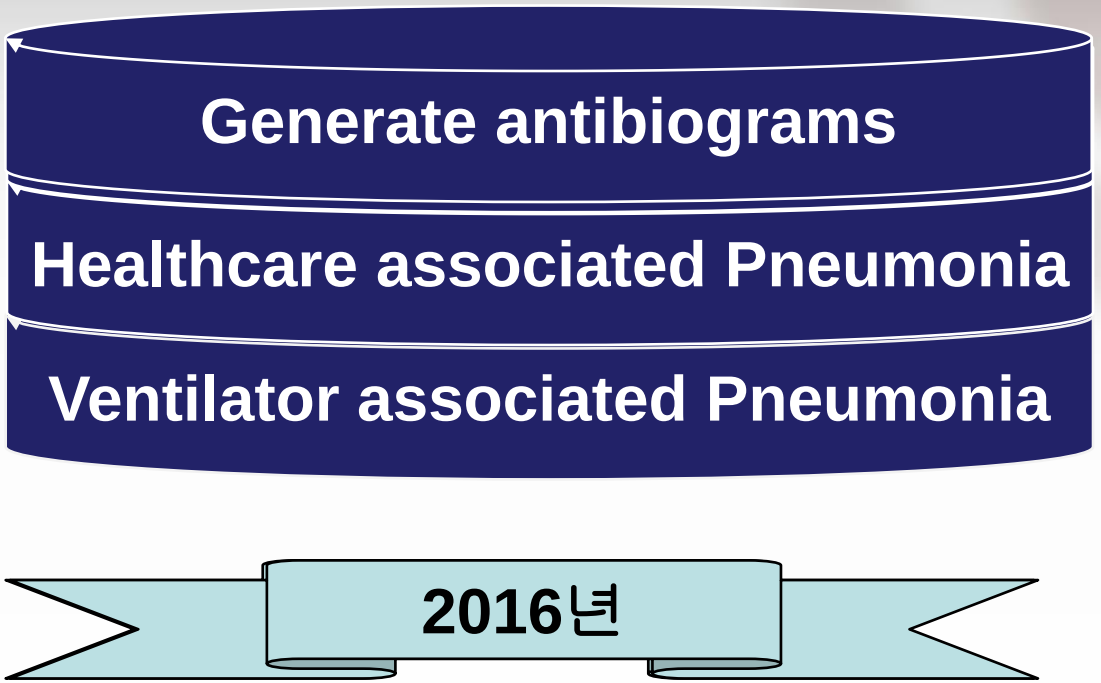
Hospital acquired Pneumonia/ Ventilator associated Pneumonia

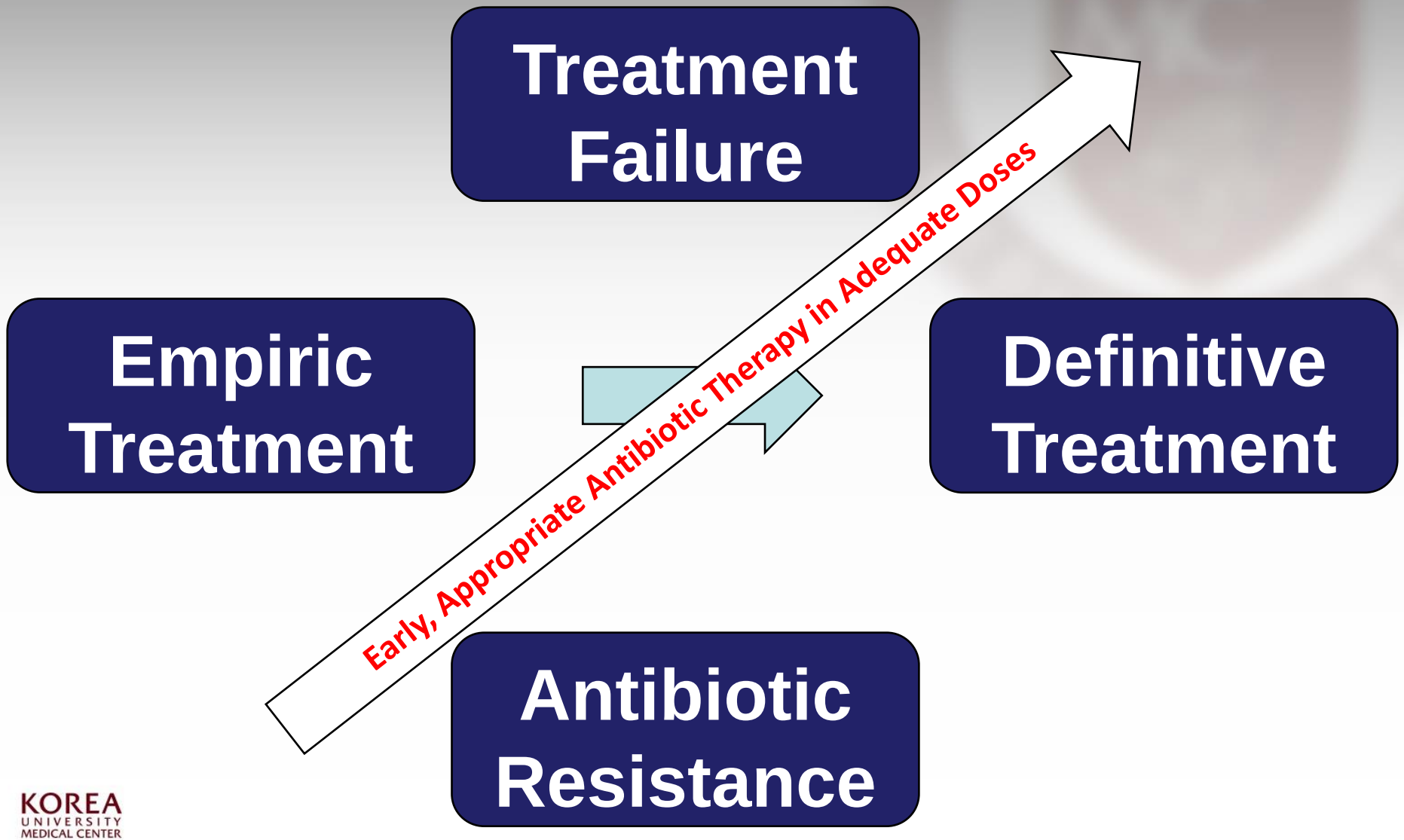
- 균 동정을 위한 기관지내시경의 역할 -

고려의대 이 영 석

Definition


Generate antibiograms
Healthcare associated Pneumonia
Ventilator associated Pneumonia
2016년

Treatments


Treatment Failure
Empiric Treatment
Definitive Treatment
Antibiotic Resistance
Early, Appropriate Antibiotic Therapy in Adequate Doses

Risk Factors for MDR Pathogens

Risk factors for MDR VAP
Prior intravenous antibiotic use within 90 days
Septic shock at time of VAP
ARDS preceding VAP
Five or more days of hospitalization prior to the occurrence of VAP
Acute renal replacement therapy prior to VAP onset
Risk factors for MDR HAP
Prior intravenous antibiotic use within 90 days
Risk factors for MRSA VAP/HAP
Prior intravenous antibiotic use within 90 days
Risk factors for MDR Pseudomonas VAP/HAP
Prior intravenous antibiotic use within 90 days

Empirical Treatments

Situation	Therapeutic class	Agent
Early VAP (< 5 days), without MDR bacteria risk factor*	Non-antipseudomonal β-lactam	Amoxicillin/clavulanic acid† OR Third generation cephalosporin
Late VAP (≥ 5 days), OR Risk factors for MDR bacteria	β-lactam active against *Pseudomonas aeruginosa* AND Non β-lactam antipseudomonal agent	Cefepime 2 g q 8 h OR Ceftazidime 2 g q 8 h OR Piperacillin–tazobactam 4 g q 6 h OR Meropenem 2 g q 8 h Amikacin 25 mg/kg/day OR Ciprofloxacin 1200 mg/day
Known MRSA colonization, or high (> 20%) MRSA prevalence in the unit	Agent active against MRSA	Vancomycin 30–45 mg/kg/day OR Linezolid 600 mg/12 h
Known colonization with carbapenem-resistant Enterobacteriaceae or Pseudomonas aeruginosa susceptible only to new beta-lactam agents	New β-lactam agent	Ceftolozane–tazobactam 3 g q 8 h‡ OR Ceftazidime–avibactam 2.5 g q 8 h‡ OR Meropenem–vaborbactam 4 g q 8 h‡ OR Imipenem–relebactam 1.5 g q 6 h‡

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Intensive Care Med 2020;46:888-906

De-escalation therapy

- To assess outcomes with de-escalation therapy
- Prospective observational study
- BAL vs. Tracheal aspirate
- De-escalation therapy (N=58)

  No de-escalation therapy (N=85)

Intensive Care Med 2007;33:1533-1540

De-escalation therapy

Primary end point	De-escalation therapy ($n = 58$)	No de-escalation therapy ($n = 85$)	p-value
Death from all causes at 15 days, n (%)	3/58 (5.1)	27/85 (31.7)	< 0.05
Quantitative tracheal aspirate	1/17 (5.8)	22/64 (34.3)	0.02
Bronchoalveolar lavage	2/41 (4.8)	5/21 (23.8)	0.02
Death from all causes at 28 days, n (%)	7/58 (12)	37/85 (43.5)	< 0.05
Quantitative tracheal aspirate	2/17 (11.6)	29/64 (45.3)	0.01
Bronchoalveolar lavage	5/41 (12.1)	8/21 (38)	0.01
Intensive care unit duration of stay, days (SD)	17.2 (1.2)	22.7 (6.3)	< 0.05
Quantitative tracheal aspirate	17.2 (1.6)	22.4 (6.4)	< 0.05
Bronchoalveolar lavage	17.2 (1.1)	23.2 (6)	< 0.05
Hospital duration of stay, days (SD)	23.7 (2.8)	29.8 (11.16)	< 0.05
Quantitative tracheal aspirate	23.1 (4.4)	29.9 (11.16)	< 0.05
Bronchoalveolar lavage	23.8 (2.4)	29.8 (11.4)	0.02

Intensive Care Med 2007;33:1533-1540

De-escalation therapy

Pathogens not associated with de-escalation therapy	Antibiotics not de-escalated Initial	Final	Patients in whom treatment was not de-escalated, *n*
Bronchoalveolar lavage			
P. aeruginosa	PT – Q	PT – Q	10
P. aeruginosa	M – Q	M – Q	11
Quantitative tracheal aspirate			
MRSA – *P. aeruginosa*	L – PT – A	L – PT – A	11
MRSA – MSSA – *P. aeruginosa*	L – M – A	L – M – A	3
Klebsiella – Morganella	M – A	M – A	5
P. aeruginosa – Streptococcus	L – M – Q	L – M – Q	5
Serratia – Proteus	M – Q	M – Q	4
MRSA – *P. aeruginosa – Serratia*	L – PT – A	L – PT – A	1
Haemophilus – E. coli	M – Q	M – Q	9
MRSA – *P. aeruginosa*	L – PT – A	L – PT – A	4
MRSA – *P. aeruginosa – Proteus*	L – M – A	L – M – A	1
MRSA – MSSA	PT – A	PT – A	1
MRSA	L	L	5
Klebsiella – Haemophilus	L	L	2
Klebsiella	M – Q	M – Q	5
Serratia	M – Q	M – Q	6
Enterococcus	L	L	2

MSSA, methicillin-sensitive *Staphyloccoccus aureus*; *MRSA*, methicillin-resistant *Staphylococcus aureus*; *L*, linezolide; *M*, meropenem; *A*, amikacin; *Q*, quinolone; *PT*, piperacillin/tazobactam; *CTZ*, ceftazidime

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Intensive Care Med 2007;33:1533-1540

Bronchoscopy

- Culture
- Sputum remove
- Endobronchial lesion evaluation
- Differential Diagnosis

Bronchoscopy

- The need for qualified personnel to perform these procedures
- Potential risks (hypoxemia, barotrauma, bleeding)
- Cost

Culture

Noninvasive Sampling with Semiquantitative Culture Results

VS.

Invasive Sampling with Quantitative Culture Results

RCT

51 patients with VAP in 1 ICUs in Spain

- Invasive (N=24) vs. Noninvasive (N=27)
- Mean age: 42 years, Male (79%)
- Moderate ARDS

Variables	Invasive	Noninvasive	P value
VAP related mortality	45%	43%	NS
Targeted therapy	42%	16%	<0.05
Ventilator day	23 days	20 days	NS
ICU stay	28 days	26 days	NS
VAP related mortality associated with isolation of Pseudomonas aeruginosa and Acinetobacter calcoaceticus			

Am J Respir Crit Care Med 1998;157:371-376

RCT

76 patients with VAP in 1 ICUs in Spain

- Noninvasive (N=39) vs. Invasive (N=37)

	Group 1 (Noninvasive Sampling)	Group 2 (Invasive Sampling)	p Value
Age, yr	65 ± 11	67 ± 13	0.65
Sex, M/F	29/10	24/13	0.37
Causes for ICU admission			
Medical ICU			
Respiratory	14	11	0.57
Cardiovascular	7	9	0.49
Neurologic	3	2	0.69
Surgical ICU			
Cardiovascular	8	7	0.86
Respiratory	5	4	0.79
Gastrointestinal	2	2	0.96
Trauma	0	2	0.23
McCabe's score			0.77
Nonfatal	5	3	
Ultimately fatal	22	23	
Rapidly fatal	12	11	
APACHE II on admission	19 ± 6	20 ± 6	0.89
Predicted mortality on admission, %	30 ± 24	27 ± 24	0.48
MOF score on admission	3.2 ± 1.8	3.5 ± 1.7	0.7
Length of mechanical ventilation on inclusion, d	6.2 ± 5	6.0 ± 4	0.42
$Pa_{O_2}/F_{I_{O_2}}$ on inclusion	203 ± 98	235 ± 117	0.19
Number of patients on antimicrobial treatment prior to VAP, n	33	26	0.13

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Am J Respir Crit Care Med 2000;162:119-125

RCT

76 patients with VAP in 1 ICUs in Spain

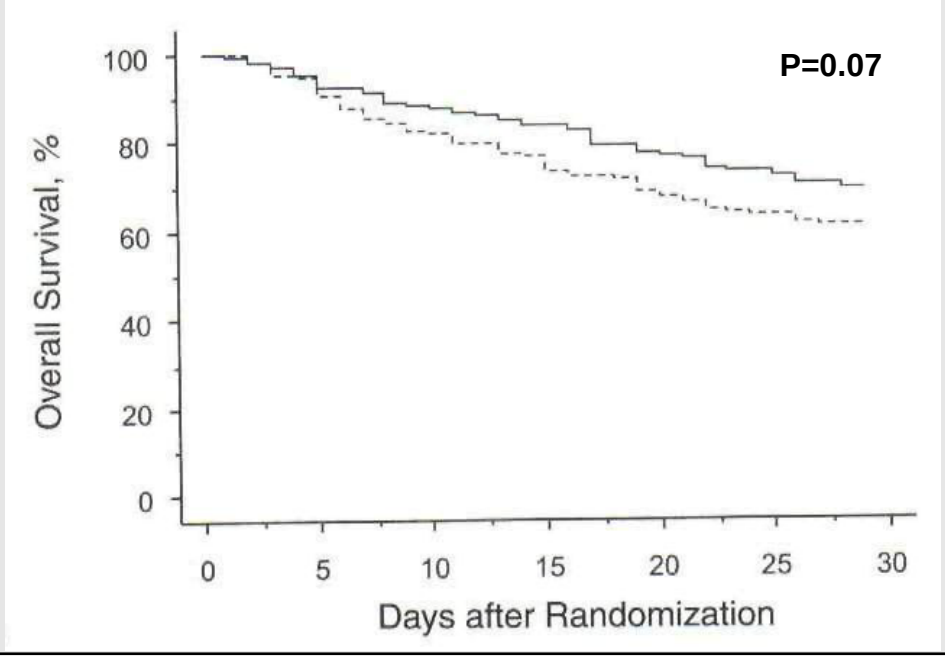
Variables	Noninvasive	Invasive	P value
30 days mortality	46%	38%	0.46
Adjusted mortality	16%	11%	0.53
Microbiological confirm	59%	62%	0.78
Targeted therapy	18%	27%	NS
Ventilator day	20 days	19 days	0.84
ICU day	21 days	21 days	0.9
Total exam cost	$ 29	$ 368	<0.001

Am J Respir Crit Care Med 2000;162:119-125

RCT

413 patients with VAP in 31 ICUs in France

- BAL (N=204) vs. Endotracheal aspirate (N=209)
- Mean age: 63 years, Male (70%)
- Mild to moderate ARDS



Ann Intern Med 2000;132:621-630

RCT

413 patients with VAP in 31 ICUs in France

End Point	Patients Who Received Invasive Management (n = 204)	Patients Who Received Clinical Management (n = 209)	Difference (95% CI)	P Value
Primary				
Mortality at 14 days, *n (%)*	33 (16.2)	54 (25.8)	−9.6 (−17.4 to −1.8)†	0.022
Multiple organ dysfunction‡§				
At 3 days				
SOFA score	6.1 ± 4.0	7.0 ± 4.3	−0.9 (−1.7 to −0.1)	0.033
ODIN score	1.7 ± 0.9	1.9 ± 1.1	−0.2 (−0.4 to −0.05)	0.014
At 7 days				
SOFA score	4.9 ± 4.0	5.8 ± 4.4	−0.9 (−1.8 to −0.03)	0.043
ODIN score	1.4 ± 1.0	1.6 ± 1.1	−0.2 (−0.4 to 0.02)	0.082
At 14 days				
SOFA score	3.9 ± 4.1	4.3 ± 4.3	−0.4 (−1.3 to 0.6)	>0.2
ODIN score	1.2 ± 1.2	1.2 ± 1.2	−0.03 (−0.3 to 0.2)	>0.2
Antibiotic-free days at 14 days, *d*‡	5.0 ± 5.1	2.2 ± 3.5	2.8 (1.9 to 3.6)	<0.001
Antibiotics per day at 14 days, *n*	1.2 ± 0.8	1.5 ± 0.7	−0.3 (−0.5 to −0.2)	<0.001
Antibiotic-treatment days at 14 days, *d*	8.7 ± 5.4	10.9 ± 4.5	−2.2 (−3.2 to −1.2)	<0.001
Secondary				
Mortality at 28 days, *n (%)*	63 (30.9)	81 (38.8)	−7.9 (−17.0 to 1.2)	0.099
Multiple organ dysfunction at 28 days‡§				
SOFA score	3.1 ± 3.4	3.1 ± 3.8	−0.02 (−1.2 to 1.1)	>0.2
ODIN score	1.0 ± 1.0	1.0 ± 1.0	−0.06 (−0.4 to 0.3)	>0.2
Antibiotic-free days at 28 days, *d*‡	11.5 ± 9.0	7.5 ± 7.6	−3.9 (−5.5 to −2.3)	<0.001
Antibiotics per day at 28 days, *n*	1.0 ± 1.8	1.3 ± 0.7	−0.3 (−0.45 to −0.16)	<0.001
Antibiotic-treatment days at 28 days, *d*	12.8 ± 8.5	14.9 ± 7.9	−2.1 (−3.7 to −0.5)	0.009
Duration of intensive care unit stay, *d*	19.3 ± 9.0	17.6 ± 9.4	1.5 (−0.3 to 3.2)	0.11
Duration of hospital stay, *d*	26.7 ± 23.9	25.1 ± 28.5	1.6 (−0.3 to 3.4)	>0.2
Mechanical ventilation–free days, *d*‡	7.8 ± 9.8	7.0 ± 9.4	0.8 (−1.0 to 2.9)	>0.2
Emergence of resistant bacteria, *n (%)*	125 (61.3)	125 (59.8)	1.5 (−7.9 to 10.9)	>0.2
Emergence of *Candida* species, *n (%)*	23 (11.3)	47 (22.5)	−11.2 (−18.3 to −4.1)	0.0025

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Ann Intern Med 2000;132:621-630

RCT

91 patients with VAP in 18 ICUs in Spain

- Quantitative (N=45) vs. Nonquantitative (N=43)

	Total Patients (n = 88)	Group A (n = 45)	Group B (n = 43)
Age (yrs)	52.9 ± 2.1	50.4 ± 3.0	55.6 ± 2.9
Male (%)	64 (72.7)	34 (75.5)	30 (69.7)
Female (%)	24 (27.3)	11 (24.5)	13 (30.3)
APACHE II on inclusion	15.4 ± 0.7	15.8 ± 0.9	15.0 ± 0.9
Predicted mortality at admission[a]	21.7 ± 2.1	23.4 ± 2.9	19.8 ± 3.1
Observed mortality rate	21.5 ± 2.0	22.2 ± 2.7	20.9 ± 2.8
Pao_2/FIO_2	181.5 ± 7.5	171.8 ± 8.6	191.7 ± 12.2
Temperature	38.6 ± 0.1	38.8 ± 0.1	38.5 ± 0.1
Leukocytes	15,137 ± 668	15,460 ± 955	14,798 ± 942
Unilateral radiographic infiltrate (%)	36 (40.9)	16 (35.5)	20 (46.5)
Bilateral radiographic infiltrate (%)	52 (59.1)	29 (64.5)	23 (53.5)
Days of MV before inclusion	7.6 ± 0.7	7.8 ± 1.1	7.3 ± 0.9
Previous antibiotic treatment (%)	35 (39.7)	16 (35.5)	19 (44.1)
Early-onset pneumonia (%)	32 (36.3)	16 (35.5)	16 (37.2)
Late-onset pneumonia (%)	56 (63.7)	29 (64.5)	27 (62.8)
Medical admissions (%)	42 (47.7)	20 (44.4)	22 (51.1)
Trauma admissions (%)	33 (37.5)	18 (40)	15 (34.8)
Surgical admissions (%)	13 (14.7)	6 (13.3)	7 (16.2)

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Crit Care Med 2000;28:2737-2741

RCT

91 patients with VAP in 18 ICUs in Spain

Variables	Quantitative	Nonquantitative	P value
Overall mortality	22.2%	20.9%	NS
15-day mortality	15.6%	11.6%	NS
Targeted therapy	33.3%	11.6%	<0.05
Ventilator day	19 days	19 days	NS
ICU day	24 days	22 days	NS

Crit Care Med 2000;28:2737-2741

The role of BAL

The analysis of 37 patients based on BAL and Open biopsy

- The diagnosed of pneumonia (N=20)

Variables	Sensitivity	Specificity	PPV	NPV
Gram stain	85%	94.1%	94.4%	84.2%
Total cellularity	90%	94.1%	94.7%	88.8%
Neutrophils	95%	94.1%	95%	94.1%
Quantitative culture	90%	94.1%	94.7%	88.8%

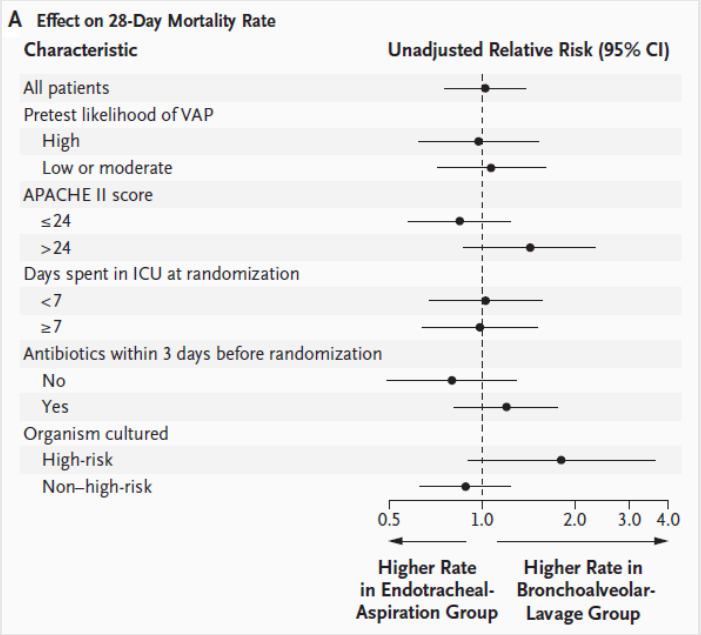
Gram stain (+), Total cellularity (400,000 cell/ml), Neutrophil (50%), Quantitative culture (+)

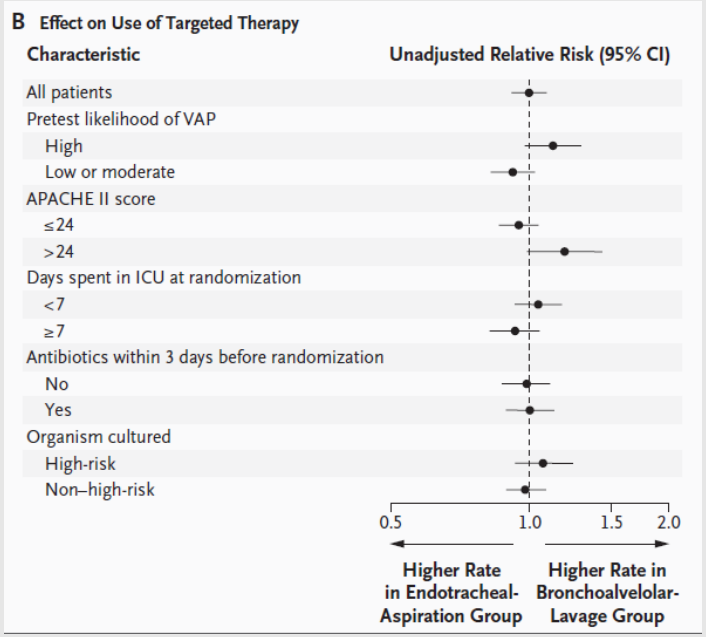
Braz J Med Biol Res 2001;34:993-1001

RCT

740 patients with VAP in 28 ICUs in Canada and US

- BAL (N=365) vs. Endotracheal aspirate (N=374)
- Mean age: 59 years, Male (70%)
- Mild to moderate ARDS





N Eng J Med 2006;355:2619-30

RCT

740 patients with VAP in 28 ICUs in Canada and US

Variables	BAL	ETA	P value
28-day mortality	18.9%	18.4%	0.94
Targeted therapy	74.2%	74.6%	0.90
Alive without antibiotics	10.4 days	10.6 days	0.86
Maximum ODS	8.3	8.6	0.26
ICU stay	12.3 days	12.2 days	0.22
Hospital stay	40.2 days	47.0 days	0.13

BAL, bronchoalveolar lavage; ETA, endotracheal aspirate; ODS, organ dysfunction score; ICU, intensive care unit

N Eng J Med 2006;355:2619-30

Cochrane Review

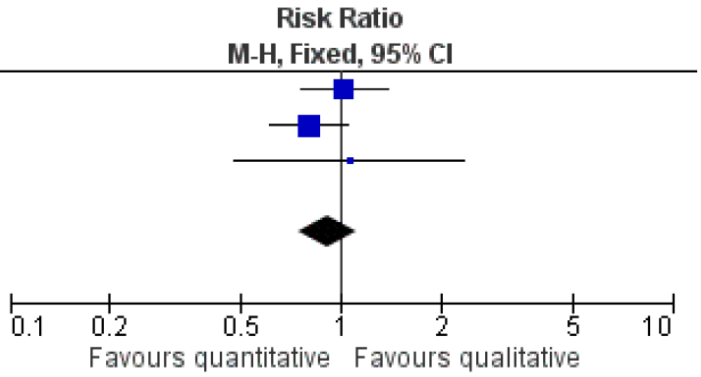
Quantitative versus qualitative cultures in patients with VAP

1.1 Mortality.

Study or Subgroup	Quantitative culture Events	Total	Qualitative culture Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
CCCTG 2006	69	365	69	374	43.3%	1.02 [0.76, 1.38]
Fagon 2000	63	204	81	209	50.8%	0.80 [0.61, 1.04]
Solé Violán 2000	10	45	9	43	5.8%	1.06 [0.48, 2.36]
Total (95% CI)		**614**		**626**	**100.0%**	**0.91 [0.75, 1.11]**
Total events	142		159			

Heterogeneity: Chi² = 1.70, df = 2 (P = 0.43); I² = 0%

Test for overall effect: Z = 0.94 (P = 0.35)



Cochrane Database Syst Rev 2014;10:CD006482

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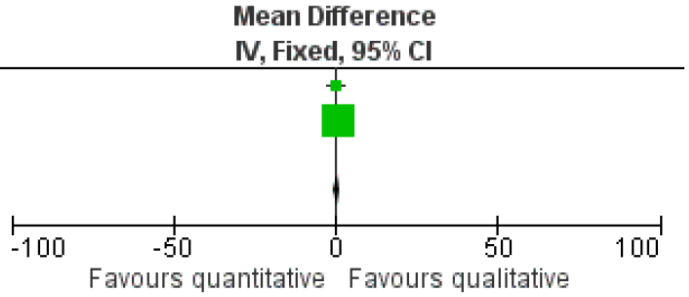
Cochrane Review

Quantitative versus qualitative cultures in patients with VAP

1.3 Duration on mechanical ventilation (days).

Study or Subgroup	Quantitative culture Mean	SD	Total	Qualitative culture Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
CCCTG 2006	8.9	16.16	365	8.8	18.34	374	19.2%	0.10 [-2.39, 2.59]
Solé Violán 2000	19.9	2.8	45	19.2	3	43	80.8%	0.70 [-0.51, 1.91]
Total (95% CI)			**410**			**417**	**100.0%**	**0.58 [-0.51, 1.68]**

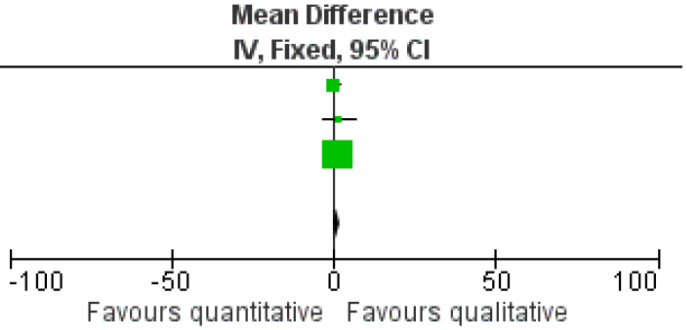
Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.05 (P = 0.29)



1.4 ICU stay (days).

Study or Subgroup	Quantitative culture Mean	SD	Total	Qualitative culture Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
CCCTG 2006	12.3	14.1	365	12.2	16.3	374	24.6%	0.10 [-2.10, 2.30]
Fagon 2000	26.7	23.9	204	25.1	28.5	209	4.6%	1.60 [-3.47, 6.67]
Solé Violán 2000	23.6	3.1	45	22.4	3.1	43	70.7%	1.20 [-0.10, 2.50]
Total (95% CI)			**614**			**626**	**100.0%**	**0.95 [-0.14, 2.04]**

Heterogeneity: Chi² = 0.78, df = 2 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.70 (P = 0.09)



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Cochrane Database Syst Rev 2014;10:CD006482

Antibiotic discontinuation

- **Antibiotic discontinuation**
  - **Negative quantitative bronchoscopy**
  - **Symptom resolution**
- **Retrospective, observational cohort study**
- **Early discontinuation (N=40)**

  Late discontinuation (N=49)

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Crit Care Med 2013;41:1656-1663

Antibiotic discontinuation

Variables	Early	Late	P
Hospital mortality	10 (25)	15 (30.6)	0.642
Abnormal temperature	15 (48.4)	21 (61.8)	0.324
Abnormal WBC persisted	20 (69)	23 (65.7)	1.00
Abnormal P/F ration persisted	21 (75)	27 (77.1)	1.00
Sputum purulence persisted	24 (66.7)	34 (80.9)	0.196
Superinfection			
Bacteremia	1 (2.5)	3 (7.1)	0.616
Respiratory infection	4 (10.0)	12 (28.6)	0.036
Bacteriuria	3 (7.5)	3 (7.1)	1.0
MDR superinfection	3 (7.5)	15 (35.7)	0.003

Crit Care Med 2013;41:1656-1663

Bacterial PCR with BAL

The Unyvero LRT BAL

Microorganisms	Resistance	Gene
Acinetobacter spp. *Chlamydia pneumoniae* *Citrobacter freundii* *Enterobacter cloacae complex* *Escherichia coli* *Haemophilus influenzae* *Klebsiella oxytoca* *Klebsiella pneumoniae* *Klebsiella variicola* *Legionella pneumophila* *Moraxella catarrhalis* *Morganella morganii* *Mycoplasma pneumoniae* *Pneumocystis jirovecii** *Proteus spp.* *Pseudomonas aeruginosa* *Serratia marcescens* *Staphylococcus aureus* *Stenotrophomonas maltophilia* *Streptococcus pneumoniae*	Carbapenem	*kpc* *ndm* *oxa*-23 *oxa*-24 *oxa*-48 *oxa*-58 *vim*
	3rd generation Cephalosporins	*ctx*-M
	Oxacillin/Cefoxitin	*mec*A
	Penicillin	*tem*

- Multicenter, randomized controlled trial
- Mutiflex bacterial PCR with BAL (N=100)

  Control group (N=108)

Lancet Respir Med 2022

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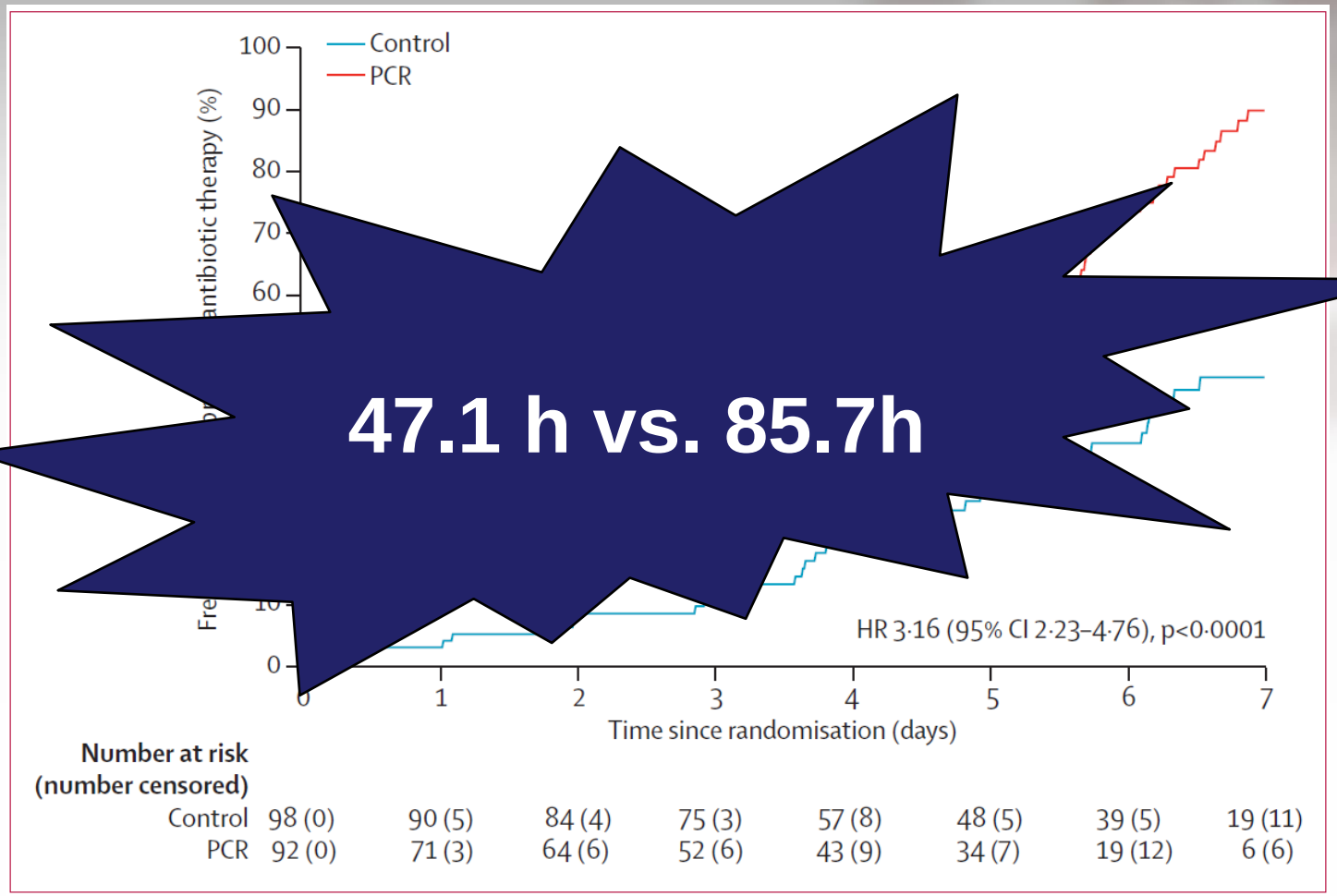
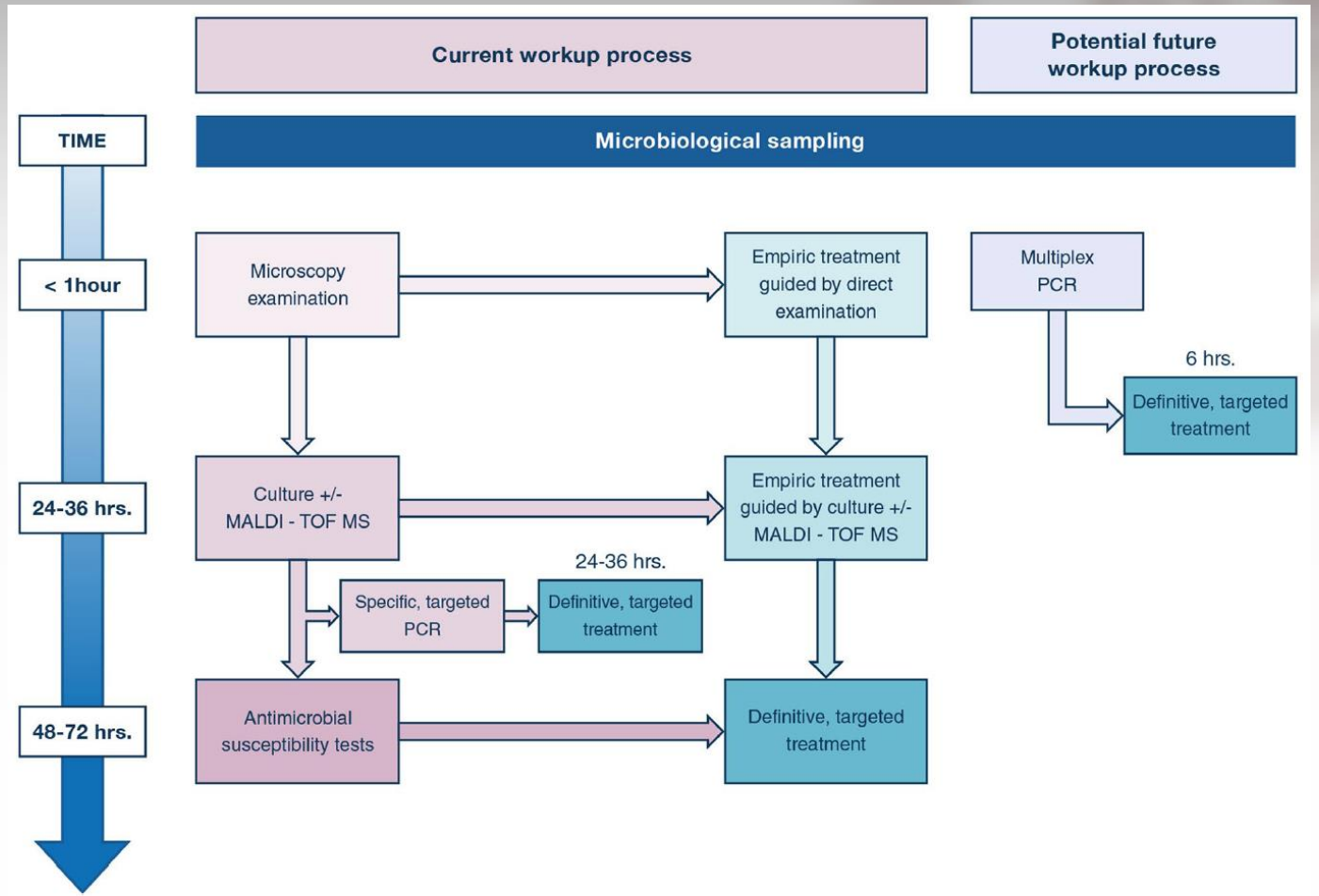
Bacterial PCR with BAL



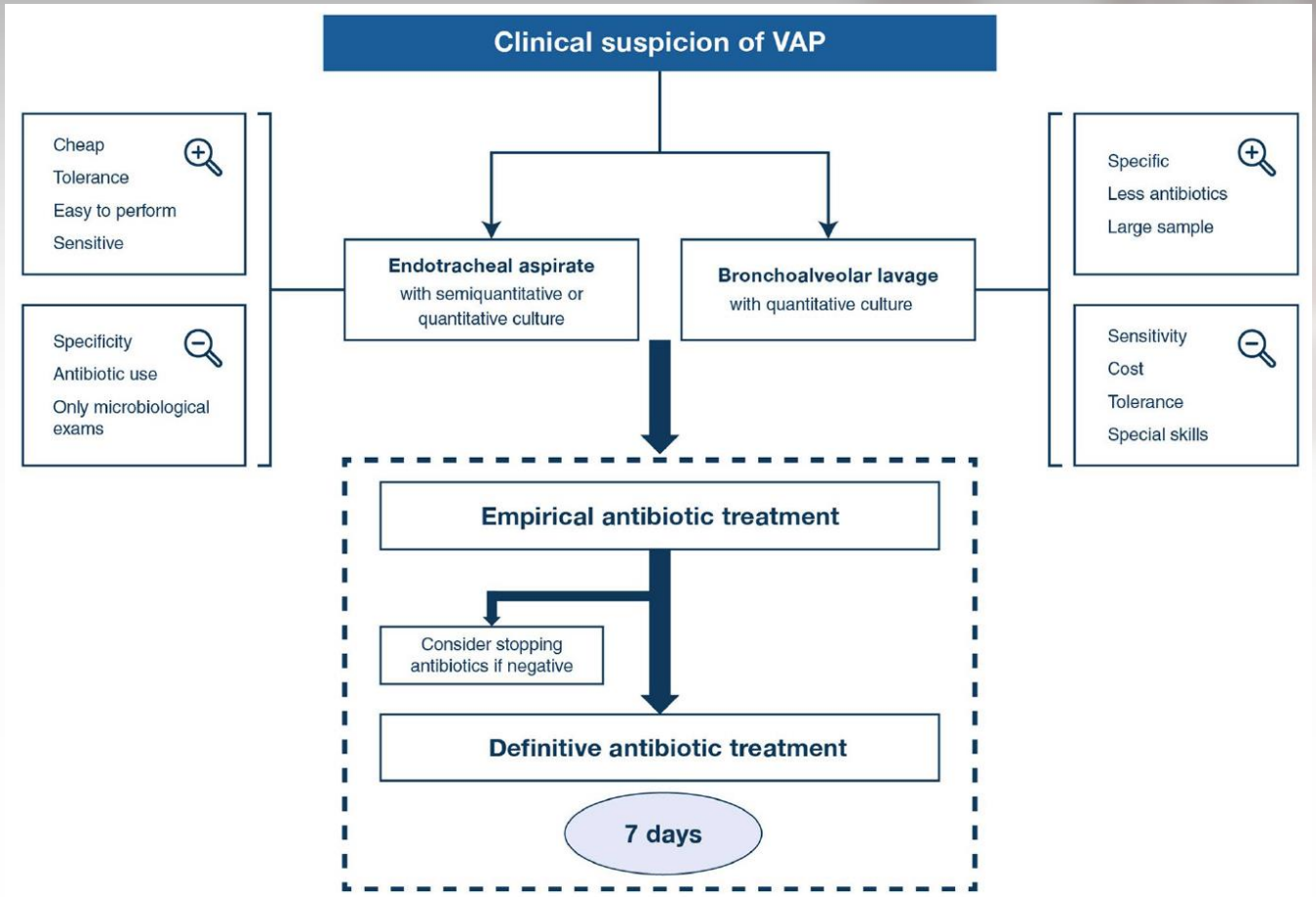
Lancet Respir Med 2022

Ventilator associated pneumonia



Intensive Care Med 2020;46:888-906

Ventilator associated pneumonia



Intensive Care Med 2020;46:888-906

Procalcitonin

- To assess the predictive capacity for the diagnosis of VAP of serum procalcitonin level
- Single center observation study
- Confirmed VAP (N=32)

  Refuted VAP (N=41)
- Day 1 procalcitonin level check

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Intensive Care Med 2008;34:1434-1440

Procalcitonin

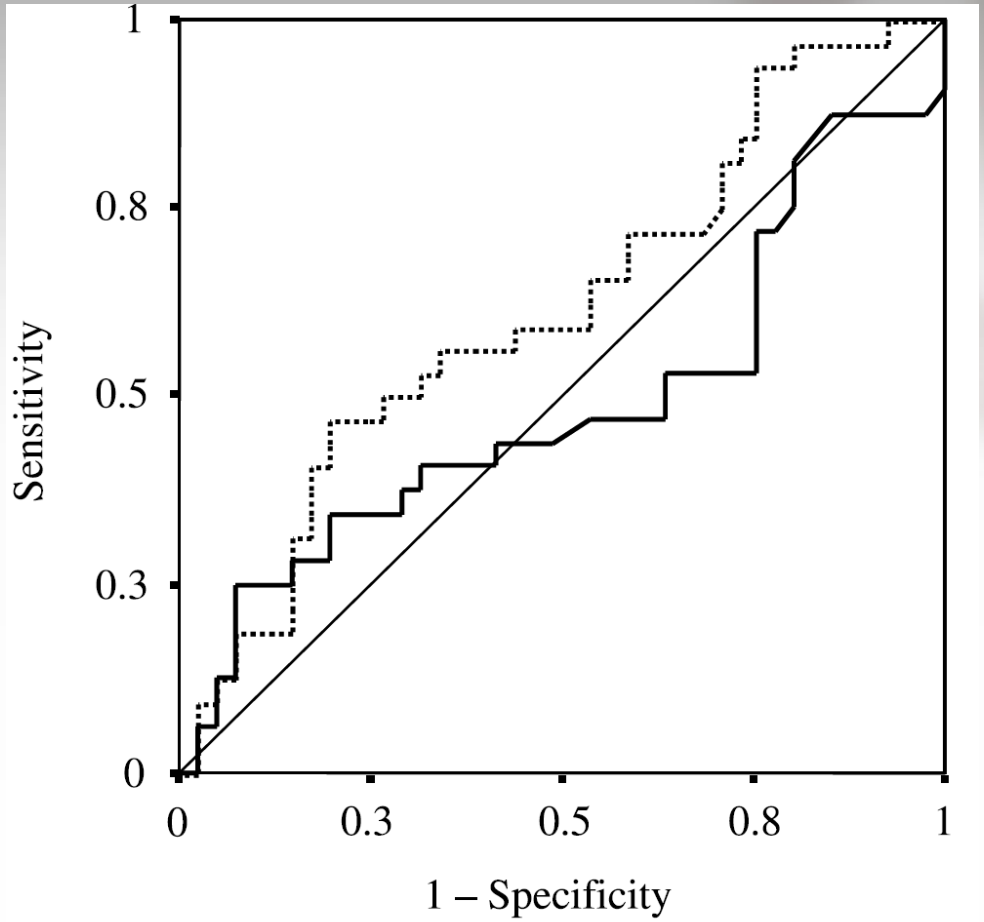

Fig. 1 ROC curves of day-1 PCT (*bold line*) and PCT increase (*dotted line*), with respective areas under the curves of 0.51 (95% CI 0.39–0.63) and 0.62 (95% CI 0.50–0.73)

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Intensive Care Med 2008;34:1434-1440

CRP, Procalcitonin

- To assess the value of biomarker kinetics in VAP prediction
- Prospective, multicenter, observational study
- 211 patients receiving mechanical ventilation
- From Day 1 to Day 6 Biomarker check

Ann Intensive Care 2016;6:32

CRP, Procalcitonin

	OR	95 % CI	*p*	aOR	95 % CI	*p*
Slope						
CRP (mg/dL)	1.641	1.229–2.192	<0.001	1.624	1.206–2.189	0.001
CRP ratio	1.516	1.021–2.250	0.039	1.480	1.060–2.067	0.021
PCT (μg/L)	0.803	0.544–1.183	0.267	0.844	0.559–1.274	0.419
Temperature (°C)	0.288	0.033–2.540	0.262	0.270	0.028–2.590	0.256
Highest						
CRP (mg/dL)	1.044	1.000–1.090	0.052	1.037	0.992–1.085	0.11
CRP ratio	1.201	1.065–1.355	0.003	1.202	1.061–1.363	0.004
PCT (μg/L)	1.032	0.987–1.079	0.168	1.020	0.974–1.068	0.392
Temperature (°C)	2.043	1.170–3.536	0.012	2.053	1.126–3.744	0.019
Δ^{max}						
CRP (mg/dL)	1.151	1.057–1.252	0.001	1.139	1.039–1.248	0.006
CRP ratio	1.213	1.030–1.428	0.021	1.186	1.018–1.381	0.029
PCT (μg/L)	1.036	0.984–1.089	0.178	1.023	0.971–1.078	0.399
Temperature (°C)	1.020	0.665–1.565	0.928	0.933	0.583–1.494	0.772

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