Ventilator associated pneumonia

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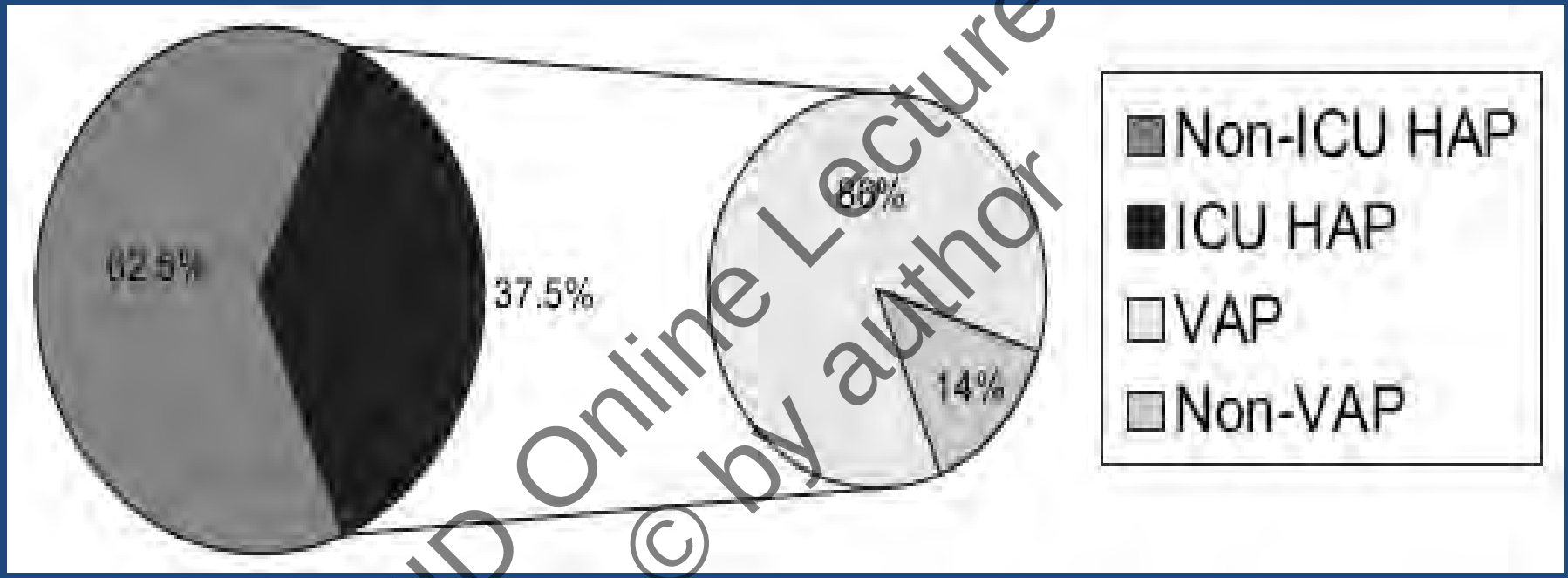
Breakdown of hospital-acquired pneumonia/intensive care unit (HAP/ICU) and HAP/ventilator-associated pneumonia (VAP).



Richards MJ et al.Crit Care Med 1999
Kampf G et al. J Clin Epidemiol 1998
Lizioli A et al. J Hosp Infect 2003
Taylor GD et al. Chest 1995

- Pneumonia in ICU patients is mostly due to the aspiration of microorganisms from the nasal, oro-pharyngeal, or gastric flora.
- These events can occur either before ICU admission, mostly when patients have abnormal upper airway functions due to coma, trauma, or surgery, or after intubation and ICU admission.
- Therefore, the term ventilator-associated pneumonia (VAP) is not appropriate and should be abandoned.
- The terms intubation-associated pneumonia for early onset and tube-associated pneumonia for late onset VAP would be more precise

Comparison of Diagnostic Criteria Frequently Used for the Diagnosis of Ventilator-Associated Pneumonia (VAP) and Tracheobronchitis (VAT)

Criterium type	VAP	VAT
Clinical signs and symptoms	At least one of temperature (>38°C), leukocyte count >12,000 leukocytes/mm^3, or leukopenia (leukocyte count <4000 leukocytes/mm^3) plus new onset of purulent endotracheal secretions or change in character of sputum or increases in respiratory secretions, suctioning requirements, new rales, bronchial breath sounds, or worsening oxygen requirements (increasing FiO_2 or PaO_2:FiO_2)	At least one of temperature (>38°C), leukocyte count >12,000 leukocytes/mm^3, or leukopenia (leukocyte count <4000 leukocytes/mm^3) plus new onset of purulent endotracheal secretions or change in character of sputum or increases in respiratory secretions, or suctioning requirements
Radiologic criteria: chest radiograph or CT	New or progressive and persistent infiltrate on chest radiograph or consolidation or cavitation	Transient infiltrate, no new infiltrate, or nondiagnostic chest radiograph or CT (eg, atelectasis, ARDS, or CHF)
Microbiologic criteria	ETA Gram stain with PMNL with or without bacteria (note morphology and color), semiquantitative ETA (moderate-to-heavy growth) or quantitative ETA $\geq 1 \times 10^6$ cfu/mL; bronchoscopic or nonbronchoscopic samples; cytospin: PMNL with or without bacteria, BAL $\geq 1 \times 10^4$ cfu/mL or PSB $\geq 1 \times 10^3$ cfu/mL	ETA Gram stain with PMNL with or without bacteria (note morphology and color), semiquantitative ETA (moderate-to-heavy growth) or quantitative ETA $\geq 1 \times 10^6$ cfu/mL; bronchoscopic or nonbronchoscopic samples (usually not done or $<1 \times 10^4$ cfu/mL criteria for VAP

Data are from [5]. ARDS, adult respiratory distress syndrome; BAL, bronchoalveolar lavage; CHF, congestive heart failure; ETA, endotracheal aspirate; FiO2, inspired oxygen concentraton; PaO2, arterial oxygen concentration; PMNL, polymorphonuclear leukocytes; PSB, protected specimen brush.

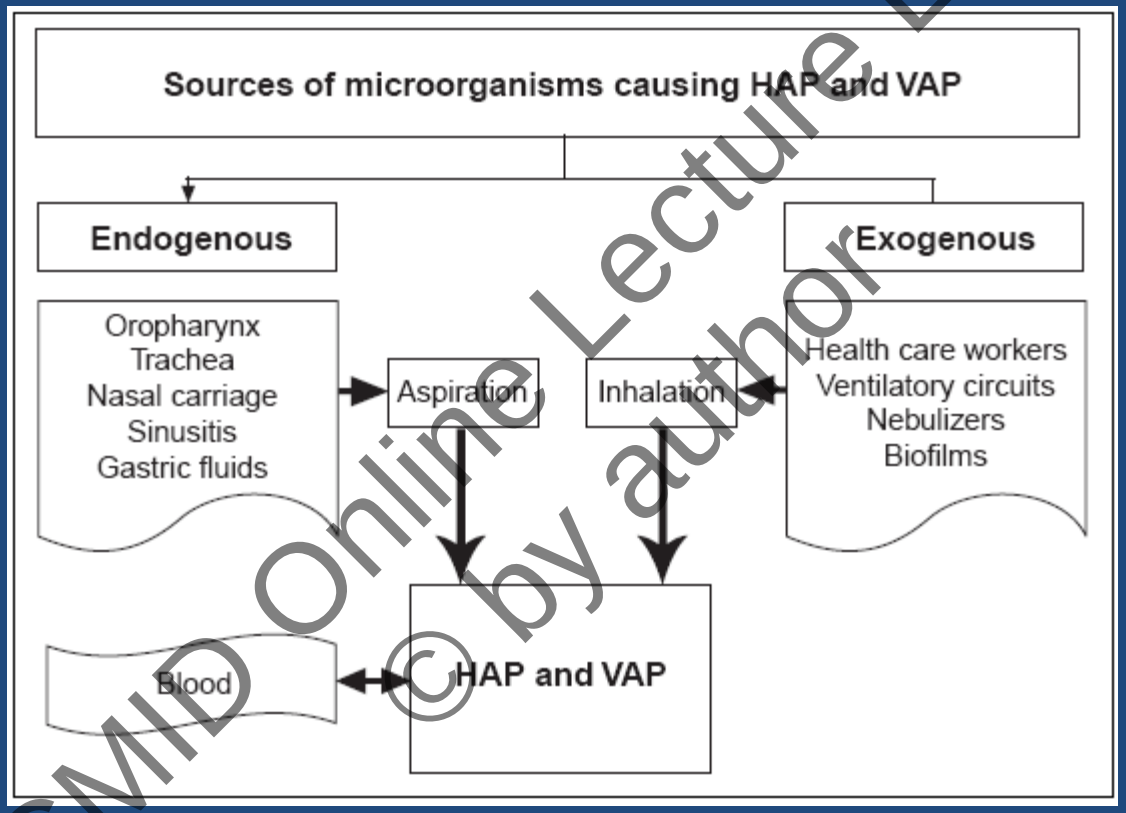
Craven DE et al. Chest **2009**

Ventilator-Associated Tracheobronchitis and Pneumonia

- **LRTIs in intubated patients include VAT and VAP. These infections are increasingly caused by MDR bacteria, which colonize the patient's oropharynx and enter the lower respiratory tract around the endotracheal tube cuff or through the lumen.**
- **Progression of colonization to VAT and, in some patients, to VAP is related to the quantity, types, and virulence of invading bacteria versus containment by host defenses.**
- **Diagnostic criteria for VAT and VAP overlap in terms of clinical signs and symptoms, and they share similar microbiologic criteria when endotracheal sputum aspirate samples are used.**
- **In addition, the diagnosis of VAP requires a new and persistent infiltrate , which may be difficult to assess in critically ill patients, and a significant bacterial culture of a endtotracheal aspirate or bronchoalveolar lavage specimen.**
- **An alternative model focused on VAT, using serial surveillance of endotracheal aspirate specimens to identify multidrug-resistant pathogens and their antibiotic susceptibilities, would allow earlier, targeted antibiotic treatment that could improve outcomes in patients, prevent VAP, and provide an attractive model for clinical research trials**

Craven DE et al. Chest **2009**

Endogenous and exogenous sources of microorganisms causing hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP)



Craven D et al. Semin Respir Infect 1990
Young PJ et al. Anaesthesia 1999

VAP. EPIDEMIOLOGY

1. The incidence of HAP and VAP together is between five and 10 cases per 1000 hospital admissions, depending on the case definition used and the study population.
2. Together, HAP and VAP are the second most common cause of hospital-acquired infection and are associated with a higher mortality than any other nosocomial infection.
3. Patients with late-onset HAP or VAP have a similar rate of mortality to those with early-onset disease.
4. Approximately 30% of HAP occurs in the ICU setting where the majority of cases (greater tham 85%) occur in patients on mechanical ventilation.

Pathogens causing HAP and VAP

HAP	Group 1	No risk factors for resistance† AND mild to moderate presentation‡	Core pathogens*
	Group 2	Risk factors for resistance† AND mild to moderate presentation‡	Core pathogens* plus MRSA and *Pseudomonas aeruginosa*
	Group 3	Severe presentation§ ± risk factors for resistance†	Core pathogens* plus MRSA, *P aeruginosa* and *Legionella* species
VAP	Group 4	No risk factors for resistance† AND mild to moderate presentation‡	Core pathogens*
	Group 5	Risk factors for resistance† AND/OR severe presentation§	Core pathogens* plus MRSA, *P aeruginosa*, *Legionella* species, *Acinetobacter* species and *Stenotrophomonas maltophilia*

* Core pathogens include Strep pneumoniae, Streptococcus sp, H influenzae, Enterobacter sp, E coli, Klebsiella sp,species, Proteus sp, Serratia marcescens and MSSA.
† Risk factors for resistance include antimicrobial therapy in the past 90 days and late-onset during hospitalization (>5 days)
‡ Mild to moderate presentation: no hypotension, intubation, sepsis syndrome, rapid progression of infiltrates or end-organ dysfunction
Severe presentation: hypotension, intubation, sepsis syndrome, rapid progression of infiltrates or end-organ dysfunction.

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Microbiological causes of hospital-acquired pneumonia and ventilator-associated pneumonia

Gram-negative bacilli	35–80
Escherichia coli	
Klebsiella species	
Enterobacter species	
Proteus species	
Serratia marcescens	
Pseudomonas aeruginosa	
Acinetobacter species	
Stenotrophomonas maltophilia	
Gram-positive cocci	9–46
Streptococcus pneumoniae	
Streptococcus species	
Staphylococcus aureus (MSSA and MRSA)	
Polymicrobial	9–80
Anaerobes	0–54
Blood culture positive	0–40
No growth	2–54

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Pneumonia - US Prevalence Study

Bacterial Pathogens*	CAP (n = 2,221)	HCAP (n = 988)	HAP (n = 835)	VAP (n = 499)
Gram-positive pathogens, %				
S aureus				
S aureus (all)	25.5†	46.7	47.1	42.5
MSSA (all)	17.2†	21.1	26.2†	28.5†
MSSA only	12.0	14.3	19.3†	19.0‡
MRSA (all)	8.9†	26.5	22.9	14.6†
MRSA only	6.2†	18.3	16.8	11.8†
All MRSA as percentage of all *S aureus*	34.8†	56.8	48.6‡	34.4†
Streptococcus nongroup	13.4†	7.8	13.9†	7.0
S pneumoniae	16.6†	5.5	3.1‡	5.8
Other Gram positive	7.1	7.7	8.1	8.6
Gram-negative pathogens, %				
Pseudomonas sp	17.1†	25.3	18.4†	21.2
Haemophilus sp	16.6†	5.8	5.6	12.2†
Klebsiella sp	9.5	7.6	7.1	8.4
Escherichia sp	4.8	5.2	4.7	6.4
Enterobacter sp	2.9	3.5	4.3	5.6
Acinetobacter sp	1.6‡	2.6	2.0	3.0
Other Gram negative	4.1†	9.5	3.7†	6.2‡

Kollef M. Chest 2005; 128: 3854-62

EARLY VS. LATE VAP

- it is unknown what is the best cut off to separate early from late onset pneumonia, since we do no know how long it takes to develop pneumonia after aspiration of micro-organisms.
- The cut off of 4 days has been used by several authors; others have used 7 days.
- it is essential to rely on hospital admission (and not intubation) as day one. Otherwise, when intubation occurs after hospital admission, nosocomial colonization of the upper airways may have already occured and consequently pneumonia may be caused by pathogens typically associated with late onset pneumonia.
- Pneumonia happening later in the course of ICU stay is called ‘‘late onset pneumonia’’. Late onset pneumonia is probably more closely related to quality of care although it is difficult to prevent in the most severely compromised patients

Excess ICU mortality attributable to VAP: The role of early vs late onset

- *Design:* Prospective cohort study.
- *Setting:* 16-bed medical-surgical ICU at a university-affiliated hospital.
- *Patients and measurements:* Patients
- receiving mechanical ventilation for > 72 h.
- Patients definitively diagnosed with VAP (*n* = 40) were cases; patients free of any infection acquired during ICU stay (*n* = 61) were controls
- VAP-attributed mortality was the difference between observed mortality and predicted mortality (SAPS II) on admission

Vallés J et al, Intensive Care Med 2007; 33:1363–1368

Clinical characteristics of patients with early and late episodes of VAP

Characteristics	Early VAP ($n=11$)	Late VAP ($n=29$)	Significance (p)
Age (years)	54 ± 19	62 ± 20	n.s.
Female (%)	19	31	n.s.
SAPS II (points)	38 ± 12	38 ± 16	n.s.
SAPS II mortality risk (%)	26 ± 16	27 ± 25	n.s.
Diagnosis (%)			
Respiratory failure	9	34	n.s.
Neurological	36	21	n.s.
Trauma	27	17	n.s.
Cardiovascular	9	10	n.s.
Cardiac arrest	18	3	n.s.
Other	–	7	n.s.
Length of MV before VAP (days)	4 ± 3	13 ± 9	0.001

Independent variables selected by multivariate analysis as associated with ICU mortality, expressed as odds ratio (OR) with 95% CI

Variable	OR (95% CI)	Significance (p)
Early-onset VAP	1.38 (0.27–6.85)	0.69
Late-onset VAP	3.60 (1.23–10.46)	0.01
Appropriateness of antibiotic treatment	1.70 (0.61–4.75)	0.30
Hosmer-Lemeshow test ($p=0.72$)		

Vallés J et al, Intensive Care Med 2007; 33:1363–1368

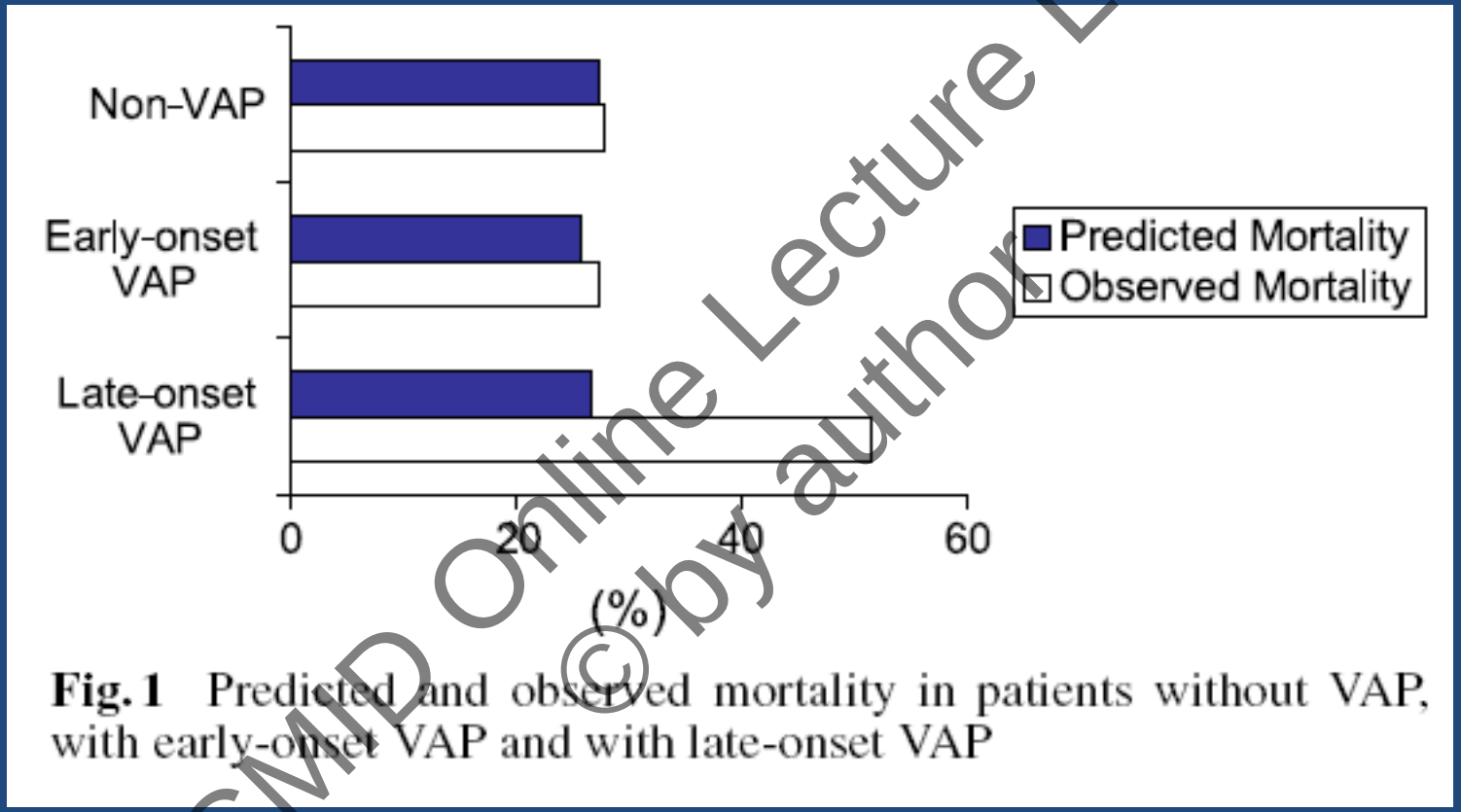

Fig. 1 Predicted and observed mortality in patients without VAP, with early-onset VAP and with late-onset VAP

Vallés J et al, Intensive Care Med 2007; 33:1363–1368

VAP. RISK FACTORS

1. Colonization of the oropharynx with pathogenic organisms is an important risk factor leading to subsequent HAP/VAP.
2. Host factors such as supine positioning, extensive burns,mechanical ventilation, cardiothoracic surgery, ARDS and head trauma are predisposing factors for VAP.
3. Nasogastric tubes and condensate in ventilator tubing are environmental factors that enhance the risk of developing VAP and should be avoided (A-2).
4. Acid-suppressing medications (eg, antacids and H2 blockers) that are employed to prevent stress ulcer bleeding in ventilated patients can increase the risk of developing VAP and careful consideration should be given to their use (A-1).

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Clinical pulmonary infection score (CPIS) chart

Diagnostic feature	CPIS points 0	1	2
Tracheal secretions	Rare	Abundant	Abundant and purulent
Chest x-ray infiltrate	None	Diffuse	Localized
Temperature (°C)	≥36.5 and ≤38.4	≥38.5 and ≤38.9	≥39 or ≤36
White blood cells ($\times 10^9$/L)	≥4.0 and ≤11.0	<4.0 or >11.0	<4.0 or >11.0 plus band forms ≥0.5
PaO_2/FiO_2 mmHg	>240 or ARDS		≤240 and no ARDS
Microbiology	Negative	Positive*	Positive plus positive Gram stain†

*Microbiology not relevant in the case of the modified clinical pulmonary infection score as described by Fartoukh et al);
†Determination is only 'positive' for the purpose of the modified clinical pulmonary infection score as described by Fartoukh et al (157). ARDS Acute respiratory distress syndrome; FiO2 Fraction of inspired oxygen; PaO2 Partial pressure of oxygen in arterial blood

Major points and recommendations for diagnosis

1. The clinical diagnosis for HAP and VAP is not sensitive or specific.
2. The CPIS score should be calculated to improve sensitivity and specificity for the diagnosis of HAP and VAP (B-2).
3. Invasive diagnostic testing has not been demonstrated to improve clinical outcomes and therefore is not recommended unless dealing with immunocompromised hosts (A-1).
4. It is recommended that for most patients a clinical approach supplemented by noninvasive quantitative cultures of respiratory tract samples is sufficient to guide appropriate antibiotic choices (C-3).
5. A low CPIS score may allow careful observation of the patient without antibiotics.
6. By the third day of calculating the CPIS, a score below a threshold of 6 may allow early discontinuation of antibiotics.

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Major points and recommendations for PK and PD issues in antimicrobial therapy of HAP and VAP

1. Institutions should develop their own guidelines for the management of HAP and VAP that incorporate local resistance patterns. These guidelines should provide recommendations for empirical therapy as well as for de-escalation and duration of therapy (B-1).
2. It is recommended that for patients treated initially with appropriate antibiotics, seven to eight days of therapy for VAP should be considered appropriate except in those patients infected with non-lactosefermenting bacteria (A-1).
3. Based on the available evidence, intravenous colistin at a dose of 2.5 mg/kg/day to 5 mg/kg/day divided in two to three doses is a reasonable option for the management of HAP and VAP caused by P aeruginosa or A baumannii where no alternative antibiotics are appropriate.
4. Additional research including randomized, controlled trials involving larger numbers of patients is needed to delineate the role of inhaled antibiotics in the management of HAP and VAP. In the interim, it is recommended that they may be used as adjunctive

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Diagnosis of VAP: a systematic review of the literature

- Clinical criteria, used in combination, is helpful in diagnosing VAP, however, the considerable interobserver variability.
- Bacteriologic data do not increase the accuracy of diagnosis as compared to clinical diagnosis. Quantitative cultures obtained by different methods, including BAL, pBAL, PSB or TBA seem to be rather equivalent in diagnosing VAP.
- The rapid availability of cytological data, including inflammatory cells and Gram stains, may be useful in initial therapeutic decisions in patients with suspected VAP.
- CRP, PCT, promising biomarkers in diagnosing VAP.

Rea-Neto A et al, Crit Care 2008; doi:10.1186/cc6877

Initial Antibiotic Therapy for VAP

- Early VAP

No risk factors for MDR bacteria. Cover for endogenous infection

(*H. influenzae, S.pneumoniae, S.aureus*)

Amox/Clav, Ceftriaxone, ertapenem

Risk factors for MDR bacteria. As per late VAP

- Late VAP

Broad-spectrum Coverage

  - *P. aeruginosa* and *A. baumannii*

    (carbapenem, Piper/Tazo, 3rd or 4th generation cephalosporin (cefepime, ceftazidime) with aminoglycosides (amikacin) or fluoroquinolone (ciprofloxacin)

  - MRSA

    Linezolid, vancomycin

Ventilated Patients: Special PK/PD Considerations

- Increased volume of distribution
- Renal dysfunction and dosage adjustments
- Penetration characteristics into pulmonary tissue
- Expected exposure (AUC) above the MIC
- Hypoalbuminemia
- Increased cardiac output if severe sepsis

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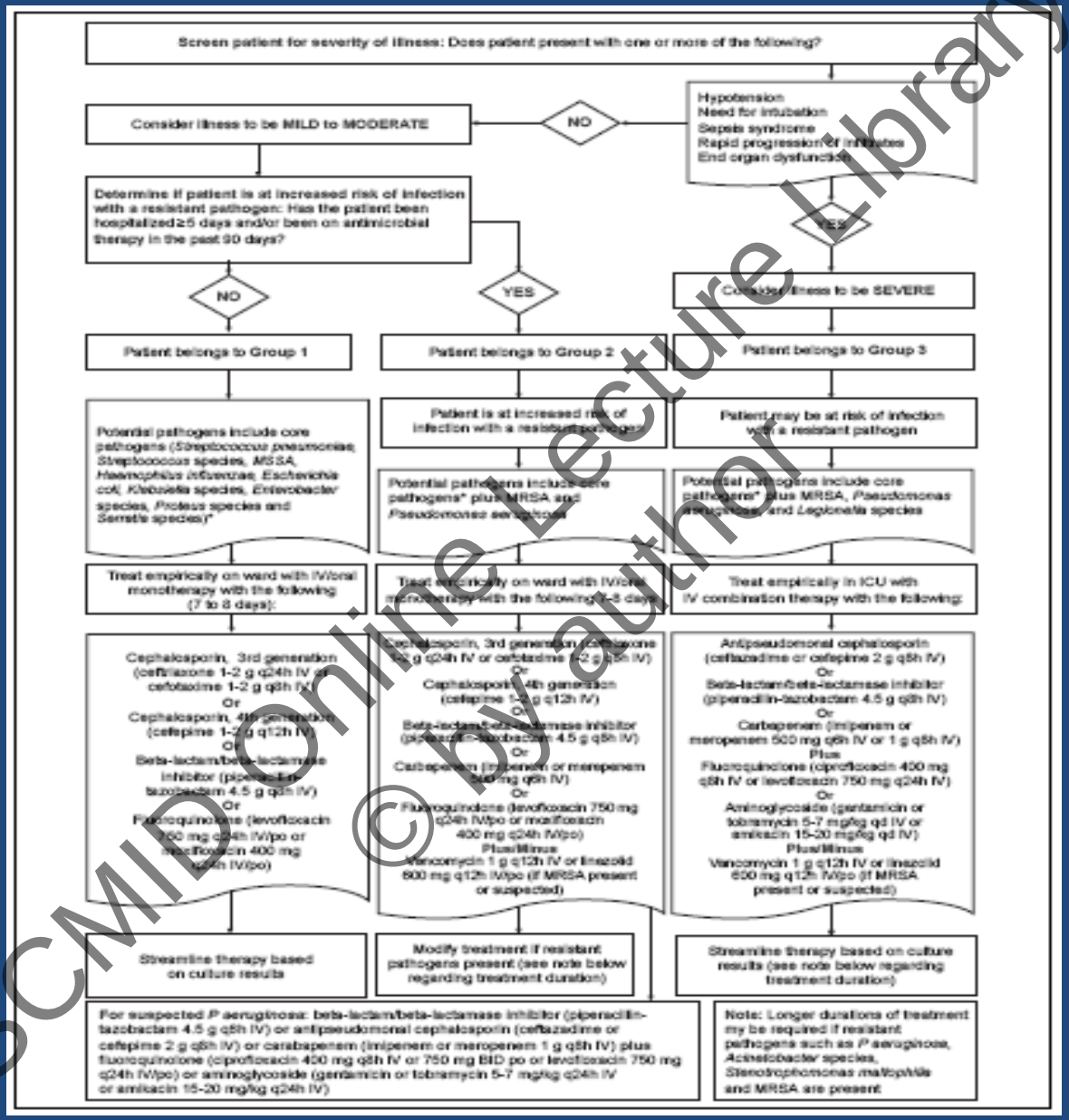
Cawley MJ. *Pharmacotherapy.* 2007;27:250-266.

De-escalation

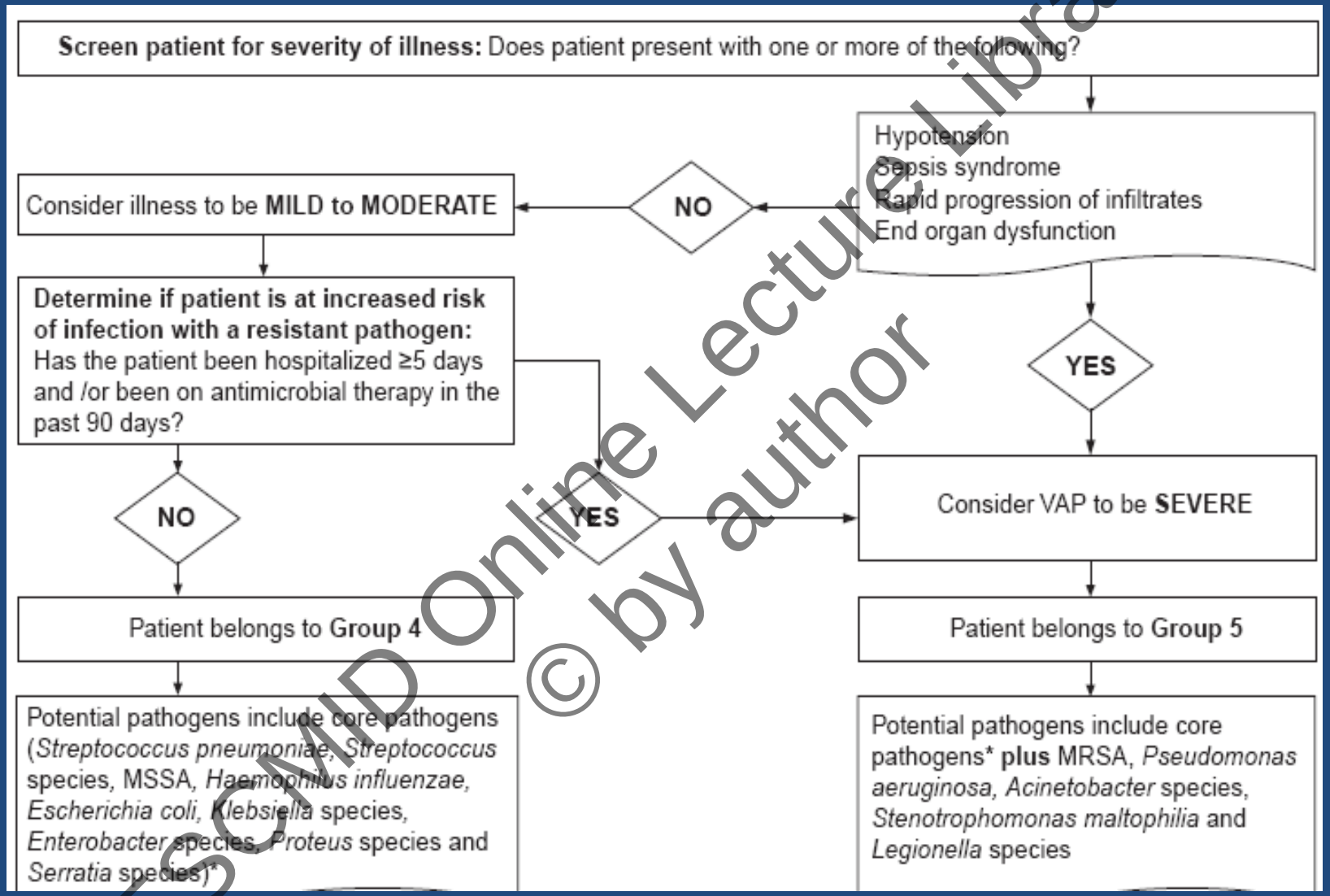
- WHY? Adequate initial therapy while minimizing the emergence of resistance
- WHEN? Based on
  - Clinical improvement
  - Microbiology findings
- HOW?
  - Diminishing antibiotic therapy
    - Spectrum
    - Number
    - Duration

Treatment algorithm for hospital-acquired pneumonia



BID Twice daily; ICU Intensive care unit; IV Intravenous; MRSA Methicillinresistant Staphylococcus aureus; MSSA Methicillin-susceptible S aureus; q Every; po By mouth

Treatment algorithm for ventilator associated pneumonia



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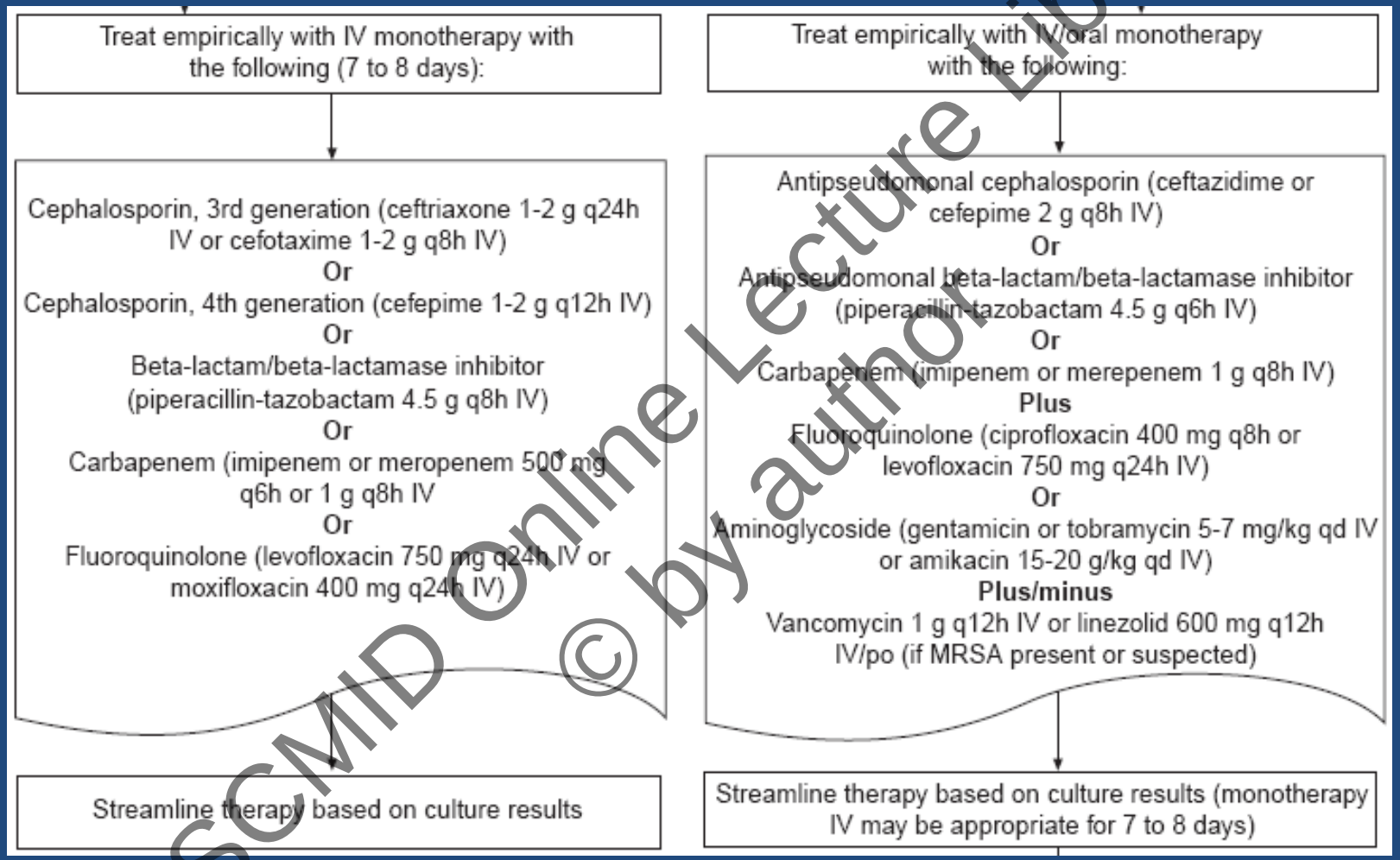
Treatment algorithm for ventilator associated pneumonia (cont)



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Major points and recommendations for prevention and risk reduction of HAP and VAP

1. To control the spread of AROs, an effective infection control program must be implemented in all institutions (A-1).
2. Oral intubation should be the preferred way for invasive mechanical ventilation (B-2).
3. Patients should be nursed in a semirecumbent position (30° to 45° angle) (A-2).
4. Kinetic beds may be useful in some carefully selected groups of patients.
5. Circuit changes should be performed not more than once a week, except if visibly soiled (A-1).
6. If not contraindicated, HME should be used and changed on a weekly basis (B-2).
7. The regular use of subglottic secretion drainage should be encouraged in intubated patients (A-2).
8. A closed suction catheter should be used for each new patient (B-2).
9. Routine prophylaxis of HAP with oral antibiotics (SDD), with or without systemic antibiotics, reduces the incidence of ICU-acquired VAP, has helped contain outbreaks of MDR bacteria, but is not recommended for routine use, especially in patients who may be colonized with MDR pathogens (B-3).
10. Modulation of oropharyngeal colonization by the use of oral chlorhexidine can prevent ICU-acquired HAP in selected patient populations (345).

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European Task Force (ETF), Centers for Disease Control and Prevention (CDC), Canadian Critical Care Society (CCCS) and American Thoracic Society and Infectious Diseases Society of America (ATS-IDSA) recommendations regarding nonpharmacological measures for VAP

	ETF	CDC	CCCS	ATS-IDSA
[Ref.]	[4]	[5]	[6]	[7]
Publication yr	2001	2004	2004	2005
Oral intubation better than nasal	Not controversial	IB	Recommended	II
Optimal pressure of endotracheal tube cuff	Not controversial	NR	NR	II
Subglottic secretion drainage	Still controversial	II	Considered	I
Early extubation	NR	IB	NR	II
Avoid re-intubation	Not controversial	II	NR	I
Noninvasive ventilation	Still controversial	II	NR	I
Tracheostomy: early better than late	NR	NR	Insufficient evidence	NR
Respiratory filters	NR	Unresolved	NR	NR
Routine change of ventilator circuits	NO: Not controversial	NO: IA in HME/II in HH	NO	NO
HME better than HH	Still controversial	Unresolved	Recommended	I: is the same
Tracheal suctioning system: closed better than open	Still controversial	Unresolved	NR	NR
Routine change of closed tracheal suctioning system	Still controversial	Unresolved	NO	NR
Sterilisation or disinfection of respiratory devices	NR	IB	NR	NR
Barrier measures	Not controversial	IA	NR	I
Kinetic or standard beds	NR	Unresolved	Considered	NR
Semirecumbent position (30–45°)	Not controversial	II	Recommended	I
Feeding: post-pyloric better than gastric	Still controversial	Unresolved	NR	NR

HME: heat and moisture exchanger; HH: heated humidifier; IB: the evidence comes from certain clinical or epidemiological studies; II: the evidence comes from welldesigned, controlled trials without randomisation; NR: the guideline did not review this issue; I: the evidence is from well-conducted, randomised controlled trials; NO: the recommendation is of no use; IA: the evidence comes from well-designed experimental, clinical or epidemiological studies.

Lorente L et al. Eur Respir J 2007

TABLE 2 European Task Force (ETF), Centers for Disease Control and Prevention (CDC), Canadian Critical Care Society (CCCS) and American Thoracic Society and Infectious Diseases Society of America (ATS-IDSA) recommendations regarding pharmacological measures for ventilator-associated pneumonia

	ETF	CDC	CCCS	ATS-IDSA
[Ref.]	[4]	[5]	[6]	[7]
Publication yr	2001	2004	2004	2005
Selective digestive decontamination	Not controversial in some patients	Unresolved	Insufficient evidence	I
Preventive intravenous antibiotics	Still controversial	Unresolved	Insufficient evidence	I at time of intubation
Chlorhexidine oral rinse	NR	II in cardiac surgery	NR	I in cardiac surgery
Sucralfate better than ranitidine	Still controversial	Unresolved	Insufficient evidence	I: is the same
Avoidance of deep sedation and paralytic agents	Not controversial	NR	NR	II

I: the evidence is from well-conducted, randomised controlled trials; NR: the guideline did not review this issue; II: the evidence is from well-designed, controlled trials without randomisation.

Lorente L et al. Eur Respir J 2007

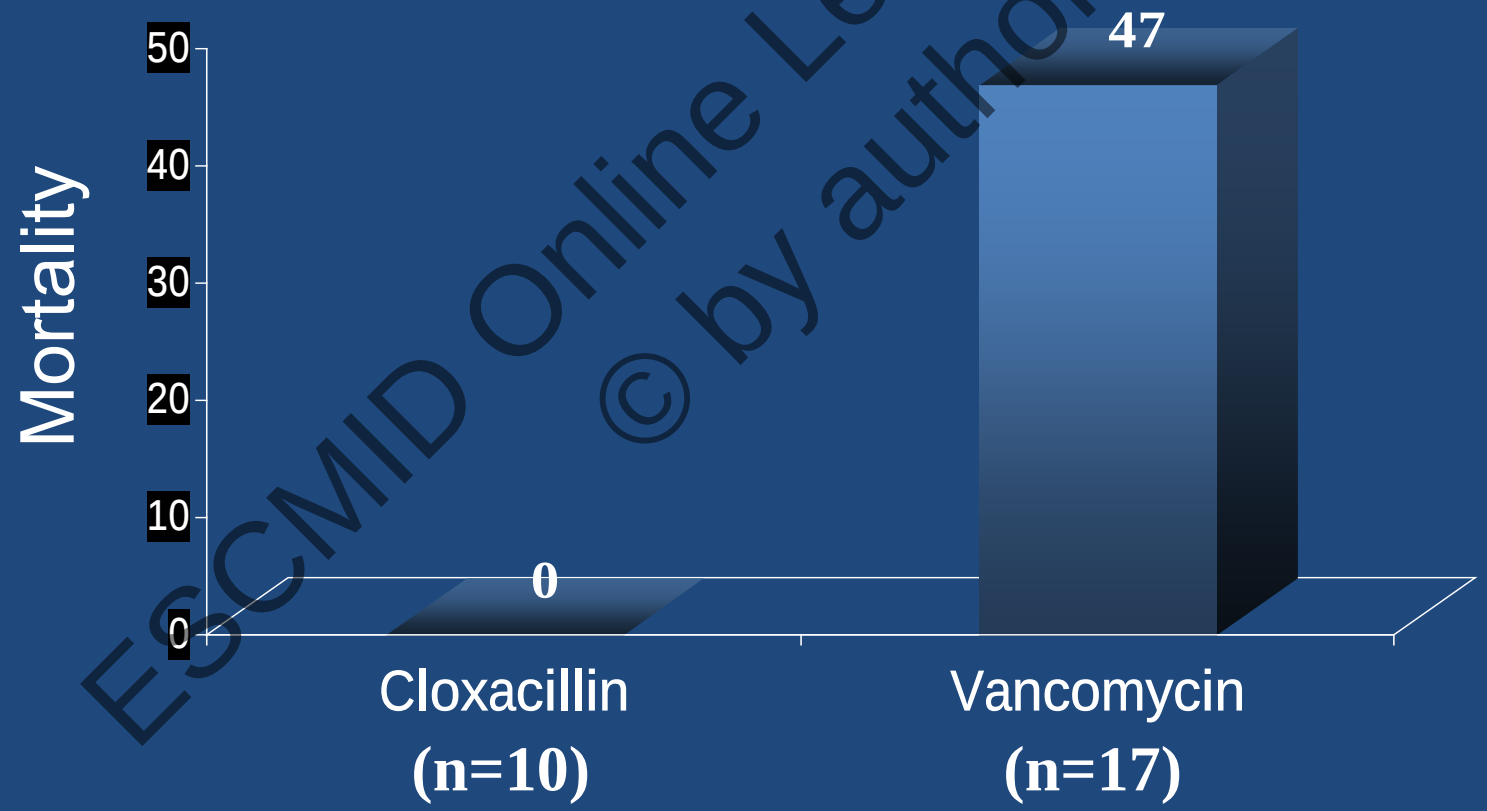
BACK UP SLIDES

Staphylococcus aureus

MSSA: Vancomycin Therapy

Gonzalez, *Clin Infect Dis*, 1999

Bacteremic MSSA Pneumonia



Vancomycin Pulmonary Penetration and ELF concentrations

Lamer C et al. *Antimicrob Agents Chemother.* 1993.

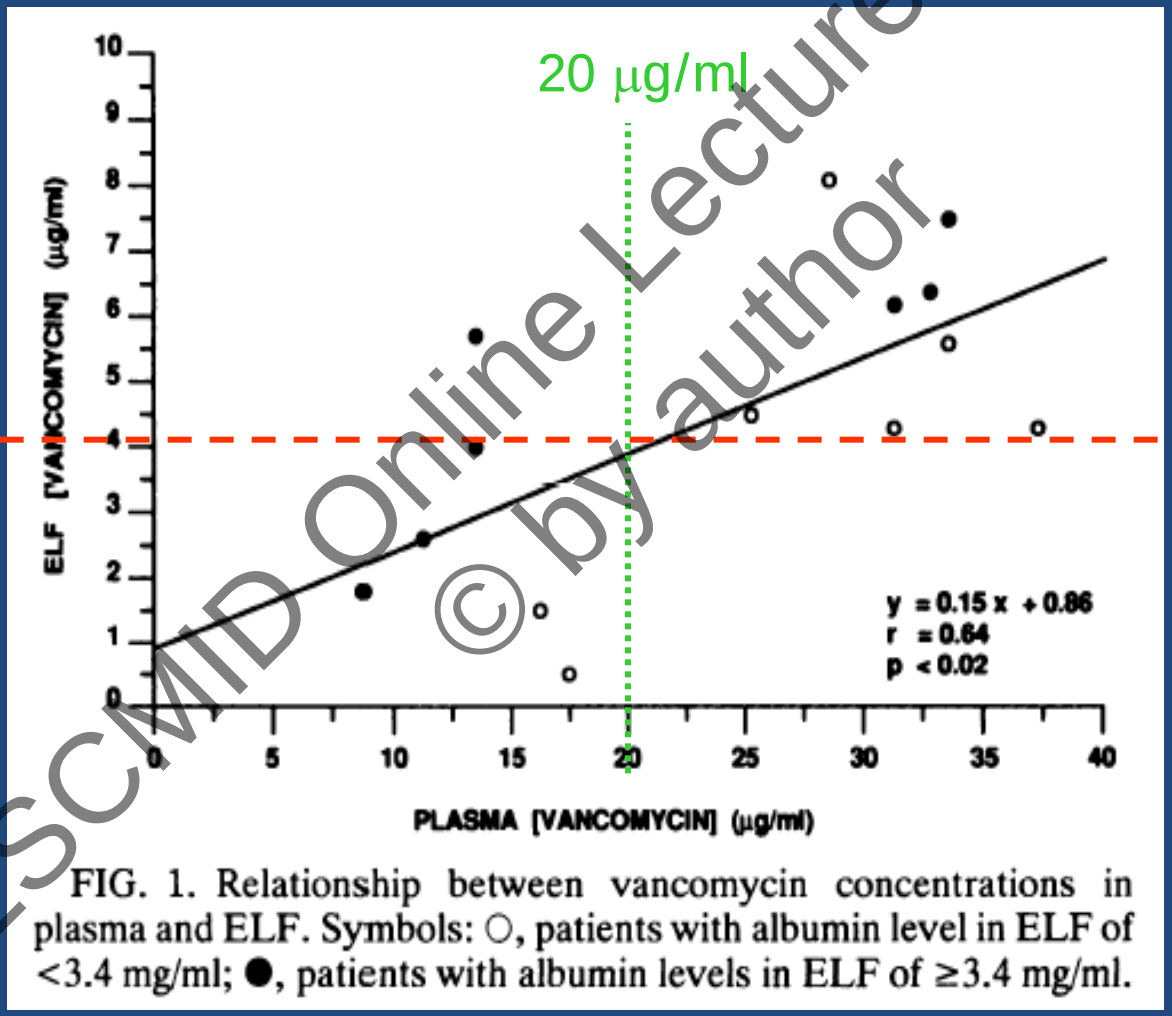
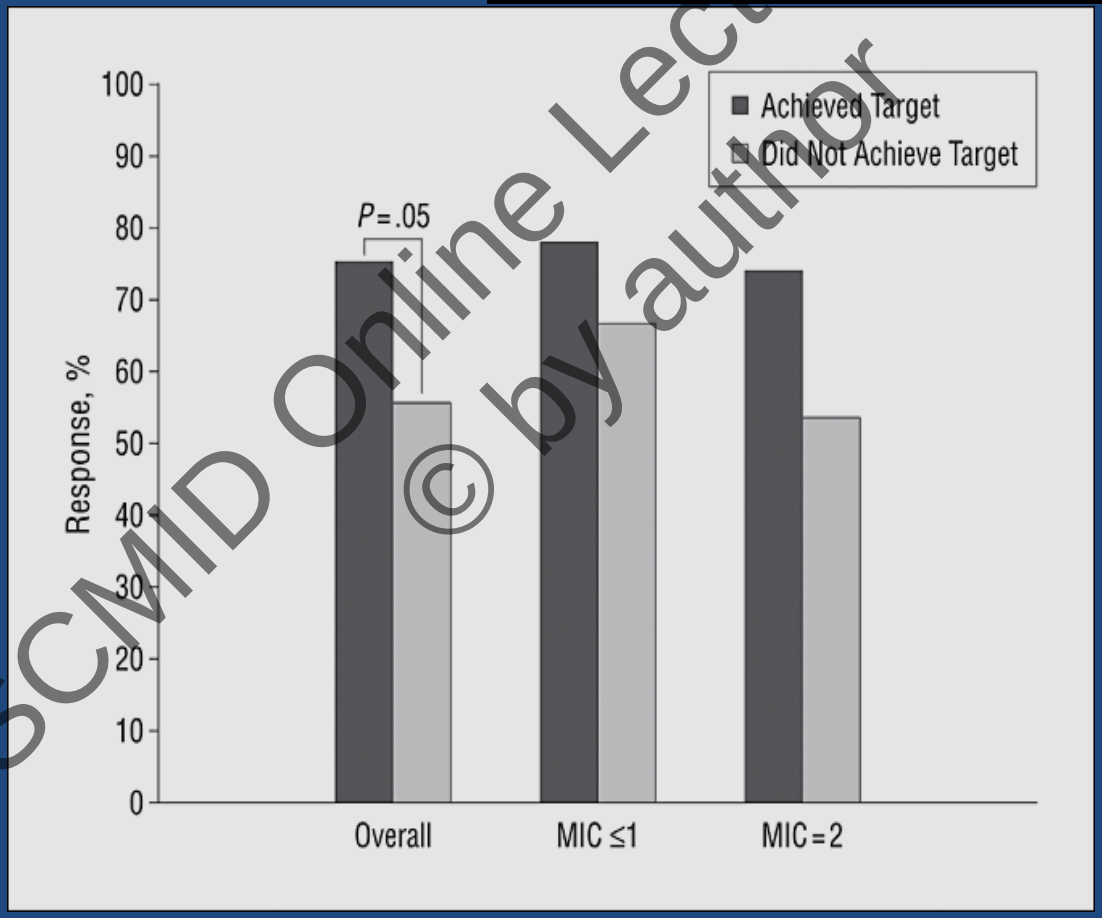


FIG. 1. Relationship between vancomycin concentrations in plasma and ELF. Symbols: ○, patients with albumin level in ELF of <3.4 mg/ml; ●, patients with albumin levels in ELF of ≥3.4 mg/ml.

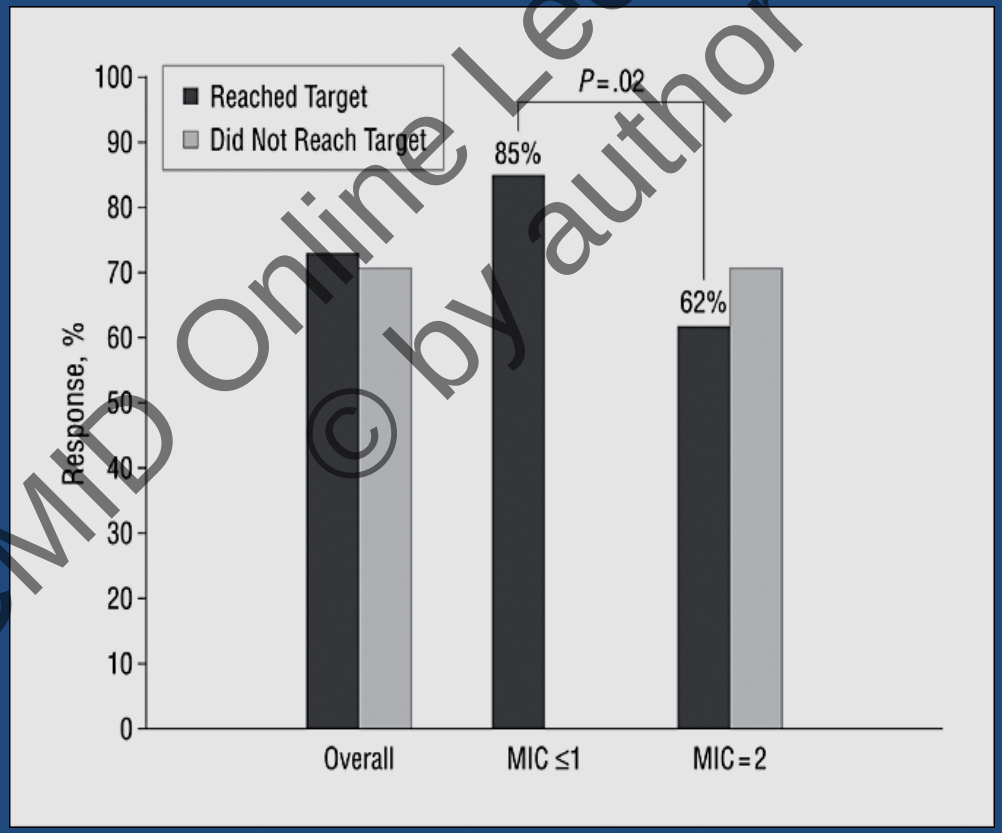
Initial response based on target trough achievement (≥15 ug/ml) in 86 patients with MRSA infection treated with vancomycin

Hidayat et al. Arch Intern Med 2006



Final response based on vancomycin target trough achievement and MIC in 86 patients with MRSA infection

Hidayat et al. Arch Intern Med 2006;166:2138-44



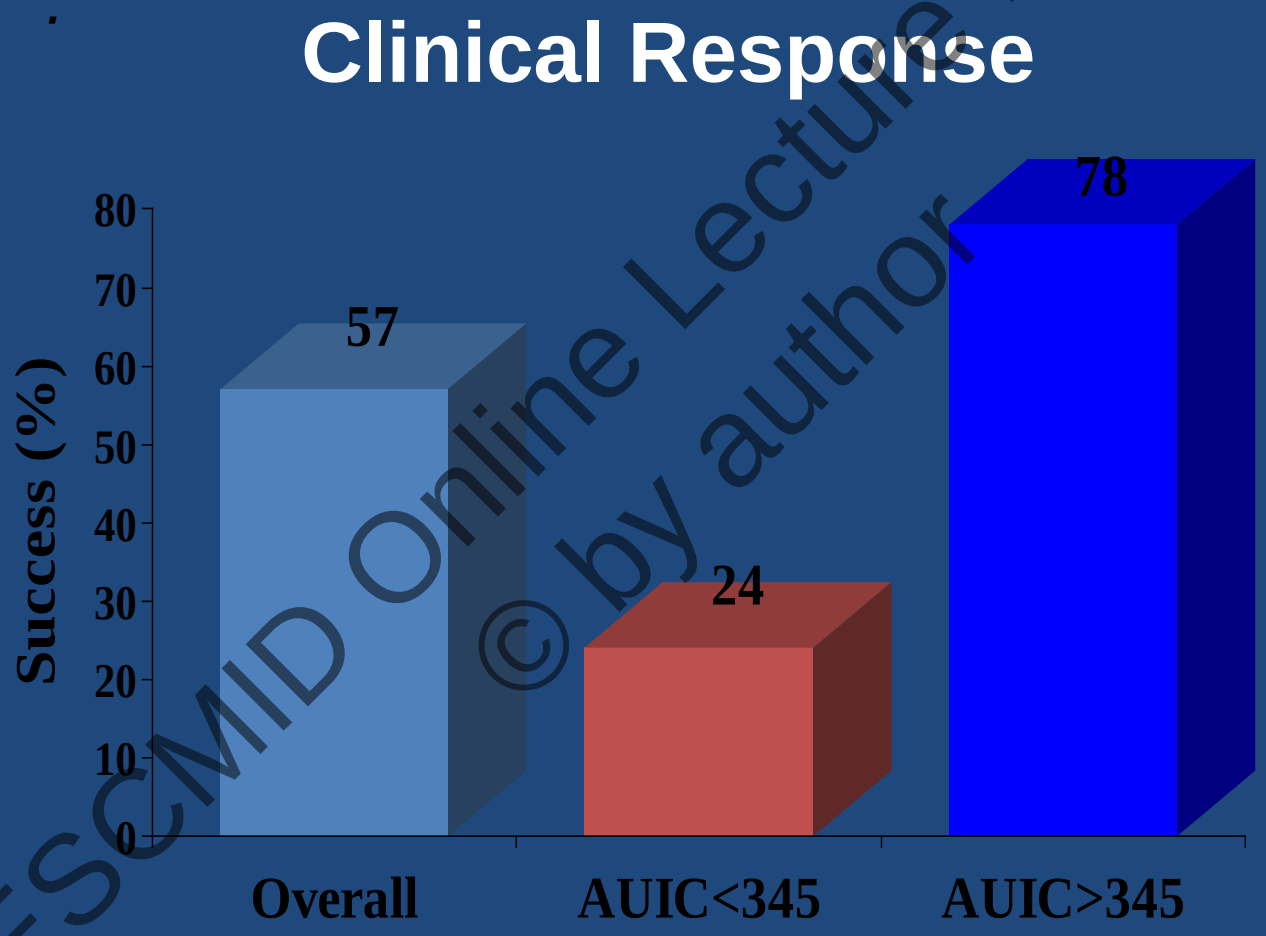
Hidayat LK et al. Arch Intern Med 2006;166:2138-44

Table 5. Predictors of Nephrotoxicity

11.6%

Variable	Nephrotoxicity: Yes* (n = 11)	Nephrotoxicity: No (n = 84)	*P* Value†
Age, mean ± SD, y	72.4 ± 15.7	73.6 ± 15.5	.80
Chronic renal insufficiency or failure	4 (36)	19 (23)	.45
Vancomycin hydrochloride			
Highest trough, mean ± SD, µg/mL	27.5 ± 8.3	19.1 ± 6.4	<.001
Overall trough, mean ± SD, µg/ml	19.0 ± 3.9	15.8 ± 4.5	.03
Trough of 15-20 µg/mL, mean (range), d	7 (0-13)	2 (0-6)	.17
Duration of vancomycin therapy, mean (range), d	17 (13-54)	11 (6-15)	.004
Serum creatinine, mg/dL			
Baseline	1.2 (0.7-2.2)	1.0 (0.7-1.9)	.40
Peak	2.4 (1.8-3.9)	1.2 (0.7-2.7)	.007
Before discharge	2.1 (1.2-3.0)	1.0 (0.6-1.8)	.006
Concomitant nephrotoxic agents‡	10 (91)	17 (20)	<.001

Vancomycin for MRSA Pneumonia



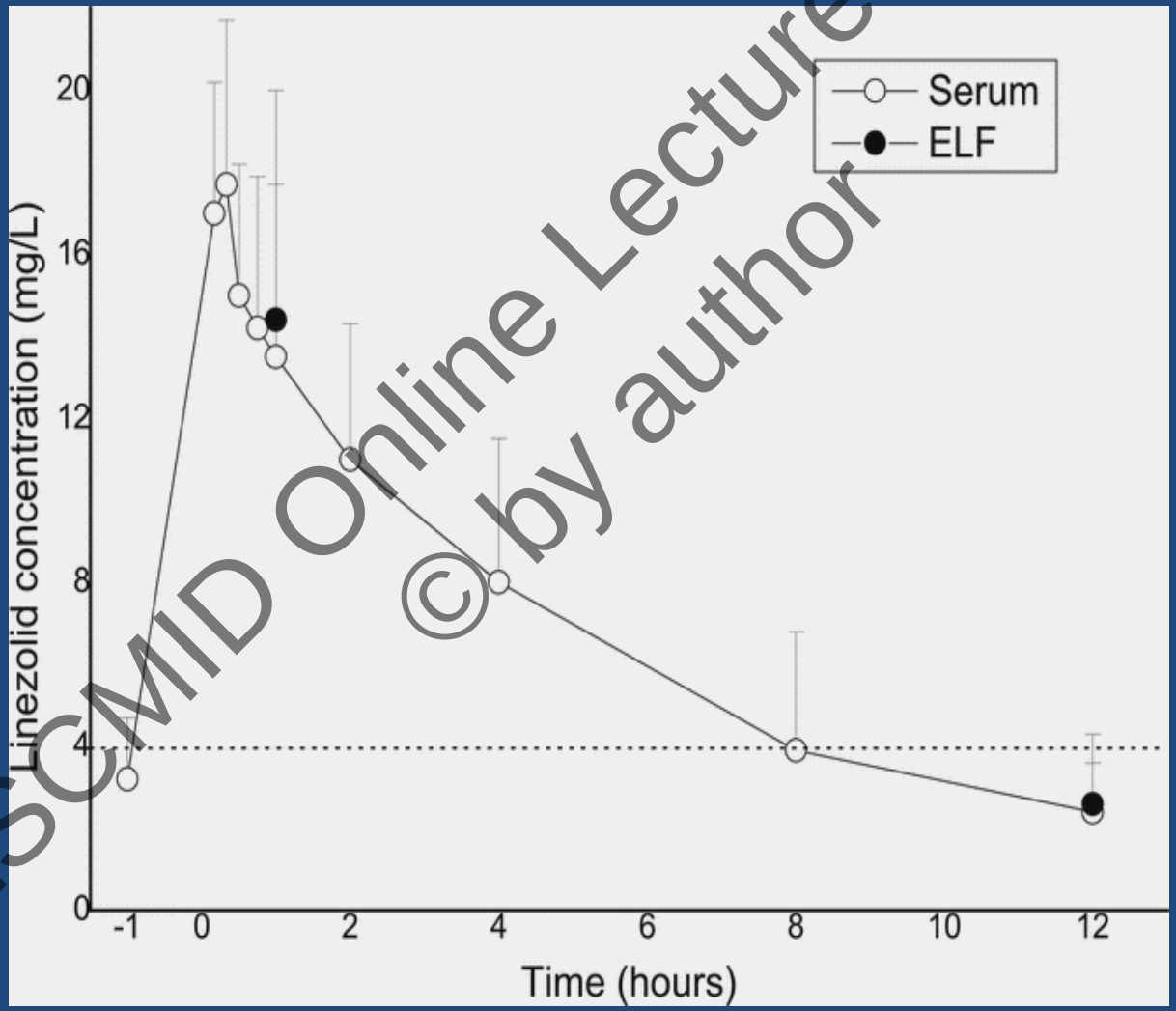
Moise PA et al. Am J Health-Syst Pharm. 2000;57:S4-S9

Limitations of vancomycin for treating MRSA VAP

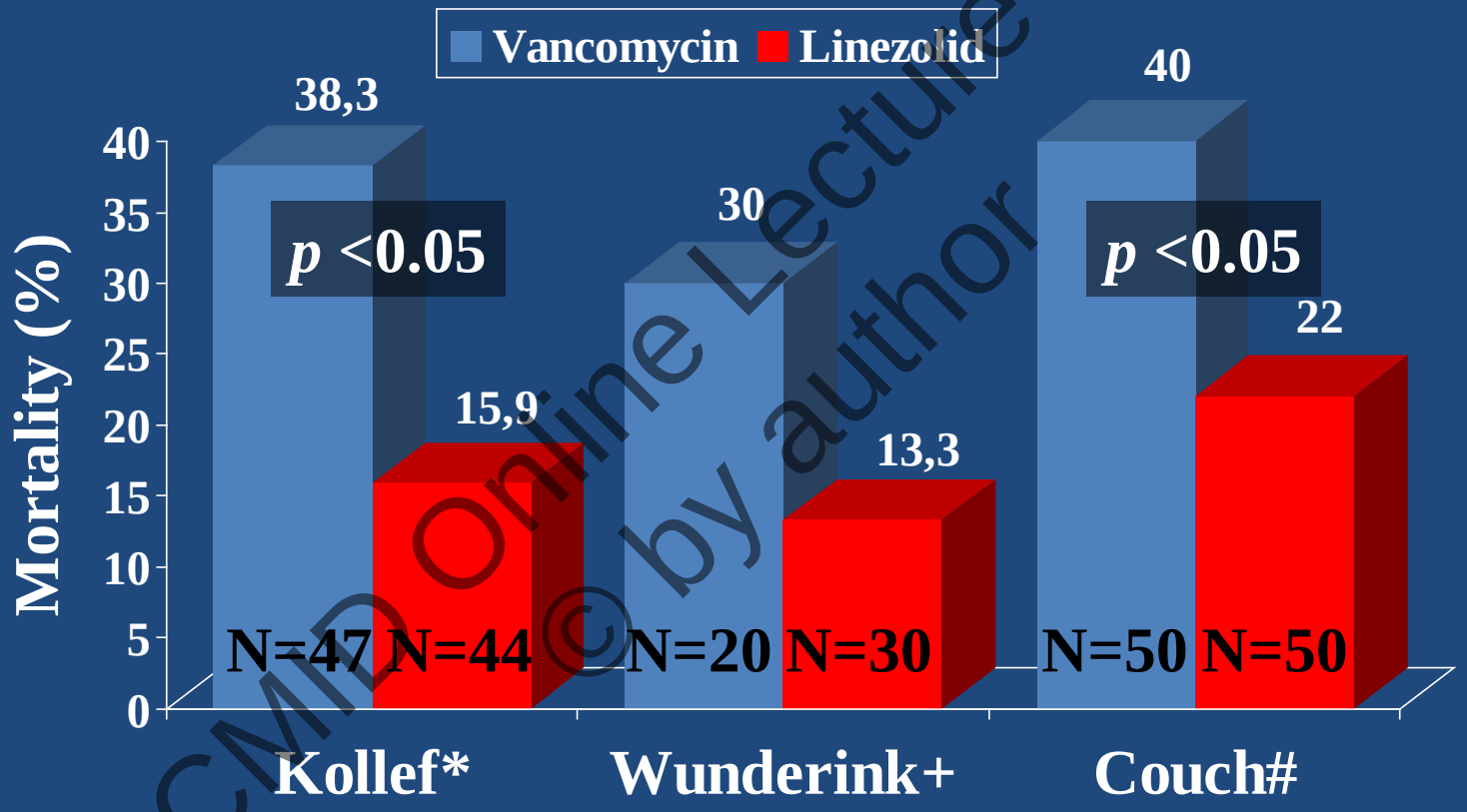
1. Relatively slow bacterial killing
2. Poor tissue penetration, particularly in the lung
3. Potential for toxicity
4. Decreased susceptibility to glycopeptides and emergence of VAN resistance

Pulmonary penetration of linezolid in 16 patients with VAP

Boselli et al. CCM 2005



Mortality of MRSA VAP



* Intensive Care Medicine, 2004
+ abstract, ATS, 2006 # abstract, IDSA, 2007

Linezolid *vs* Vancomycin for Treatment of Severe Gram-positive Pneumonia: Potential Pittfalls and Limitations of Aforementioned Trials

1. Subgroup analysis
2. Potential imbalances in the two groups
3. Low trough vancomycin levels target (5-10 ug/mL)
4. Failure to show a statistically significant in the S. aureus subgroups (all patients with MSSA or MRSA)

HAP: Current Treatment Guidelines

- Linezolid is an alternative to vancomycin for the treatment of MRSA VAP and *may be preferred* on the basis of a subset analysis of two prospsective randomized trials (Level II).
- This agent may also be preferred if patients have renal insufficiency or are receiving other nephrotoxic agents.

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

Pseudomonas aeruginosa

PSEUDOMONAS AERUGINOSA BACTEREMIA: PREDICTORS OF EARLY MORTALITY

MULTIVARIATE ANALYSIS

Shock	OR 5.9; CI 95% 1.1-23	p=0.012
Inappropriate Empirical Antibiotic treatemnt	OR 4; CI 95% 1.1-15	p=0.03
Pulmonary infection	OR 3.5; CI95% 1-12	p=0.04;

Pascual V et al, 49th ICAAC, San Francisco 2009

Percent of VAP caused by *P. aeruginosa* in ICUs

	Type of ICU																	
	Burn		Coronary care		Cardio-thoracic		Medical		Medical/ surgical		Neuro-surgical		Pediatric		General surgery		Trauma		Total	
Pathogen	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Enterobacter spp	51	8.0	207	9.8	375	13.1	512	8.6	1022	10.6	257	10.5	182	9.8	1557	12.8	281	13.4	4444	11.2
E coli	21	3.4	88	4.2	139	4.8	211	3.5	402	4.1	112	4.6	66	3.6	593	4.9	93	4.4	1725	4.3
K pneumoniae	34	5.3	176	8.4	169	5.9	461	7.7	720	7.4	182	7.5	99	5.4	878	7.2	146	7.0	2865	7.2
H influenzae	42	6.6	65	3.1	165	5.8	87	1.5	340	3.5	181	7.4	171	9.3	532	4.4	155	7.4	1738	4.3
P aeruginosa	137	21.5	314	14.9	375	13.1	1264	21.2	1507	15.5	294	12.1	414	22.4	2087	17.2	360	17.1	6752	17.0
S aureus	157	24.7	425	20.2	326	11.3	1273	21.4	1750	18.0	527	21.6	303	16.4	2065	17.0	379	18.1	7205	18.1
Enterococcus spp	12	1.9	37	1.8	66	2.3	102	1.7	177	1.8	32	1.3	17	0.9	215	1.8	24	1.1	682	1.7
C albicans	18	2.8	133	6.3	180	6.3	298	5.0	592	6.1	104	4.3	37	2.0	468	3.9	32	1.5	1862	4.7
All other pathogens	164	25.8	658	31.3	1073	37.4	1752	29.4	3197	33.0	749	30.7	559	30.2	3759	30.9	626	29.9	12537	31.5
Total	636	100.0	2103	100.0	2868	100.0	5960	100.0	9707	100.0	2438	100.0	1848	100.0	12154	100.0	2096	100.0	39810	100.0

*Includes all ICU infections reported from hospitals performing either the ICU or hospital-wide surveillance components during the time period.

National Nosocomial Infections Surveillance (NNIS) System Report, Data Summary from January 1990-May 1999, Issued June 1999, Am J Infect Control, Volume 27(6).December 1999.520-532

Treatment options for P aeruginosa infections

- Fluoroquinolones (ciprofloxacin vs. levofloxacin)
- Ceftazidime, aztreonam
- Cefepime
- Carbapenems (imipenem, meropenem)
- Aminoglycosides (amikacin vs tobramycin)
- Polymixins (polymixin B, colistin)
- Rifampicin

COMBINATION THERAPY VS MONOTHERAPY IN SUSCEPTIBLE P AERUGINOSA

- A recent consensus (ATS/IDSA), monotherapy with newer agents (FQs, ceftazidime, cefepime, Piperacillin/Tazobactam, carbapenems) preferred for patients with non-risk of infection with non-drug-resistant organisms and without severe infection[1]
- The most recent metaanalysis of randomized trials (B-lactam monotherapy vs. B-lactam + Ag) against a variety of mixed infections,-8 trials analysed, 6 using late generation agents-, no differences in mortality or emergence of resistance[2]

1. ATS guidelines. Am J crit Care Med 2005;171:388
2. Bliziotis et al, Clin Infect Dis 2005;41:149

Therapy for P aeruginosa VAP: an observational, multicenter study comparing monotherapy with combination antibiotic therapy.

- Five intensive care units in Spanish university hospitals
- Adult patients identified to have monomicrobial episodes of VAP with significant quantitative respiratory cultures for *P. aeruginosa*.

Garnacho-Montero J et al, Crit Care Med. 2007;35:1888-95

Variables independently associated with mortality using Cox proportional regression analysis

	aHR*	95%CI	P Value
Age	1.02	1.01-1.04	0.005
CHF	1.90	1.04-3.47	0.035
Efective antimicrobial therapy			
Combined therapy	1		
Monotherapy	0.90	0.50-1.63	0.73
Inappropriate therapy	1.85	1.07-3.10	0.02

*Adjusted hazard ratio

Garnacho-Montero J et al, Crit Care Med. 2007;35:1888-95.

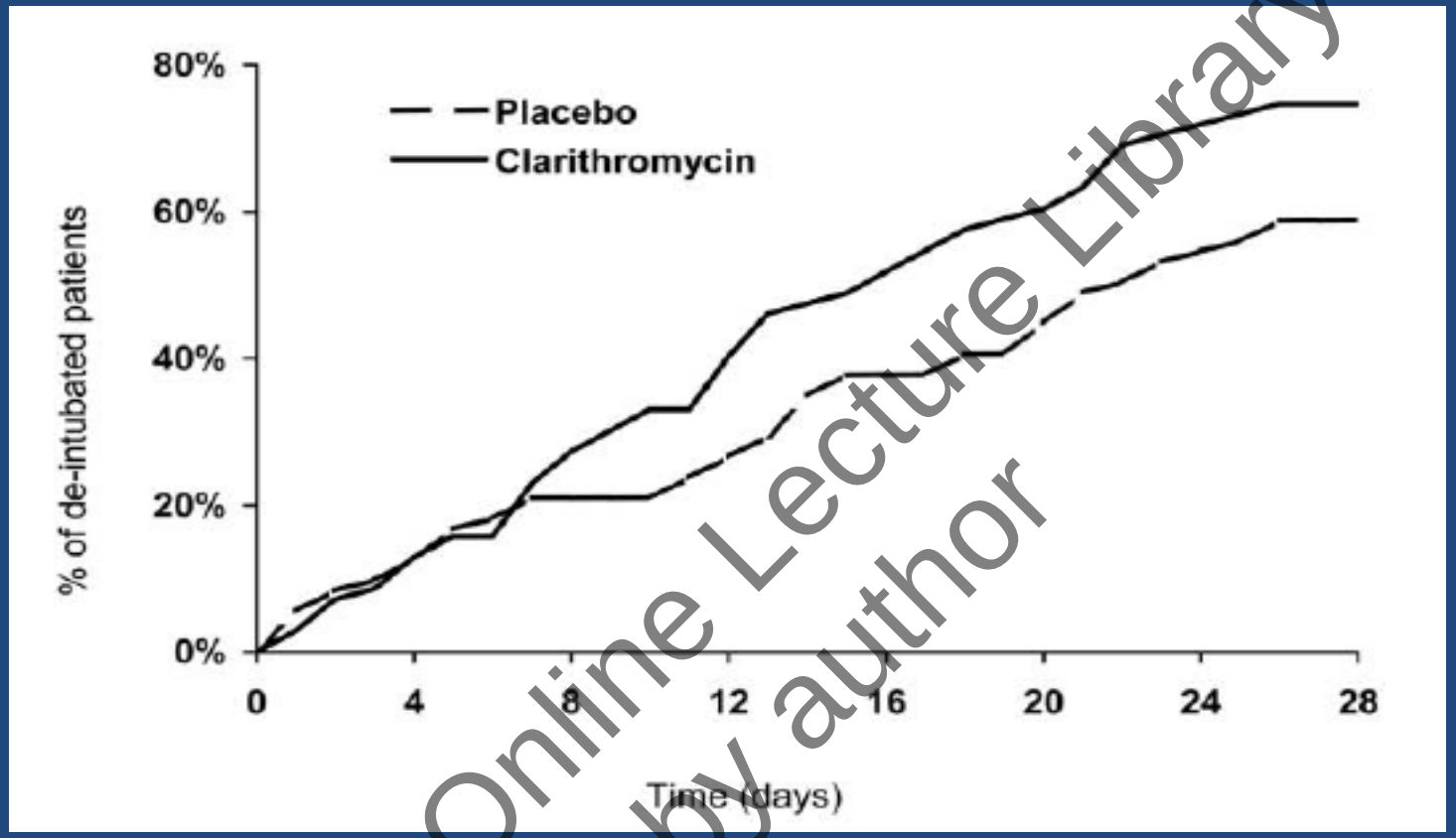
Importance of PK/PD - Efficacy

- PK/PD breakpoints are lower than CLSI breakpoints
  - For *P. aeruginosa*
    - Piperacillin/tazobactam (16 vs. 64)
  - For all GNR
    - Quinolones (0.25 vs 1-2)
  - 20-30% of *P. aeruginosa* isolates are within the "gray zone"
  - 50% of ESBLs in "gray zone" for quinolones

Frei CR. JAC 2008;621-628
Colodner R. DMID 2007

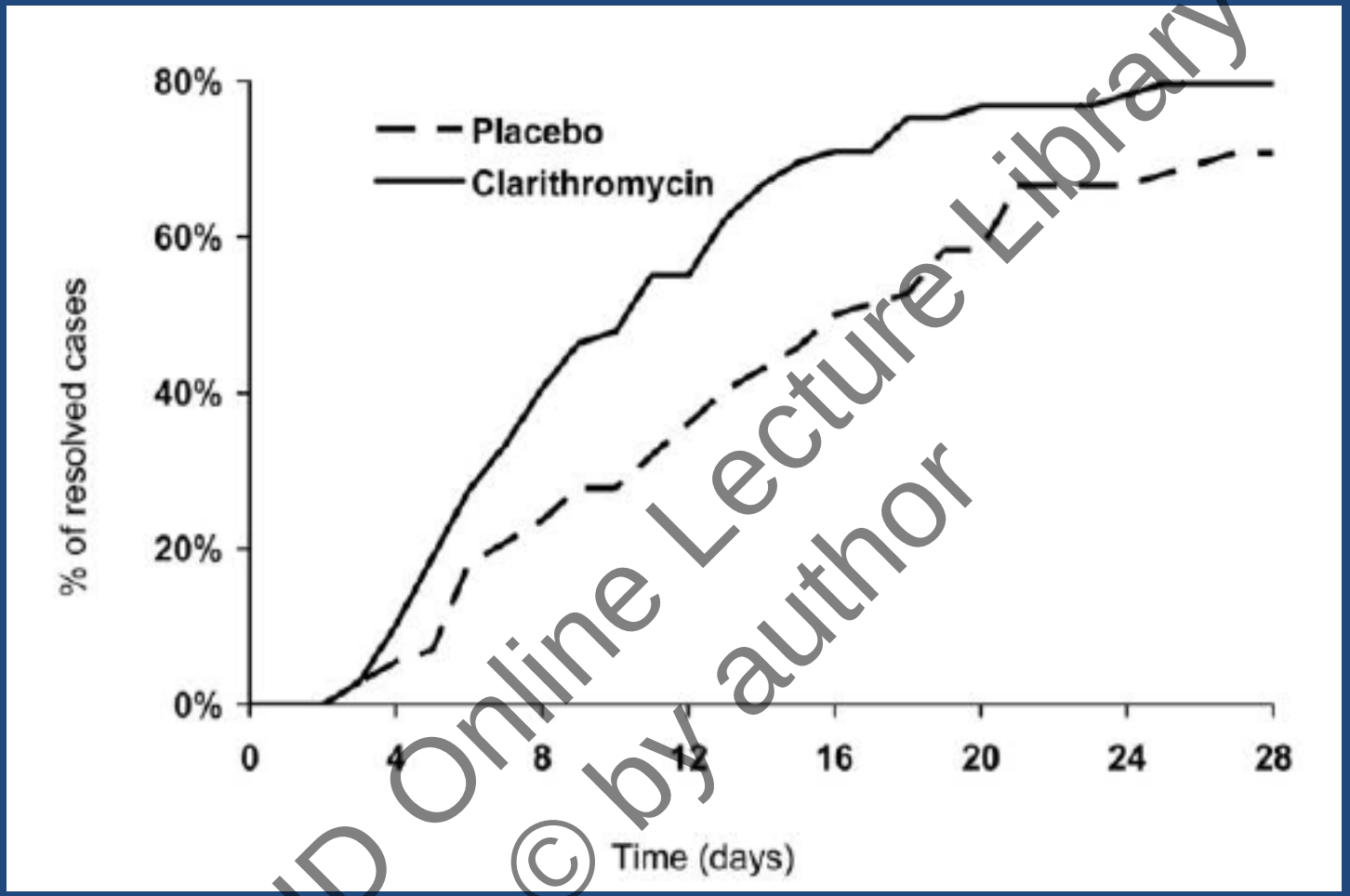
- All these considerations are becoming important for the clinician because attainment of pharmacodynamic targets has been associated with a decreased likelihood of a negative outcome.

Ambrose PG, Bhavnani SM, Rubino CM, et al. Pharmacokinetics pharmacodynamics of antimicrobial therapy: It's not just for mice anymore.
Clin Infect Dis. 2007;44:79-86)



Cumulative time to weaning from mechanical ventilation among placebo-treated and clarithromycin-treated patients. Analysis comprised patients who survived until the 28th day (*n*p141). *P*p.049, by Mantel-Cox log rank test.

Giamarellos-Bourboulis EJ et al, Clin Infect Dis 2008; 46:1157–64



Cumulative incidence of the resolution of ventilator-associated pneumonia within the follow-up period of 28 days. Analysis comprised patients who survived until the 28th day (*n*p141). *P*p.036, by Mantel-Cox log rank test; *P*p.017, by Tarone-Ware test; *P*p.011, by the Breslow test.

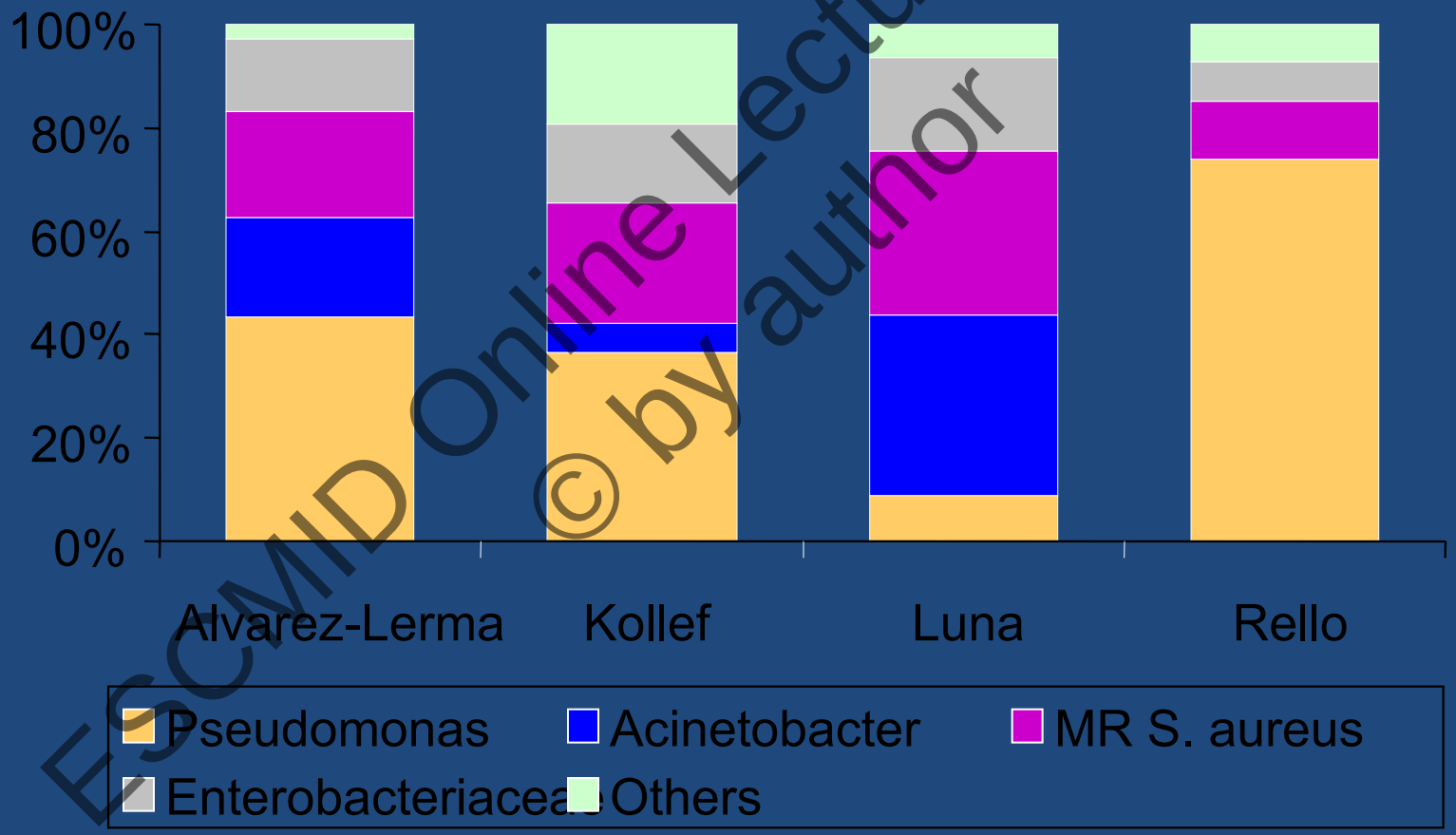
Table 2. Primary study outcomes as assessed in the registry of the trial.

Outcomes	Treatment with		P
	Placebo (n = 100)	Clarithromycin (n = 100)	
Crude mortality for any reason	28	31	.76
Mortality at 7 days	8	6	.78
Sepsis-related mortality at 28 days, no. of patients/total patients, excluding those who died of other causes (%)	24/96 (25.0)	21/90 (23.3)	.86
Progression to MODS among the total enrolled patients	8	14	.26
Time until progression to MODS, mean days ± SD	3.38 ± 1.06	5.78 ± 3.52	.047
Time until resolution of VAP, median days (IQR)	11.5 (2 to >28)	7.0 (2–24)	.006
Time in ICU after diagnosis of VAP for patients who survived, mean days ± SD	21.58 ± 8.22	23.36 ± 7.05	.17

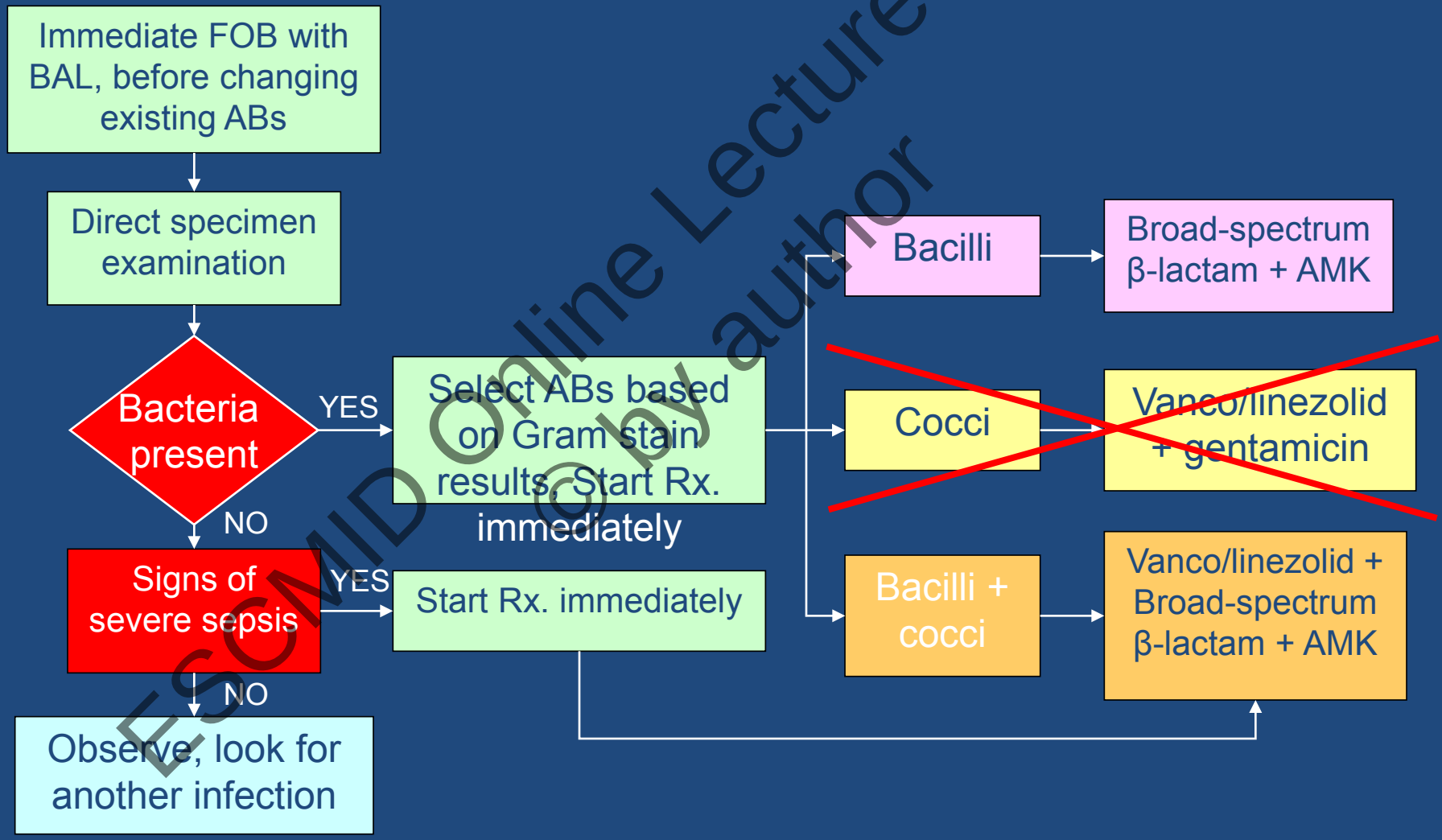
NOTE. Data are no. of patients, unless otherwise indicated. Clinical registry of the trial (NCT00297674) is available at http://www.clinicaltrials.gov/. ICU, intensive care unit; IQR, interquartile range; MODS, multiple-organ dysfunction; VAP, ventilator-associated pneumonia.

Giamarellos-Bourboulis EJ et al, Clin Infect Dis 2008; 46:1157–64

Pathogens Associated with Inappropriate Initial Therapy in Patients with VAP



Starting Therapy Using Broad-spectrum Drugs in Patients with Risk Factors for Potentially Drug-Resistant Pathogens

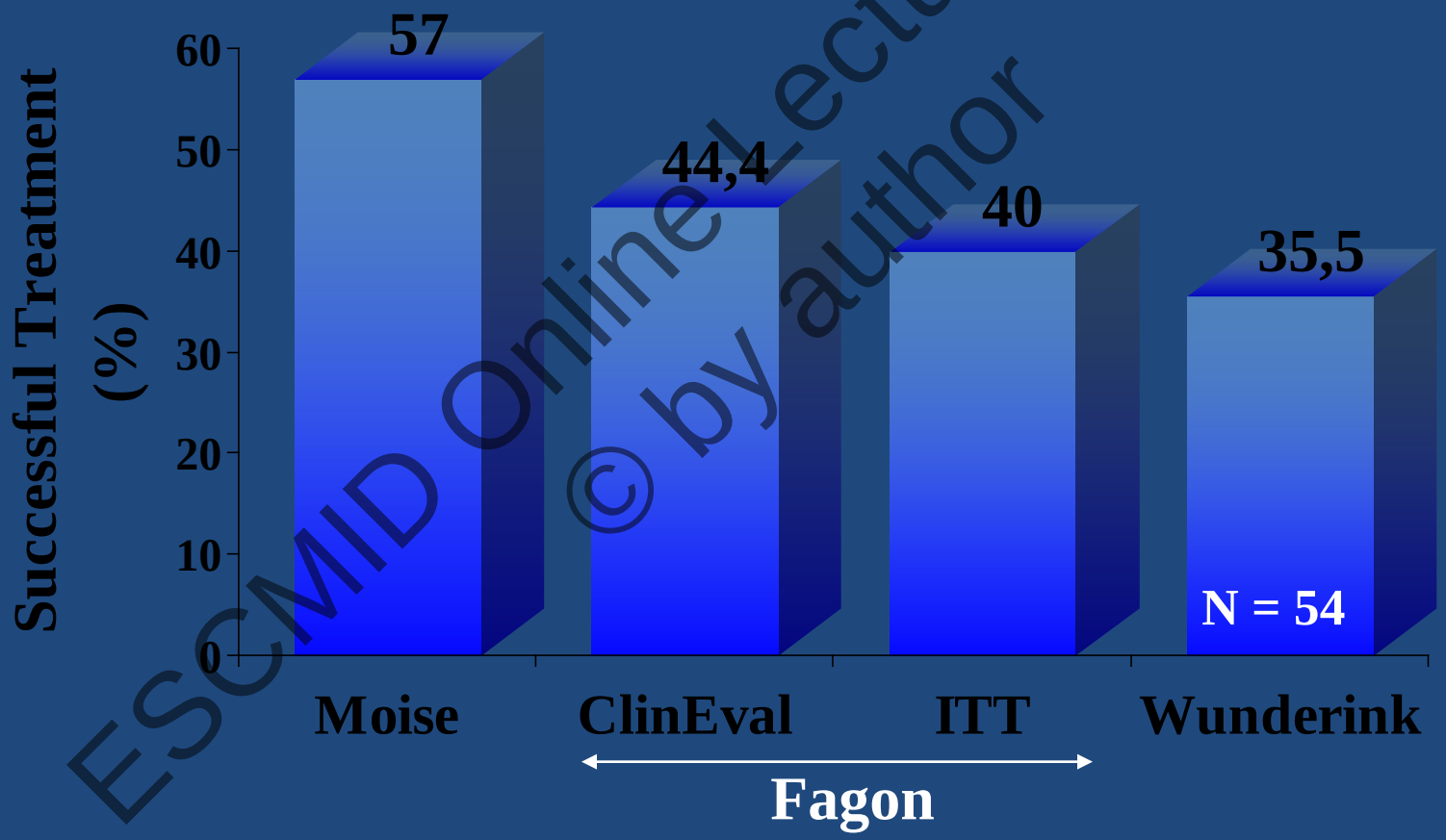


Failure of Vancomycin Therapy in MRSA Pneumonia

- Penetration
- Inadequate serum levels
- Bacterial clearance
- Rising MICs
- AgrII polymorphism
- Toxin production

Never proven to be an adequate pneumonia drug

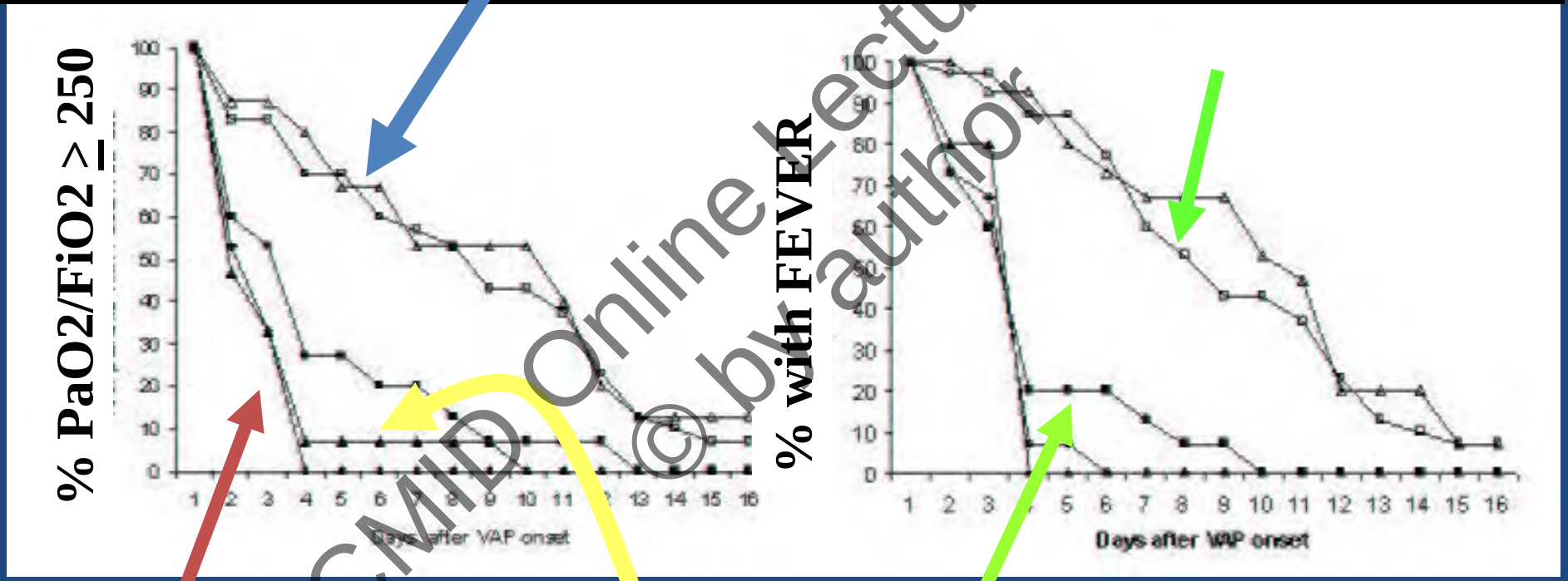
Treatment with Vancomycin of Patients with MRSA HAP



Improve treatment decisions: Which organisms to cover?

- Diagnostics
  - Appropriate cultures before treatment
  - Improve time to diagnosis
    - Rapid testing (conventional or molecular)
      - Delivery, Processing, Reporting
- Individualized decision
  - Severity of infection
    - Escalating vs. de-escalating therapy
  - Suspected pathogens
  - Resistance patterns
    - Affected patient characteristics
    - Local epidemiology

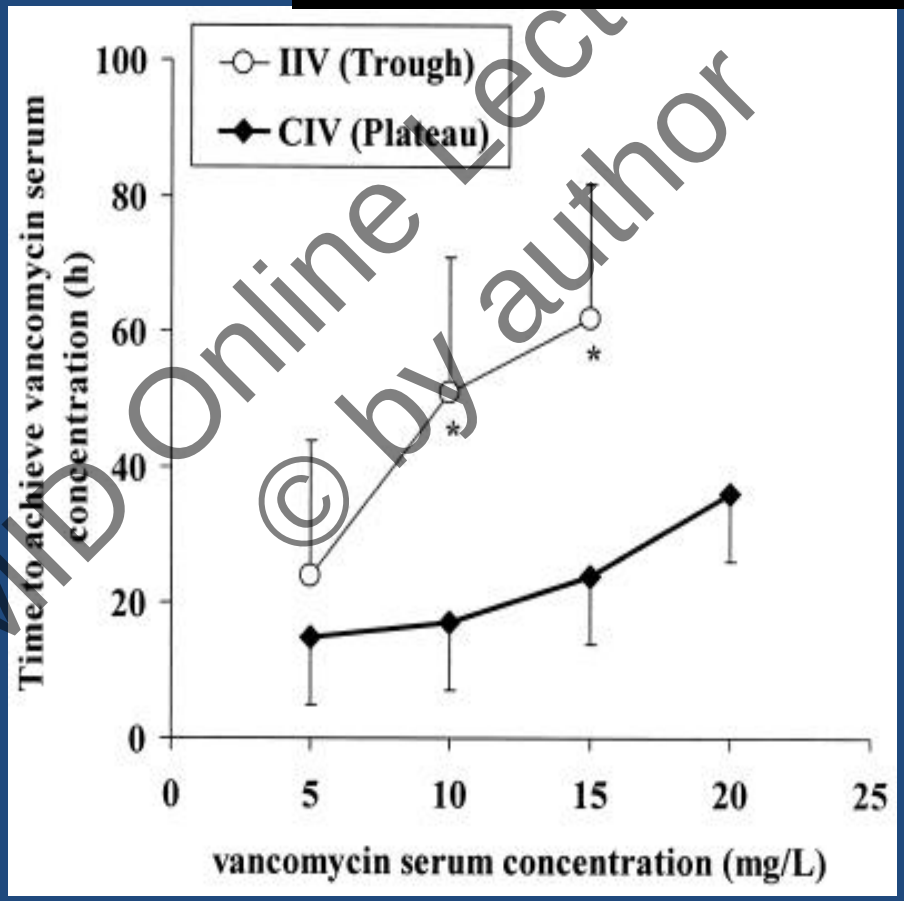
Effect of Microorganism and Initially Appropriate Antibiotics on VAP Resolution



Vidaur L et al, Chest 2008;133:March

Continuous *vs* intermittent infusion in MRSA infections: A prospective randomized study in 119 patients

Wysocki M et al. JAC 2001;45:2460-7



Clinical characteristics on ICU admission

Characteristics	VAP ($n=40$)	Non-VAP ($n=61$)
Age (years)	60 ± 20	63 ± 17
Female (%)	33	28
SAPS II (points)	38 ± 15	35 ± 16
SAPS II mortality risk (%)	26 ± 22	27 ± 20
Diagnosis (%)		
Respiratory failure	28	31
Neurological	30	26
Trauma	20	15
Cardiovascular	10	15
Cardiac arrest	7	8
Other	5	5
Length of mechanical ventilation before VAP or length of MV in non-VAP group (days)	13.3 ± 8.5	11.5 ± 9

All results were non-significant

Vallés J et al, Intensive Care Med 2007; 33:1363–1368

- Antibiotic treatment of *P aeruginosa* infections is extremely challenging, because it is endowed with multiple resistance mechanisms, including b-lactamases, efflux pumps, and a rather impermeable outer membrane.
- These mechanisms often result in higher MICs for *P. aeruginosa* than for other common gram-negative pathogens in the hospital environment
- Consequently, antimicrobial chemotherapy for *P. aeruginosa* often produces suboptimal results

LINEZOLID AEs

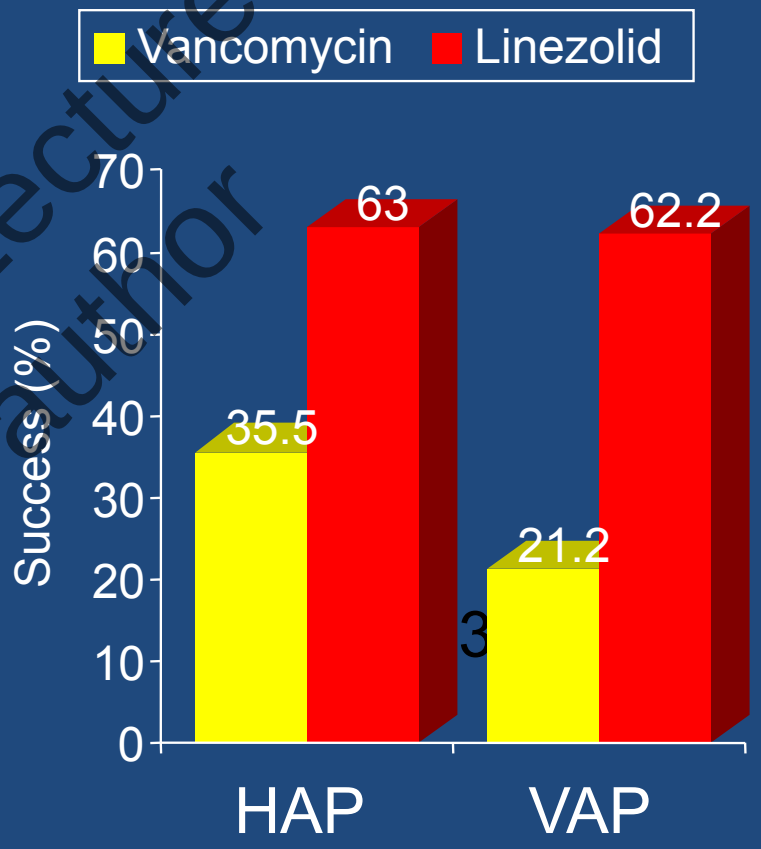
	Rubinstein E et al. *Clin Infect Dis 2001;32:402*		Wunderink RG et al. *Clin Ther 2003;25:980*	
	Linezolid	Vancomycin	Linezolid	Vancomycin
Diarrhea	4,4%	2,6%	3,7%	3,0%
Increased ALT	1,0%	1,6%	ND	ND
Rash	0	1,6%	0,6%	1,7%
Renal dysfunction	ND	ND	0,3%	0,7%

MRSA Nosocomial Pneumonia: Clinical Response

- 116 patients from 2 Phase III trials
- Intention to Treat

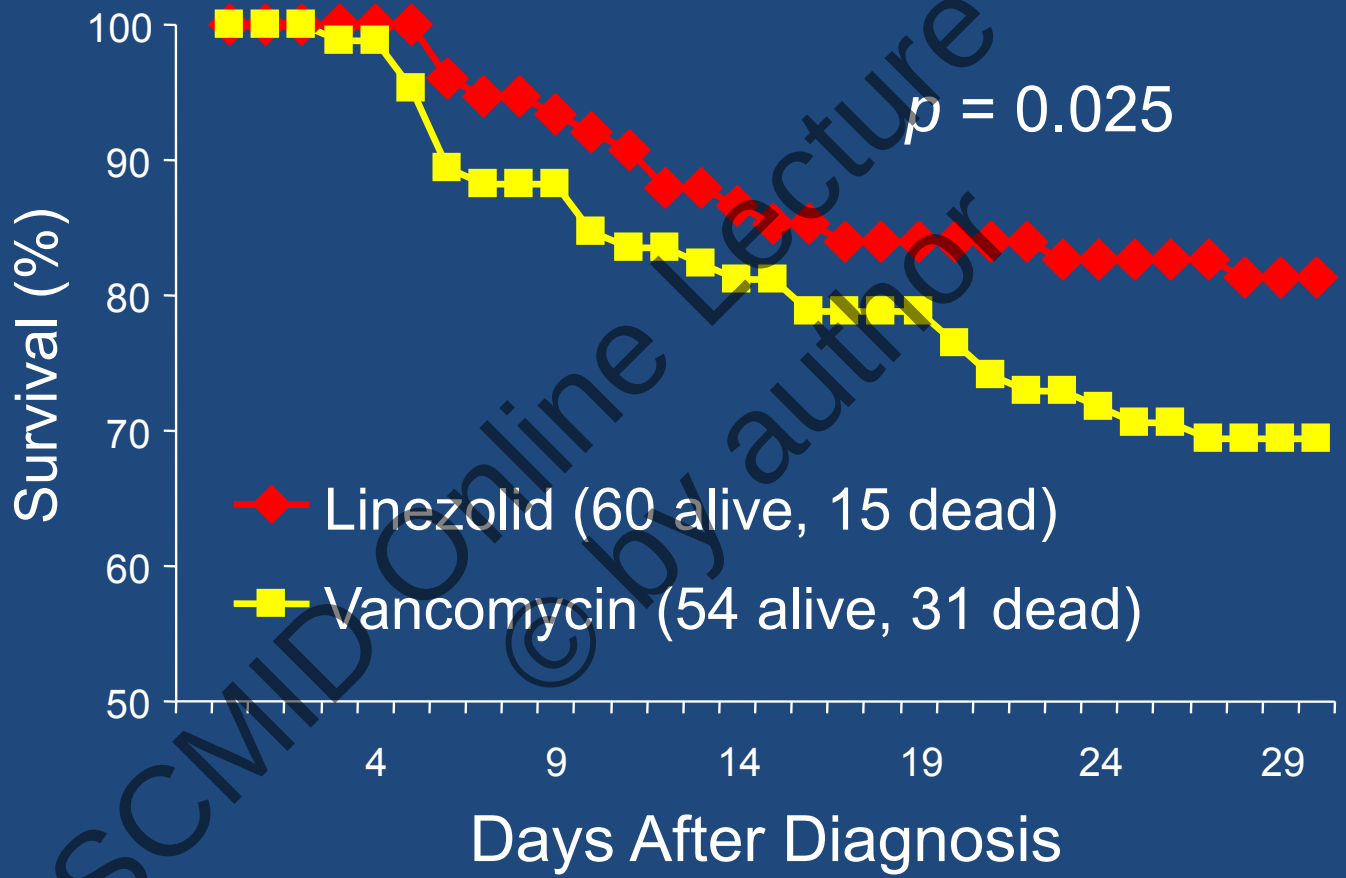
<u>Failure Multivariate analysis</u>

- vancomycin (OR 3.59, $p = 0.0073$)
- multi-lobe
- ventilator
- renal comorbidity
- oncologic comorbidity



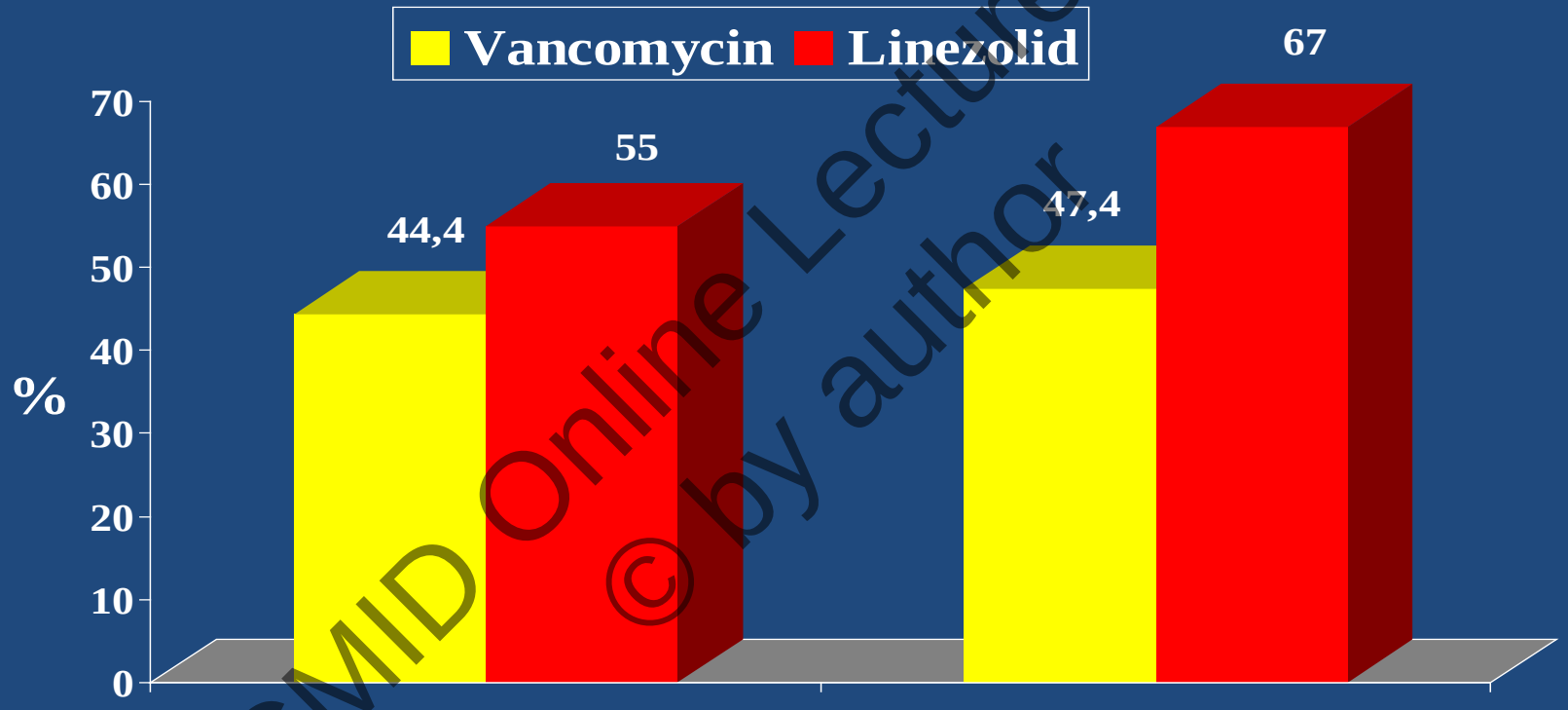
Wunderink, Chest, 2003

Hospital-acquired MRSA Pneumonia



Wunderink, Chest, 2003

Microbiologic Response in Confirmed MRSA VAP



Wunderink, abst. ATS, 2006

COMBINATION THERAPY VS MONOTHERAPY-SUSCEPTIBLE P AERUGINOSA

- Analysis of historical controls (115 episodes), each categorized as adequate or inadequate on the basis of S results, “The risk of death (30 days) was significantly greater for patients receiving adequate empirical monotherapy than those receiving adequate empirical combination therapy”. However, adequate definitive therapy did not influence outcome[1]

- These results support the concept that combination therapy is superior to monotherapy as the initial empirical approach to *P aeruginosa* serious infections (bacteremia, pneumonia)

1. Chamot E et al, AAC 2003;47:2756

CONCLUSIONS

- The presence of shock, inappropriate empirical treatment and pneumonia were associated with increased early mortality. Only empirical antimicrobial therapy is susceptible of modification.

- The high proportion of inappropriate empirical therapy regimens used in the group of EM was mainly due to an unexpected PA infection rather than to the presence of multidrug resistant *P aeruginosa* infecting strains.

- Identification of risk factors for PA BSI is paramount at the time of choosing empirical therapy if the overuse of antimicrobial agents is to be avoided.