Traitement antibiotique des pneumonies nosocomiales

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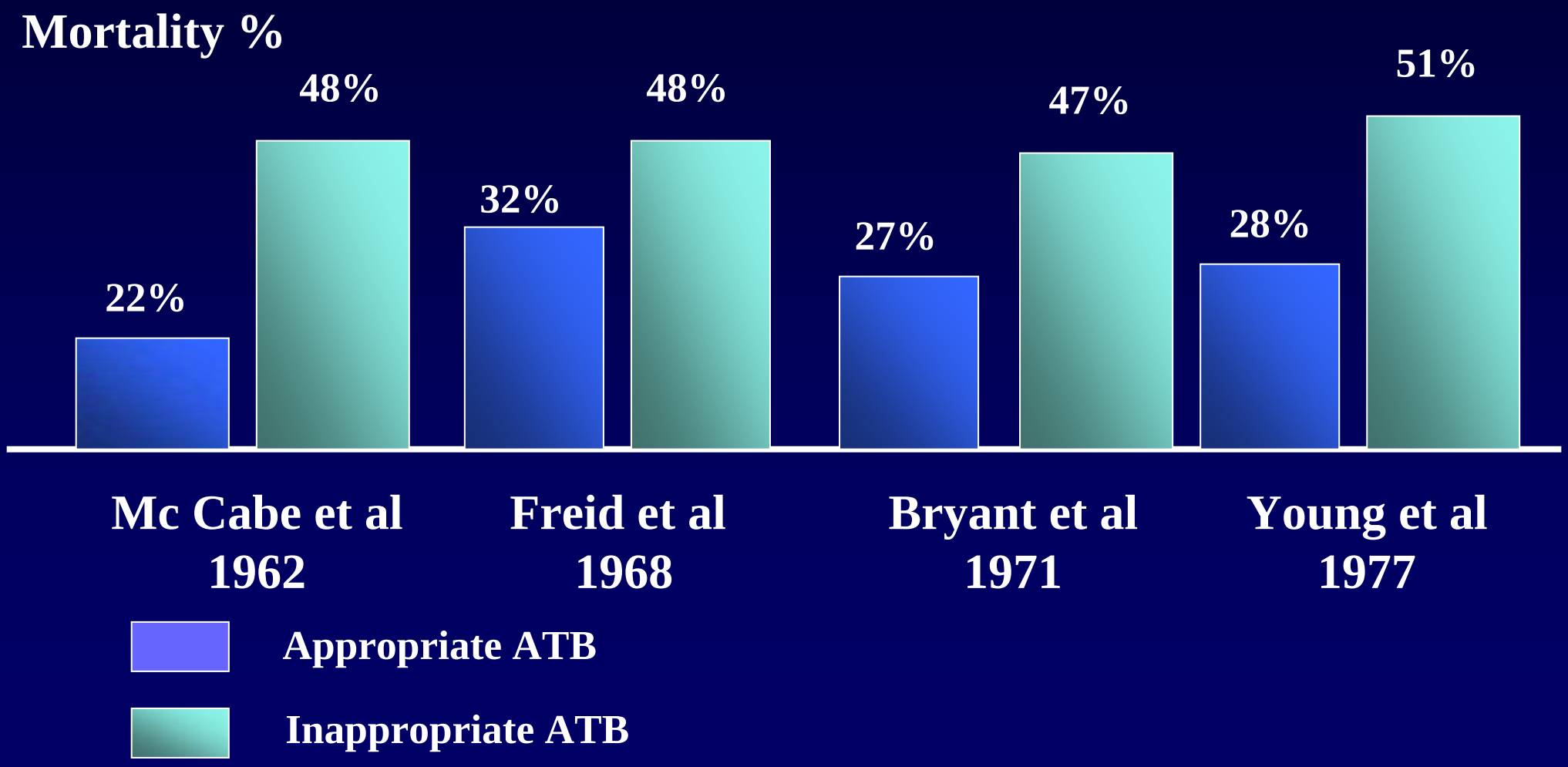
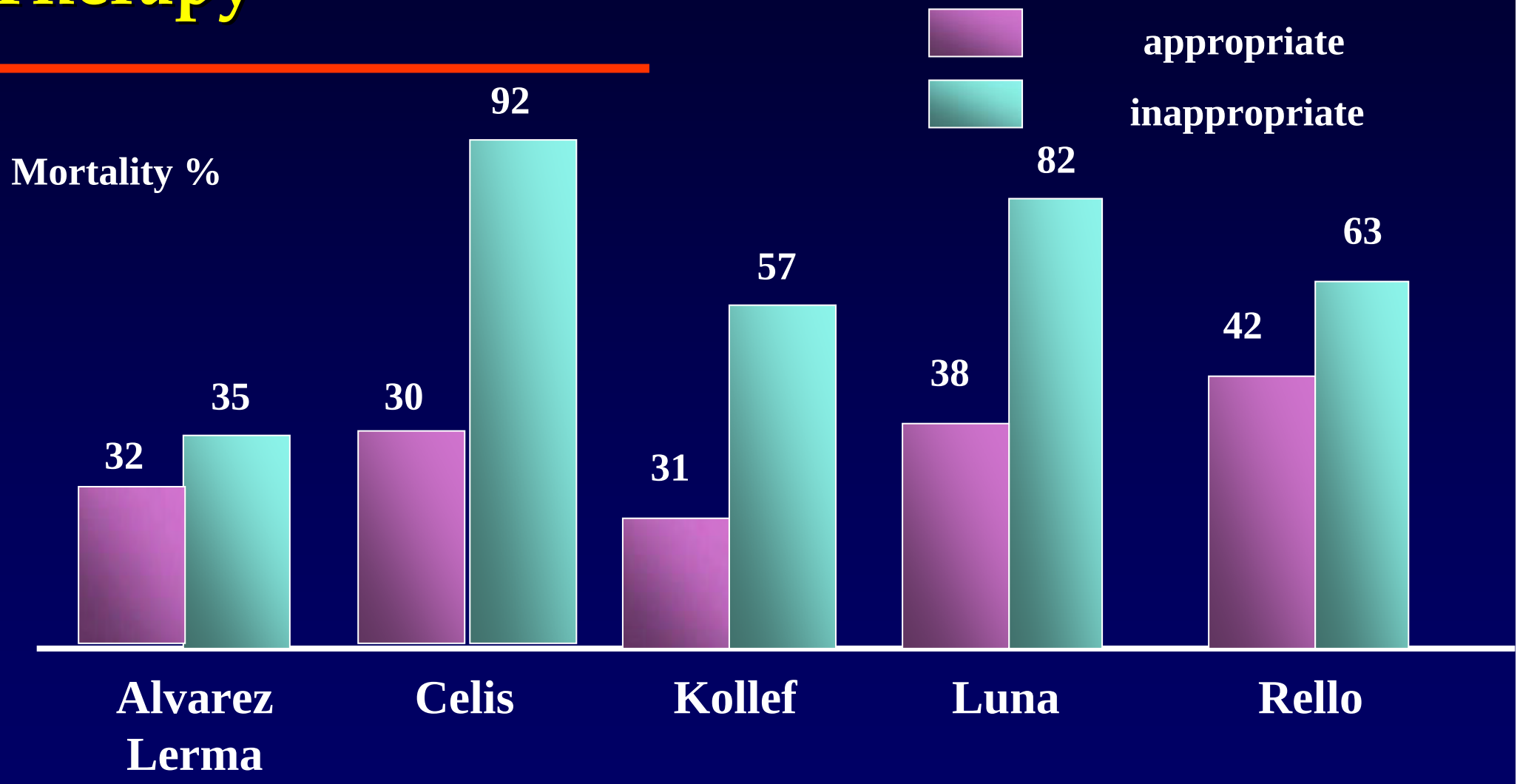
Appropriateness of Antibiotic Therapy and Mortality of Gram-negative Bacteremia



VAP Mortality and Appropriateness of ATB Therapy



La mortalité des PAVM

(pneumonies acquises sous ventilation mécanique)

est très élevée si le traitement initial n'est pas adapté,

même lorsque ce traitement est adapté secondairement

Alvarez-Lerma F et al. *Intensive Care Med* 1996.
Luna CM et al. *Chest* 1997.
Rello et al. *Am J Resp Crit Care Med* 1997.
Kollef et Ward. *Chest* 1998.
Iregui M et al. *Chest* 2002.

Pathogens with Inappropriate Therapy in VAP

Pseudomonas
40-75%

Acinetobacter
20-40%

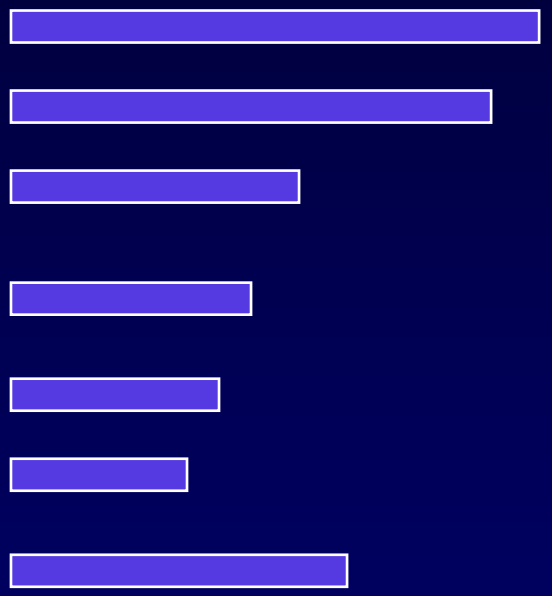
S. aureus
10-40%

Enterobactriaceae
7-20%

Alvarez – Lerma
Kollef

Luna
Rello

Bactéries responsables de pneumonies nosocomiales



S. aureus	32%
P. aeruginosa	29%
Acinetobacter	12%
K. pneumoniae	9%
Enterobacter	8%
E. coli	7%
Levures	13%

EPIIC Study 29 Avril 1992

Bactéries responsables de pneumonies nosocomiales

n = 8891	%	rang 1992	rang 1988	rang 1984
S. aureus	20	1	2	2
P. aeruginosa	16	2	1	1
Enterobacter	11	3	3	4
K. pneumoniae	7	4	4	3
H. influenzae	5	5	6	-
C. albicans	5	6	8	8
Acinetobacter	4	7	10	-
E. coli	4	8	5	5

NNIS Registry 1984-1992

Bactériologie des pneumonies : Importance de l'antibiothérapie antérieure

Bactéries	VM ≤ 7 j ATB non	VM ≤ 7 ATB oui	VM > 7j ATB non	VM >7j ATB oui
P. aer. Acineto (%)	0	24	9	33
Enterobactéries (%)	19	19	22	11
H. influenzae	19	10	3	2
SAMR	0	5	3	20
SAMS	14	0	22	3
Streptococcus	23	24	28	11

Trouillet et coll AJRCCM 1998 , 157 , 531-539

Early-onset vs Late-onset : Days of Hospitalization or Days in the ICU ?

- **420 ICU patients :**

  -235 : « early-onset » (≤96h) (48,5% hospitalized ≥ 24h before ICU admission . 77.9% received antibiotics)

  - 185 : late-onset (>96h)

Organisms	«Early-onset » (n=235)	Late-onset (n=185)	p
P.aeruginosa	25%	38,5%	0.003
MSSA	18%	11%	0.043
MRSA	18%	21%	
S. maltophilia	7%	11%	
Enterobacter spp	10%	10%	
H. influenzae	6%	3%	
K. pneumoniae	6%	6%	
Candida	5%	4%	

Ibrahim et al Chest 2000, 117, 1434-42

Variations in Etiology of VAP across Three ICUs

< 7 days, absence of antibiotics

	Barcelona	Montevideo	Séville
P. aeruginosa	2	1	0
A. baumanii	0	4	2
MRSA	0	0	0
Enterobacteriaceae	*3*	5	3
H. influenzae	10	5	4
MSSA	14	7	2
S. pneumoniae	8	7	1

J. Rello et al AJRCCM 1999, 160, 608-613

Variations in Etiology of VAP across Three ICUs

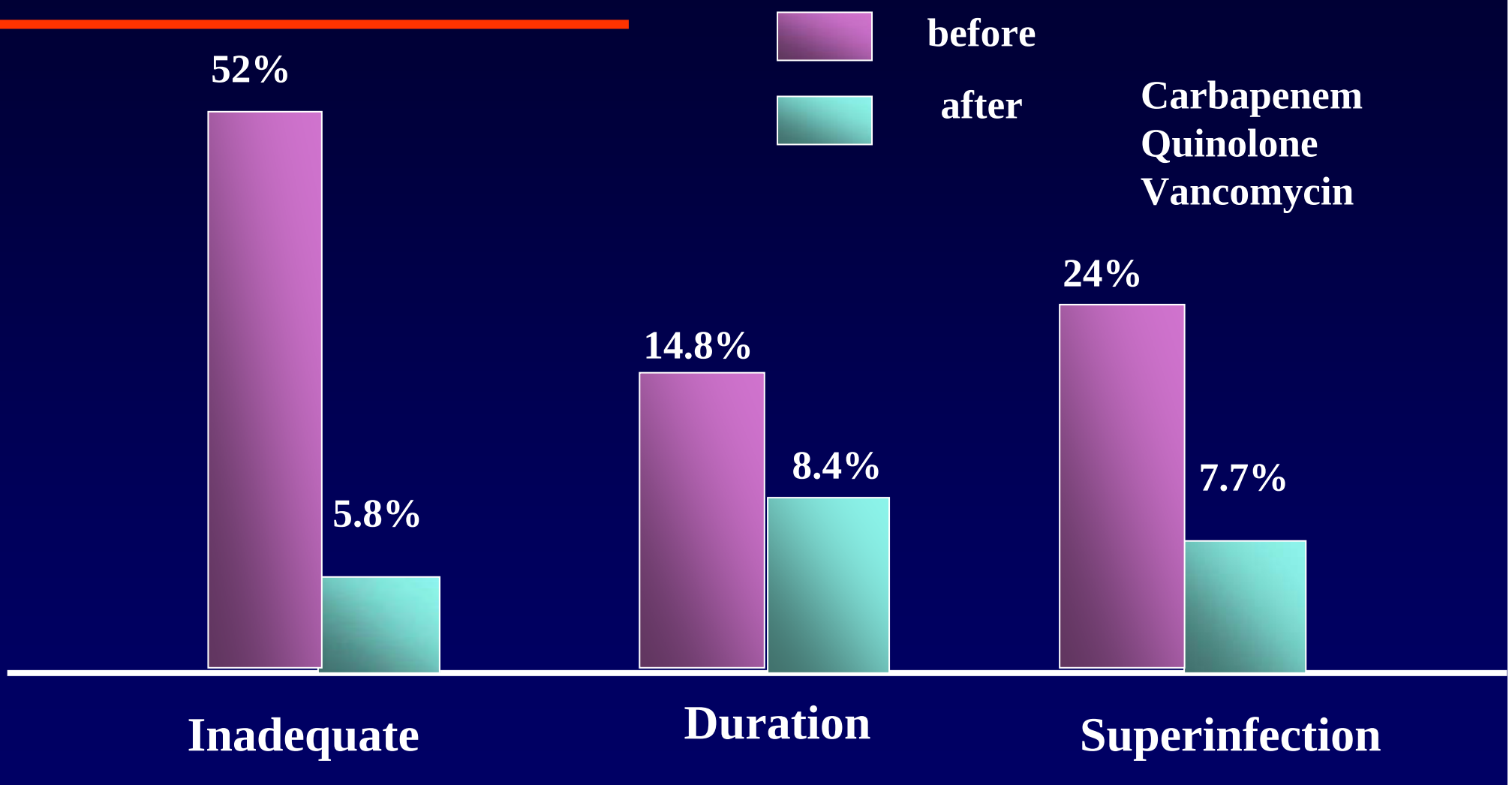
> 7 days, absence of antibiotics

	Barcelona	Montevideo	Séville
P. aeruginosa	48	12	3
A. baumanii	0	11	5
MRSA	1	6	0
Enterobacteriaceae	2	11	13
H. influenzae	0	0	0
MSSA	1	3	2
S. pneumoniae	0	2	3

J. Rello et al AJRCCM 1999, 160, 608-613

Connaître l'écologie locale

Importance of an Adequate protocol



Ibrahim et al Crit Care Med 2001

Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia

This official statement of the American Thoracic Society and the Infectious Diseases Society of America was approved by the ATS Board of Directors, December 2004 and the IDSA Guideline Committee, October 2004

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EXECUTIVE SUMMARY

Since the initial 1996 American Thoracic Society (ATS) guideline on nosocomial pneumonia, a number of new developments have appeared, mandating a new evidence-based guideline for hospital-acquired pneumonia (HAP), including healthcare-associated pneumonia (HCAP) and ventilator-associated pneumonia (VAP). This document, prepared by a joint committee of the ATS and Infectious Diseases Society of America (IDSA), focuses on the epidemiology and pathogenesis of bacterial pneumonia in adults, and emphasizes modifiable risk factors for infection. In addition, the microbiology of HAP is reviewed, with an emphasis on multidrug-resistant (MDR) bacterial pathogens, such as *Pseudomonas aeruginosa*, *Acinetobacter* species, and methicillin-resistant *Staphylococcus aureus*. Controversies about diagnosis are discussed, emphasizing initial examination of lower respiratory tract samples for bacteria, and the rationale for both clinical and bacteriologic approaches, using either "semiquantitative" or "quantitative" microbiologic methods that help direct selection of appropriate antibiotic therapy. We also provide recommendations for additional diagnostic and therapeutic evaluations in patients with nonresolving pneumonia. This is an evidence-based document that emphasizes the issues of VAP, because there are far fewer data available about HAP in nonintubated patients and about HCAP. By extrapolation, patients who are not intubated and mechanically ventilated should be managed like patients with VAP, using the same approach to identify risk factors for infection with specific pathogens.

The major goals of this evidence-based guideline for the management of HAP, VAP, and HCAP emphasize early, appropriate antibiotics in adequate doses, while avoiding excessive antibiotics by de-escalation of initial antibiotic therapy, based on microbiologic cultures and the clinical response of the patient, and shortening the duration of therapy to the minimum effective period. The guideline recognizes the variability of bacteriology from one hospital to another and from one time period to another and recommends taking local microbiologic data into account when adapting treatment recommendations to any specific clinical setting. The initial, empiric antibiotic therapy algorithm includes two groups of patients: one with no need for broad-spectrum therapy, because these patients have early-onset HAP, VAP, or HCAP and no risk factors for MDR pathogens, and a second group that requires broad-spectrum therapy, because of late-onset pneumonia or other risk factors for infection with MDR pathogens.

Some of the key recommendations and principles in this new, evidence-based guideline are as follows:

- HCAP is included in the spectrum of HAP and VAP, and patients with HCAP need therapy for MDR pathogens.
- A lower respiratory tract culture needs to be collected from all patients before antibiotic therapy, but collection of cultures should not delay the initiation of therapy in critically ill patients.
- Either "semiquantitative" or "quantitative" culture data can be used for the management of patients with HAP.
- Lower respiratory tract cultures can be obtained broncho-

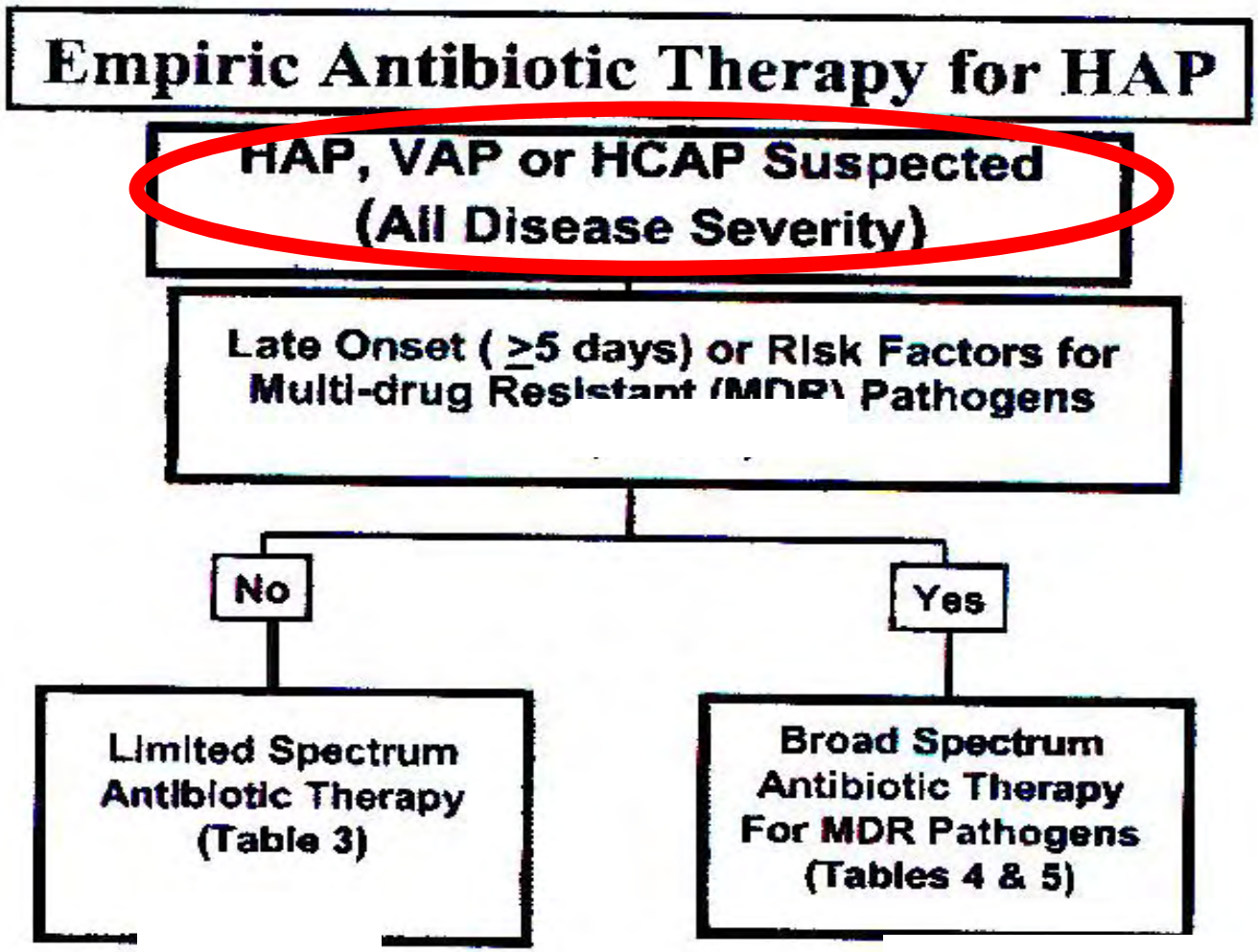
Am J Respir Crit Care Med Vol 171. pp 388–416, 2005
DOI: 10.1164/rccm.200405-644ST
Internet address: www.atsjournals.org

Reprinted from American Journal of Respiratory and Critical Care Medicine
Vol. 171, No. 4, January 2005, pages 388-416

American Thoracic Society Documents

TABLE 2. RISK FACTORS FOR MULTIDRUG-RESISTANT PATHOGENS CAUSING HOSPITAL-ACQUIRED PNEUMONIA, HEALTHCARE-ASSOCIATED PNEUMONIA, AND VENTILATOR-ASSOCIATED PNEUMONIA

- Antimicrobial therapy in preceding 90 d
- Current hospitalization of 5 d or more
- High frequency of antibiotic resistance in the community or in the specific hospital unit
- Presence of risk factors for HCAP:
  - Hospitalization for 2 d or more in the preceding 90 d
  - Residence in a nursing home or extended care facility
  - Home infusion therapy (including antibiotics)
  - Chronic dialysis within 30 d
  - Home wound care
  - Family member with multidrug-resistant pathogen
- Immunosuppressive disease and/or therapy


Empiric Antibiotic Therapy for HAP
HAP, VAP or HCAP Suspected
(All Disease Severity)
Late Onset (≥5 days) or Risk Factors for
Multi-drug Resistant (MDR) Pathogens
No
Yes
Limited Spectrum
Antibiotic Therapy
(Table 3)
Broad Spectrum
Antibiotic Therapy
For MDR Pathogens
(Tables 4 & 5)

HAP ATS 2005 .

No risk factors for MRB , early onset .

. **Enterobacteriaciae (non-*Pseudomonas*)**
- ***Enterobacter spp.***
- ***Escherichia coli***
- ***Klebsiella spp.***
- ***Proteus spp.***
- ***Serratia marcescens***

. ***H. influenzae***

. ***S. aureus*** **MS**

. ***Streptococcus pneumoniae***

3rd GC non-anti-pseudomonal

β-lactamin/inhibitor (Augmentin)

Levofloxacin , moxifloxacin , ciprofloxacin

Ertapenem

AJRCCM,2005,171,388-416

HAP ATS 2005 .

Risk factor for MRB or late onset

Organisms

. ***Pseudomonas aeruginosa***

. ***K pneumoniae (ESBL)***

. ***Acinetobacter spp***

. **MRSA**

. ***L. pneumophila***

AMG

or

Ciprofloxacin or levofloxacin

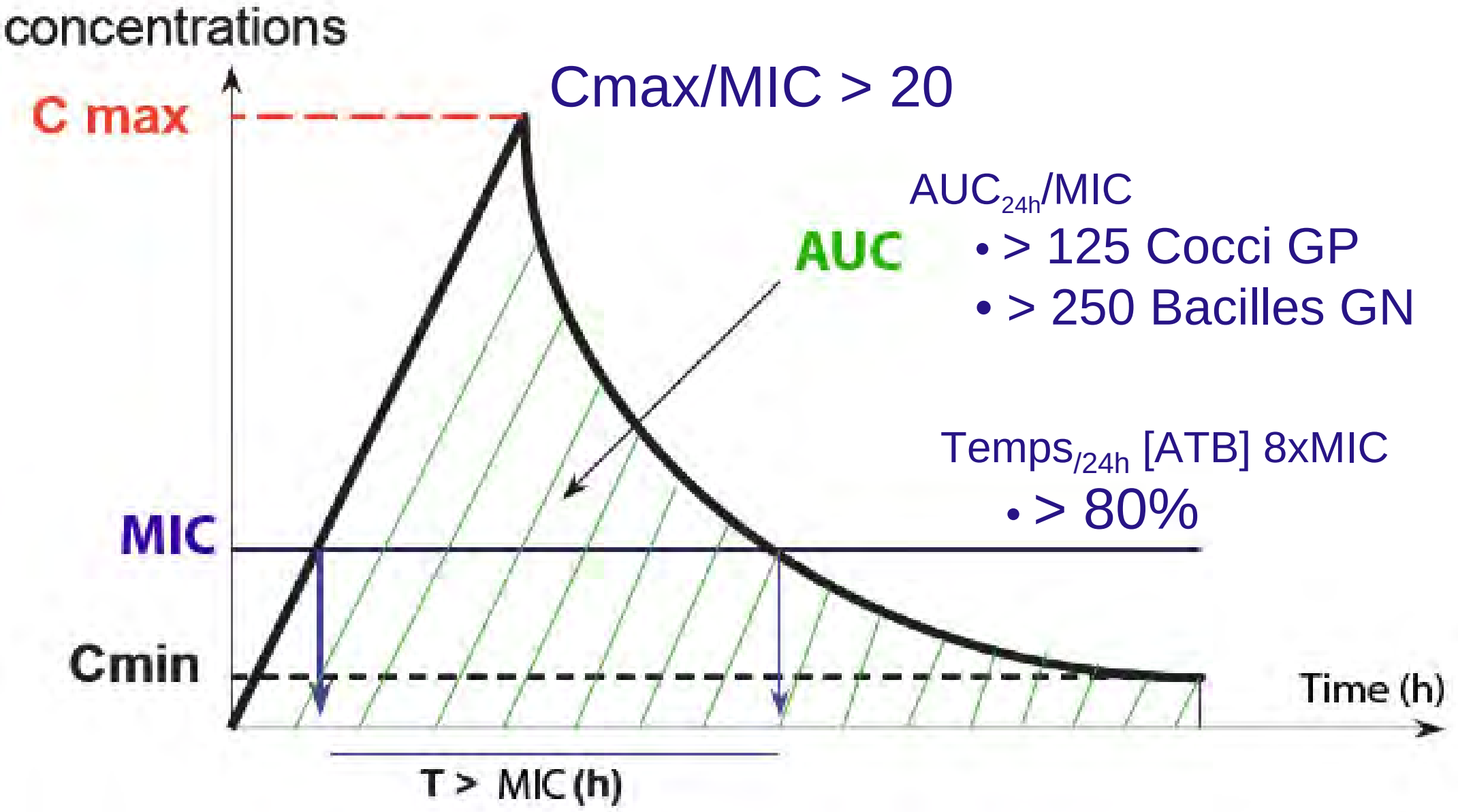
+

- **β-lactamin/Inhibitor (Pip- tazo)**
- **ceftazidime,cefepime**
- **imipenem,meropenem**

+

Vancomycin or linezolid

Objectifs pK/pD



Cmax/MIC > 20

AUC_{24h}/MIC

- > 125 Cocci GP
- > 250 Bacilles GN

$Temps_{/24h}$ [ATB] 8xMIC

- > 80%

Koenig SM. Clin Microbiol Rev 2006;19:637

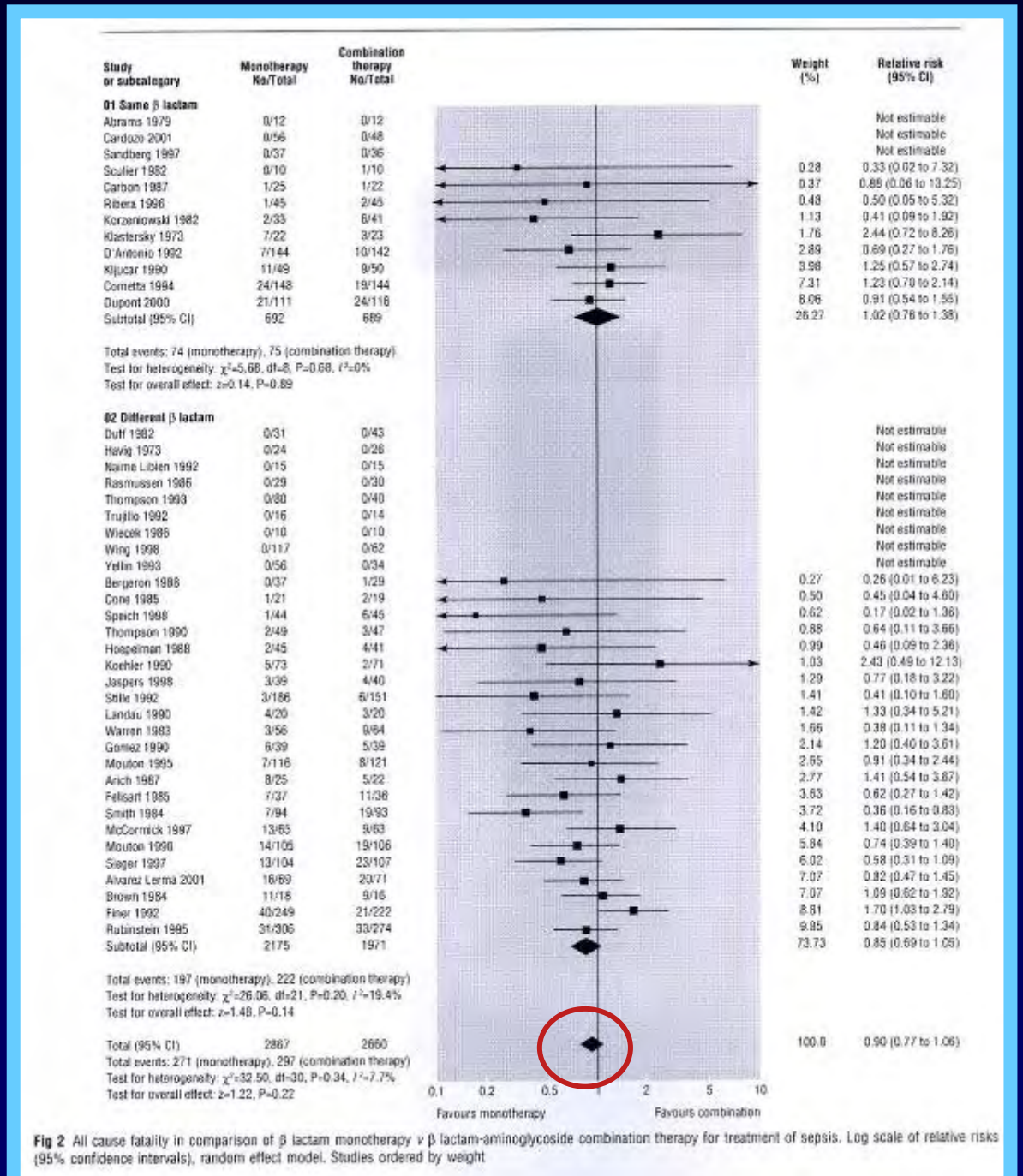
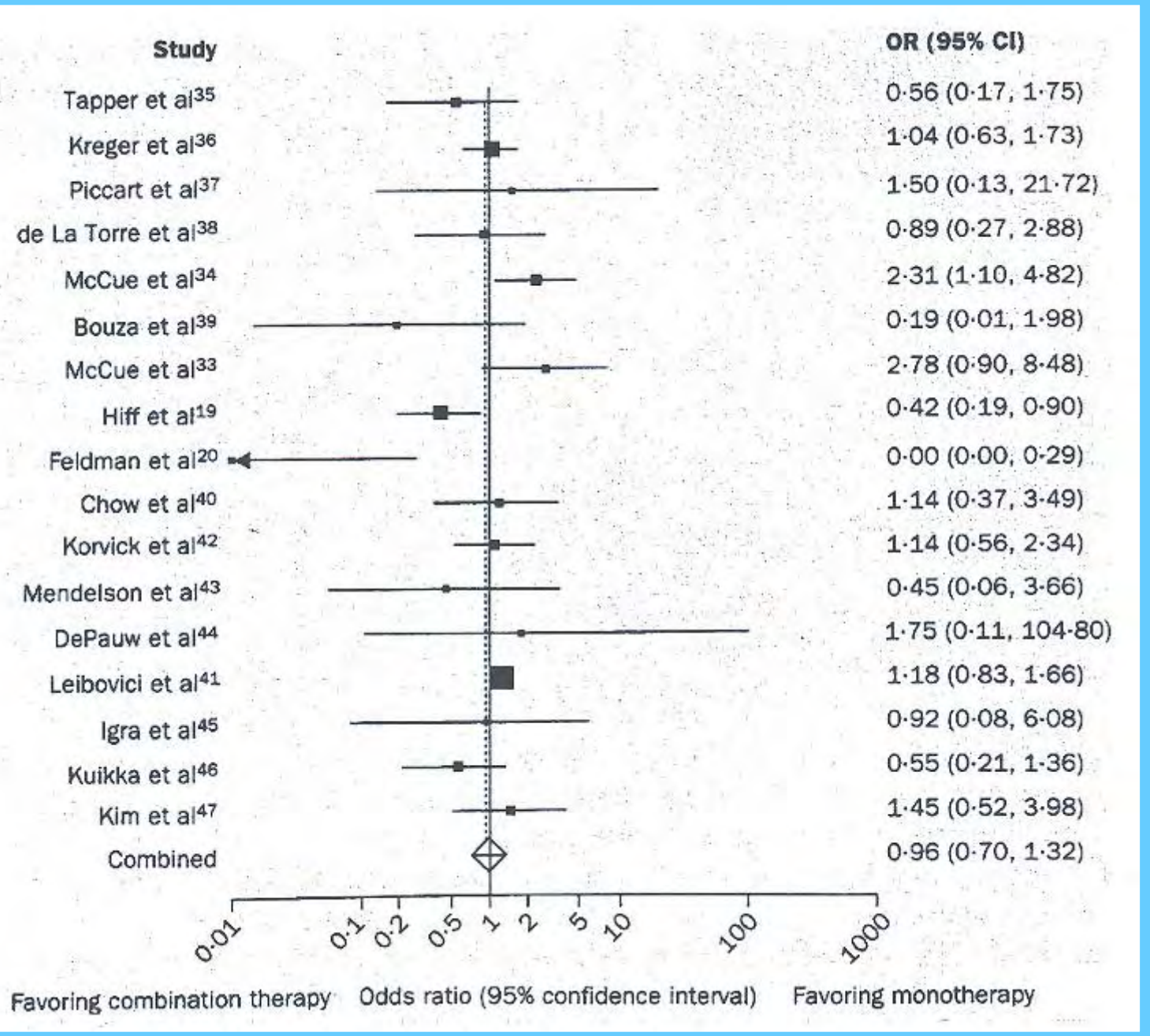


Fig 2 All cause fatality in comparison of β lactam monotherapy *v* β lactam-aminoglycoside combination therapy for treatment of sepsis. Log scale of relative risks (95% confidence intervals), random effect model. Studies ordered by weight

All cause fatality :

β-lactam or β-lactam + AMG in Immunocompetent Patients

Paul et al BMJ 2004, Online First bmj.com



Bacteremia : All cause fatality

Safdar et al
Lancet ID 2004 , 4
519-527

Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia*

Daren K. Heyland, MD; Peter Dodek, MD; John Muscedere, MD; Andrew Day, MSc; Deborah Cook, MD; for the Canadian Critical Care Trials Group

Objective: To compare a strategy of combination therapy with a strategy of monotherapy with broad-spectrum antibiotics for suspected late ventilator-associated pneumonia.

Design: Randomized trial.

Setting: Twenty-eight intensive care units in Canada and the United States.

Patients: The study included 740 mechanically ventilated patients who developed suspected ventilator-associated pneumonia after 96 hrs in the intensive care unit. Patients known to be colonized or infected with *Pseudomonas* or methicillin-resistant *Staphylococcus aureus* or who were immunocompromised were excluded from the study.

Interventions: As initial unblinded therapy, patients were allocated to receive meropenem (1 g every 8 hrs) and ciprofloxacin (400 mg every 12 hrs) or meropenem alone. Before starting antibiotics, patients were also randomized to bronchoalveolar lavage with quantitative cultures or endotracheal aspirates. When culture results were available, physicians were encouraged to adjust antibiotics. Adequacy of antibiotics was defined as the organism present in the enrollment culture having *in vitro* susceptibility to one or more of the study antibiotics.

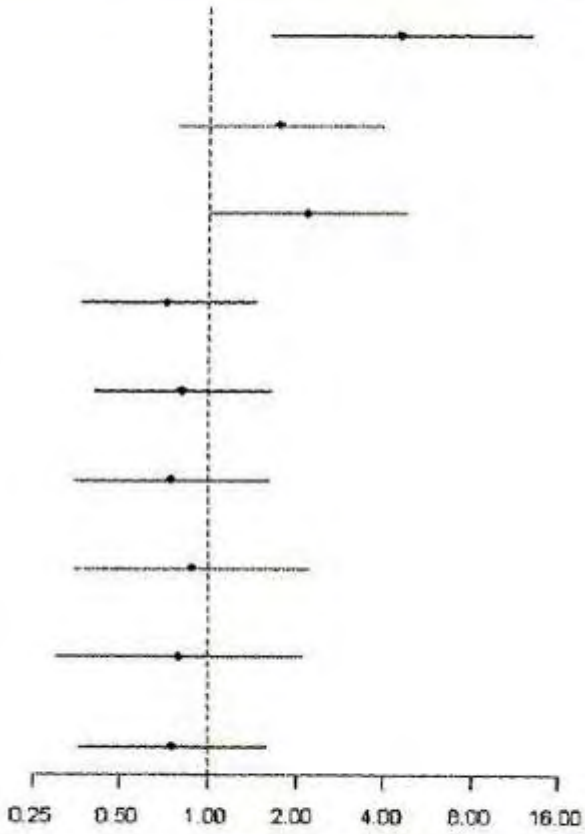
Measurements and Main Results: Baseline characteristics and etiologies of ventilator-associated pneumonia were similar in the two groups. There was no difference in 28-day mortality between the combination and monotherapy groups (relative risk = 1.05, 95% confidence interval 0.78–1.42, $p = .74$). Duration of intensive care unit and hospital stay, clinical and microbiological treatment response, emergence of antibiotic-resistant bacteria, isolation of *Clostridium difficile* in stool, and fungal colonization were also similar in the two groups. In a subgroup of patients who had infection due to *Pseudomonas* species, *Acinetobacter* species, and multidrug-resistant Gram-negative bacilli at enrollment (n = 56), the adequacy of initial antibiotics (84.2% vs. 18.8%, $p < .001$) and microbiological eradication of infecting organisms (64.1% vs. 29.4%, $p = .05$) was higher in the combination group compared with the monotherapy group, but there were no differences in clinical outcomes.

Conclusions: For critically ill patients who have suspected late ventilator-associated pneumonia and who are at low risk for difficult-to-treat Gram-negative bacteria, monotherapy is associated with similar outcomes compared with combination therapy. For those patients at high risk of difficult-to-treat Gram-negative bacteria, combination therapy is safe and may be associated with better microbiological and clinical outcomes. (Crit Care Med 2008; 36:737–744)

Key Words: ventilator-associated pneumonia; antibiotics; empirical therapy; combination therapy; randomized controlled trial; outcomes; broad spectrum antimicrobials

Table 6. Subgroup analysis of patients with difficult-to-treat Gram-negative bacilli on enrollment (*Pseudomonas* species, *Acinetobacter* species, and other multidrug-resistant Gram-negative bacilli)

	Combination Therapy (n = 39)	Monotherapy (n = 17)	Combo/Mono RR (95% CI)[a]
Adequacy of empiric therapy, n (%)[b]	32 (84.2)	3 (18.8)	
Clinical resolution at 28 days, n (%)	20 (51.3)	5 (29.4)	
Microbiological resolution at 28 days, n (%)[c]	25 (64.1)	5 (29.4)	
Duration of mechanical ventilation[d]	10.7 (3.3, .)	15.0 (9.3, .)	
Duration of ICU stay[d]	14.2 (8.1, .)	21.2 (14.1, .)	
Duration of hospital stay[d]	55.0 (33.0, .)	111.4 (27.8, .)	
28-day mortality, n (%)	10 (25.6)	5 (29.4)	
ICU mortality, n (%)	9 (23.1)	5 (29.4)	
Hospital mortality, n (%)	13 (33.3)	7 (41.2)	



RR, relative risk; CI, confidence interval; ICU, intensive care unit.

[a]RR and 95% CI are adjusted for Acute Physiology and Chronic Health Evaluation II score and diagnostic technique by the stratified Mantel-Haenszel method for binary outcomes and the proportional hazards model for duration outcomes; [b]adequacy of therapy not available for one patient in each group, n = 38 for combination group, n = 16 for monotherapy group ($p < .001$); [c]$p = .014$; [d]median (interquarile range): The upper quartile range of the time to discharge is undefined for both groups because >25 of patients did not achieve the particular event.

Empiric antibiotic therapy for suspected ventilator-associated pneumonia: A systematic review and meta-analysis of randomized trials

Mary-Anne W. Aarts, MD, MSc, FRCSC; Jennifer N. Hancock, MD; Daren Heyland, MD, MSc, FRCPC; Robin S. McLeod, MD, FRCSC; John C. Marshall, MD, FRCSC

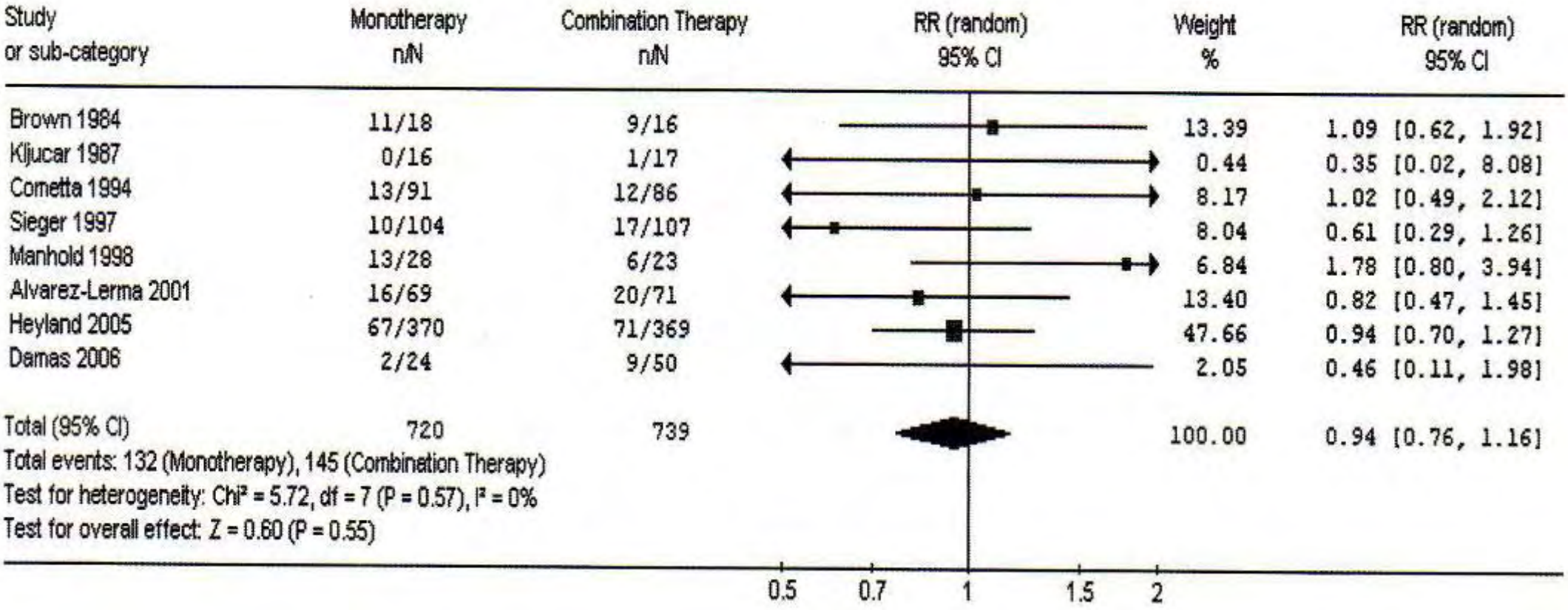
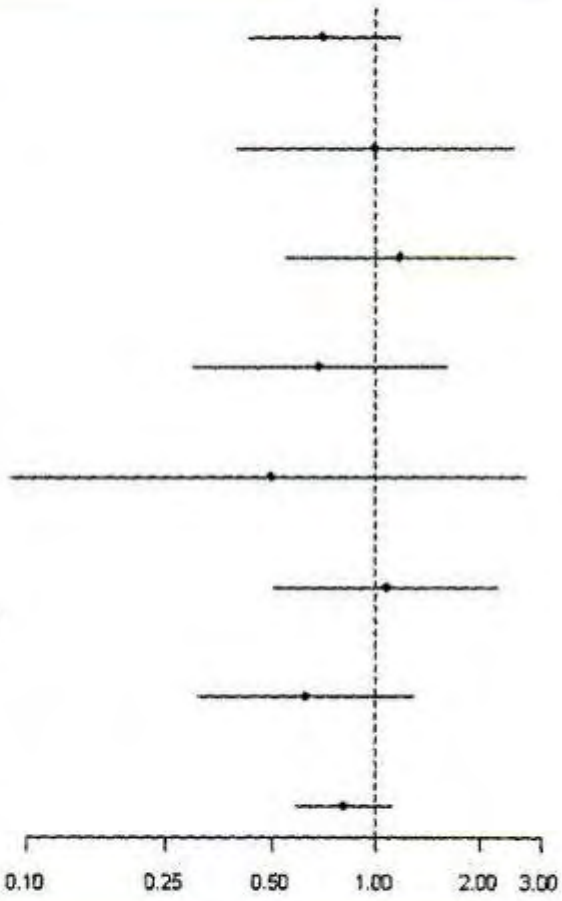


Table 5. Frequency of organisms acquired after randomization

Organism	Combination Therapy (n = 369)	Monotherapy (n = 370)	All (n = 739)	Combo/Mono RR (95% CI)[a]
Pseudomonas species	25 (6.8)	35 (9.5)	60 (8.1)	
Acinetobacter species	9 (2.4)	9 (2.4)	18 (2.4)	
Methicillin-resistant *Staphylococcus aureus*	14 (3.8)	12 (3.2)	26 (3.5)	
Stenotrophomonas maltophilia	9 (2.4)	13 (3.5)	22 (3.0)	
Vancomycin-resistant *Enterococcus*	2 (0.5)	4 (1.1)	6 (0.8)	
Yeast species	14 (3.8)	13 (3.5)	27 (3.7)	
Multidrug-resistant Gram-negative bacteria	12 (3.3)	19 (5.1)	31 (4.2)	
Total high risk[b]	57 (15.4)	71 (19.2)	128 (17.3)	



RR, relative risk; CI, confidence interval.

[a]RR and 95% CI estimated by the Mantel-Haenszel method stratified by Acute Physiology and Chronic Health Evaluation II score (≤24 vs. >24) and diagnostic technique (endotracheal aspirates vs. bronchoalveolar lavage); [b]includes *Acinetobacter* species, *Pseudomonas* species, methicillin-resistant *S. aureus, S. maltophilia* and multiresistant organisms. They do not add up to the individual row totals, because some of the *Pseudomonas* species and *Acinetobacter* species are multidrug-resistant pathogens as well. Values are n (%).

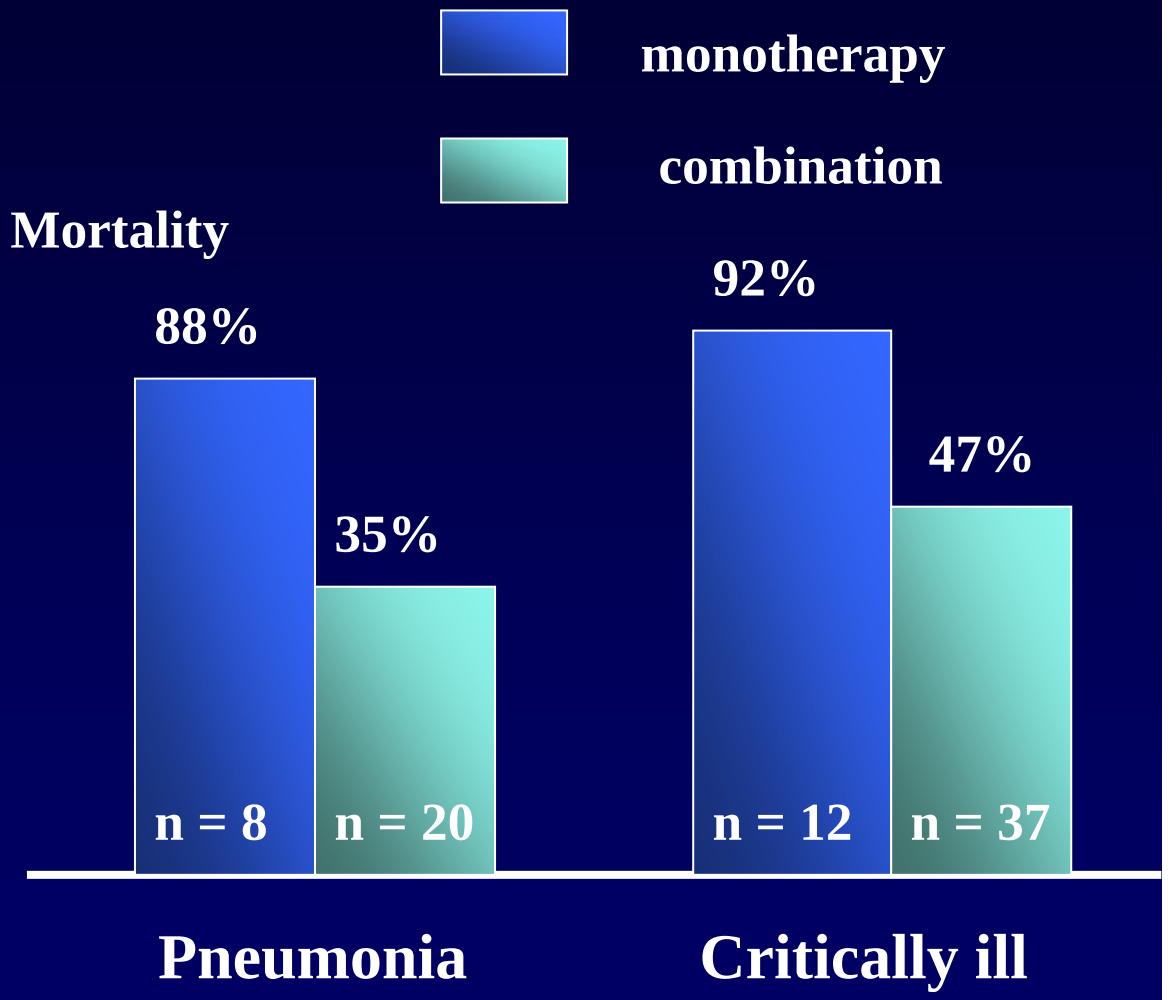
P. aeruginosa Bacteremia : Monotherapy or Combination ?

	Mortality		
	Combination	Monotherapy	P
All (n= 186)	27%	47%	0.02
Nosocomial infections (n = 143)	32%	51%	0.04
Pneumonia (n = 28)	35%	88%	0.03
Shock, coma (n = 49)	47%	92%	0.01
Neutropenia (n = 49)	37%	57%	NS

Hilf et al. Am. J. Med 1989, 87,540

Pseudomonas : Combination?

200 patients with bacteremia
Only two received CAZ or IMP
No benefit of synergistic vs not



Hilf et al Am J Med 1989

β-lactam or β-lactam + AMG in Immunocompetent Patients (P. aeruginosa)

All cause fatality
(2 studies, 29 patients)

RR 1.5 (0.07-32.84)

Clinical failure
(12 studies, 302 patients)

RR 1.9 (0.65-1.83)

Paul et al BMJ 2004, Online First bmj.com

Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: An observational, multicenter study comparing monotherapy with combination antibiotic therapy*

Jose Garnacho-Montero, MD, PhD; Marcio Sa-Borges, MD; Jordi Sole-Violan, MD; Fernando Barcenilla, MD; Ana Escoresca-Ortega, MD; Miriam Ochoa, MD; Aurelio Cayuela, MD, PhD, MPH; Jordi Rello, MD, PhD

Objective: To evaluate whether one antibiotic achieves equal outcomes compared with combination antibiotic therapy in patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia.

Design: A retrospective, multicenter, observational, cohort study.

Setting: Five intensive care units in Spanish university hospitals.

Patients: Adult patients identified to have monomicrobial episodes of ventilator-associated pneumonia with significant quantitative respiratory cultures for *P. aeruginosa.*

Interventions: None.

Measurement and Main Results: A total of 183 episodes of monomicrobial *P. aeruginosa* ventilator-associated pneumonia were analyzed. Monotherapy alone was used empirically in 67 episodes, being significantly associated with inappropriate therapy (56.7% vs. 90.5%, $p < .001$). Hospital mortality was significantly higher in the 40 patients with inappropriate therapy compared with those at least on antibiotic with activity *in vitro* (72.5% vs. 23.1%, $p < .05$). Excess mortality associated with monotherapy was estimated to be 13.6% (95% confidence interval 2.6 to 29.9). The use of monotherapy or combination therapy in the definitive regimen did not influence mortality, length of stay, development of resistance to the definitive treatment, or appearance of recurrences. Inappropriate empirical therapy was associated with increased mortality (adjusted hazard ratio 1.85; 95% confidence interval 1.07–3.10; $p = .02$) in a Cox proportional hazard regression analysis, after adjustment for disease severity, but not effective monotherapy (adjusted hazard ratio 0.90; 95% confidence interval 0.50–1.63; $p = .73$) compared with effective combination therapy (adjusted hazard ratio 1). The other two variables also independently associated with mortality were age (adjusted hazard ratio 1.02; 95% confidence interval 1.01–1.04; $p = .005$) and chronic cardiac insufficiency (adjusted hazard ratio 1.90; 95% confidence interval 1.04–3.47, p = .035).

Conclusions: Initial use of combination therapy significantly reduces the likelihood of inappropriate therapy, which is associated with higher risk of death. However, administration of only one effective antimicrobial or combination therapy provides similar outcomes, suggesting that switching to monotherapy once the susceptibility is documented is feasible and safe. (Crit Care Med 2007; 35:1888–1895)

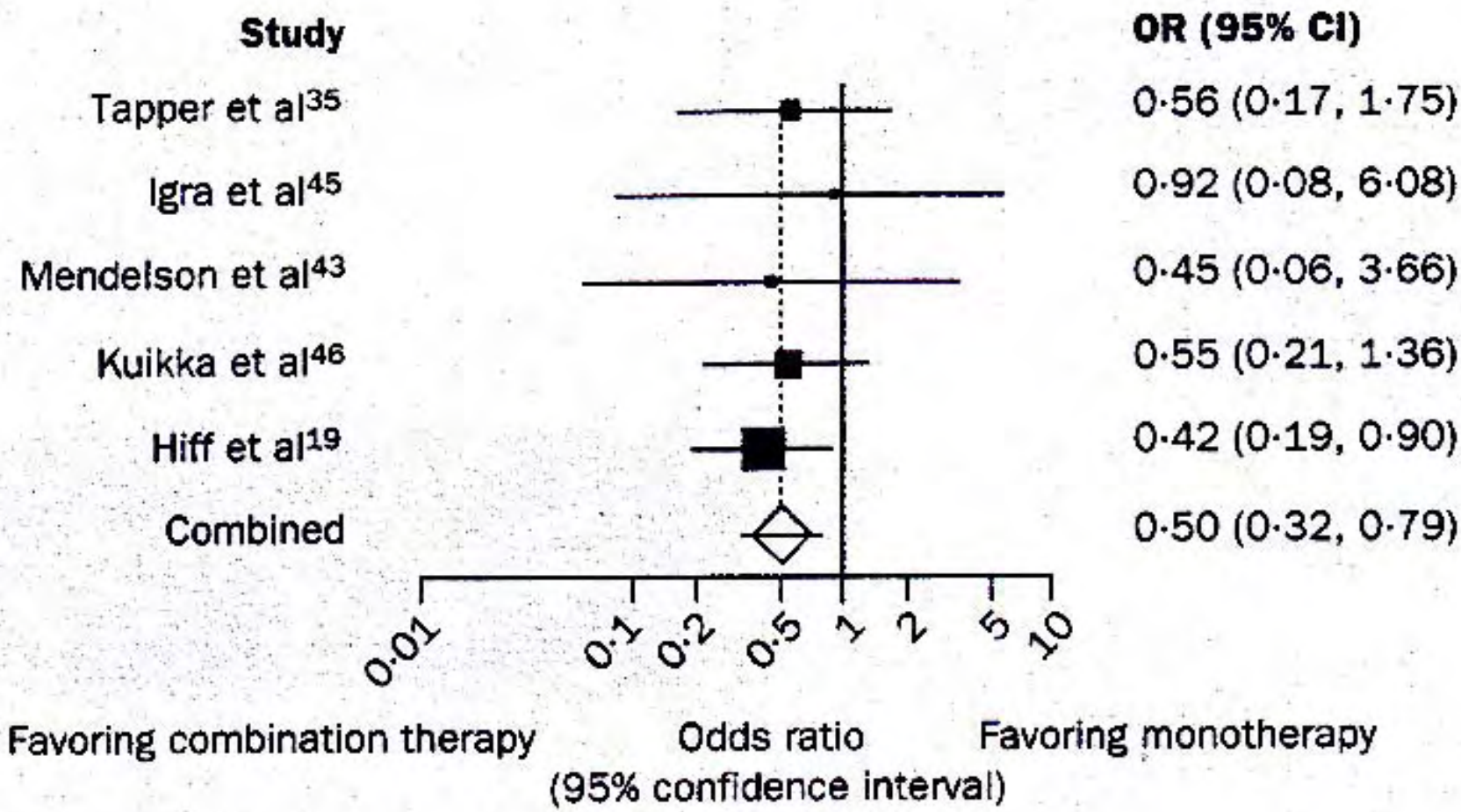
KEY WORDS: ventilator-associated pneumonia; *Pseudomonas aeruginosa*; antimicrobial therapy; mortality

Table 5. Variables independently associated with mortality using Cox proportional regression analysis

	aHR	95% CI	*p*
Age	1.02	1.01–1.04	.005
Chronic cardiac failure	1.90	1.04–3.47	.035
Effective empirical therapy			.02
Combined therapy	1		
Monotherapy	0.90	0.50–1.63	.73
Inappropriate therapy	1.85	1.07–3.10	.02

aHR, adjusted hazard ratio; CI, confidence interval.

Pseudomonas Bacteremia



Safdar et al Lancet ID 2004 , 4 , 519-527

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Advance Access publication 31 May 2007

JAC

Efficacy of ertapenem in the treatment of early ventilator-associated pneumonia caused by extended-spectrum β-lactamase-producing organisms in an intensive care unit

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Objectives: Ventilator-associated pneumonia (VAP) is a frequent complication of patients admitted to intensive care units (ICUs). Ertapenem is a newer carbapenem with good *in vitro* activity against extended-spectrum β-lactamase (ESBL)-producing organisms. However, there are no clinical data to support the use of ertapenem in VAP. Our purpose is to evaluate the usefulness and safety of ertapenem in the treatment of VAP caused by susceptible ESBL strains.

Methods: Ertapenem 1 g daily intravenously was given to adult patients with signs and symptoms of VAP beginning within 7 days of mechanical ventilation and caused by ESBL-producing Gram-negative organisms.

Results: From June 2005 to June 2006, we enrolled 20 adult patients hospitalized in an ICU and diagnosed with VAP due to Gram-negative ESBL strains. Causative organisms identified as ESBL producers susceptible to ertapenem were *Klebsiella pneumoniae* (alone in 10 cases and with methicillin-resistant *Staphylococcus aureus* in 4 cases), *Enterobacter cloacae* (2), *Proteus mirabilis* (2) and *Citrobacter freundii* (2). Clinical success was achieved in 16/20 (80%) of the clinically evaluable patients and in 15/20 (75%) of the microbiologically evaluable patients. The drug was well-tolerated; one patient presented a transient increase in liver enzymes.

Conclusions: We believe this is one of the first reports to demonstrate that ertapenem has clinical utility in treating serious infections caused by ESBL-producing organisms. Ertapenem appears to be suitable for ESBL VAP therapy. This pilot study suggests subsequent controlled randomized trials in this indication.

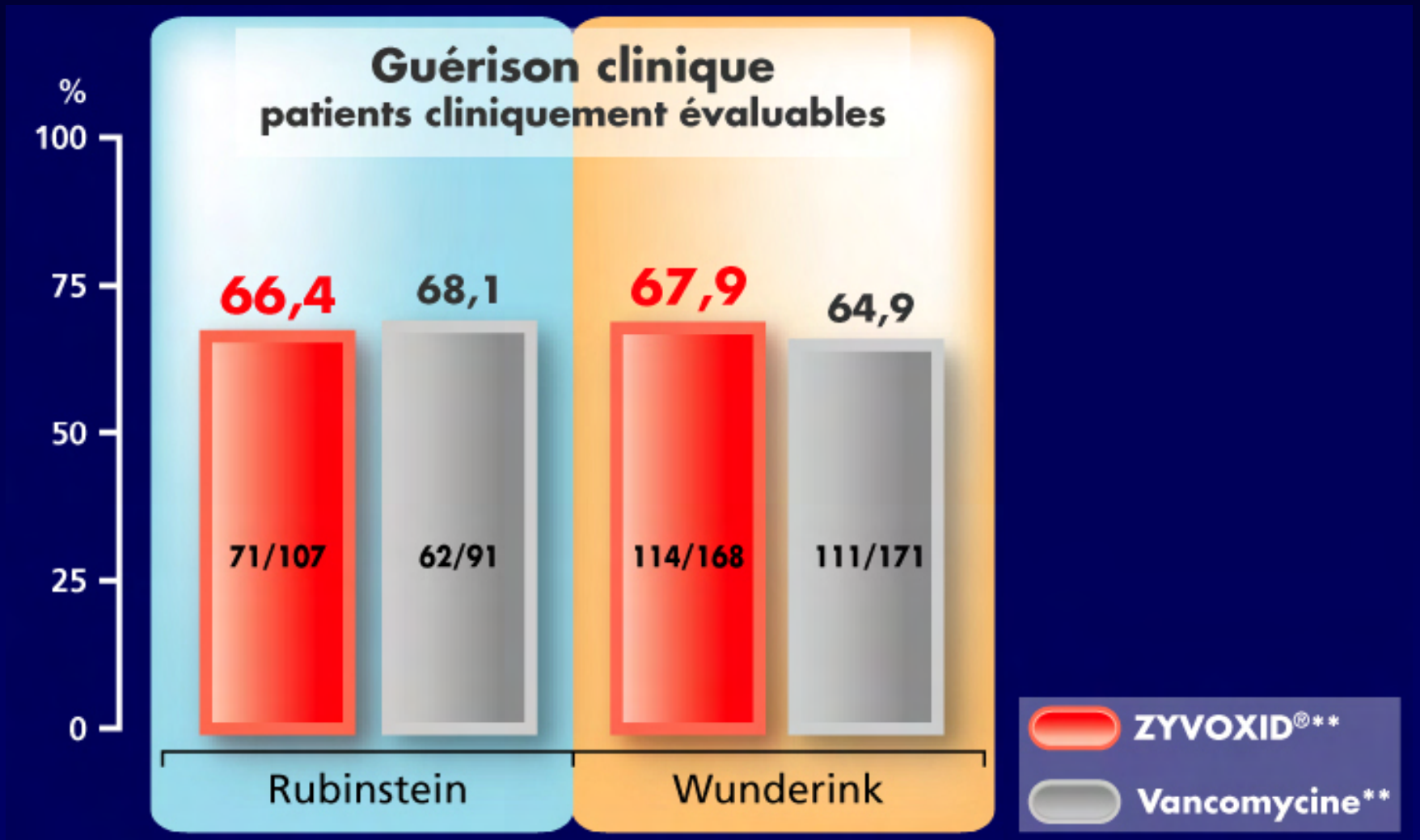
Synercid® (quinopristine - dalfopristine) ? (± aztreonam ou tobramycine)

298 patients de réanimation

	Synercid® (7,5mg/kg/j)	Vancomycine (2g/j)
Guéris/améliorés	56,3%	58,3%
Eradication	57%	59%
Effets secondaires	15,3%	9,5%

Fagon et coll AJRCCM 2000, 161, 753-762

Linézolide : études de phase III

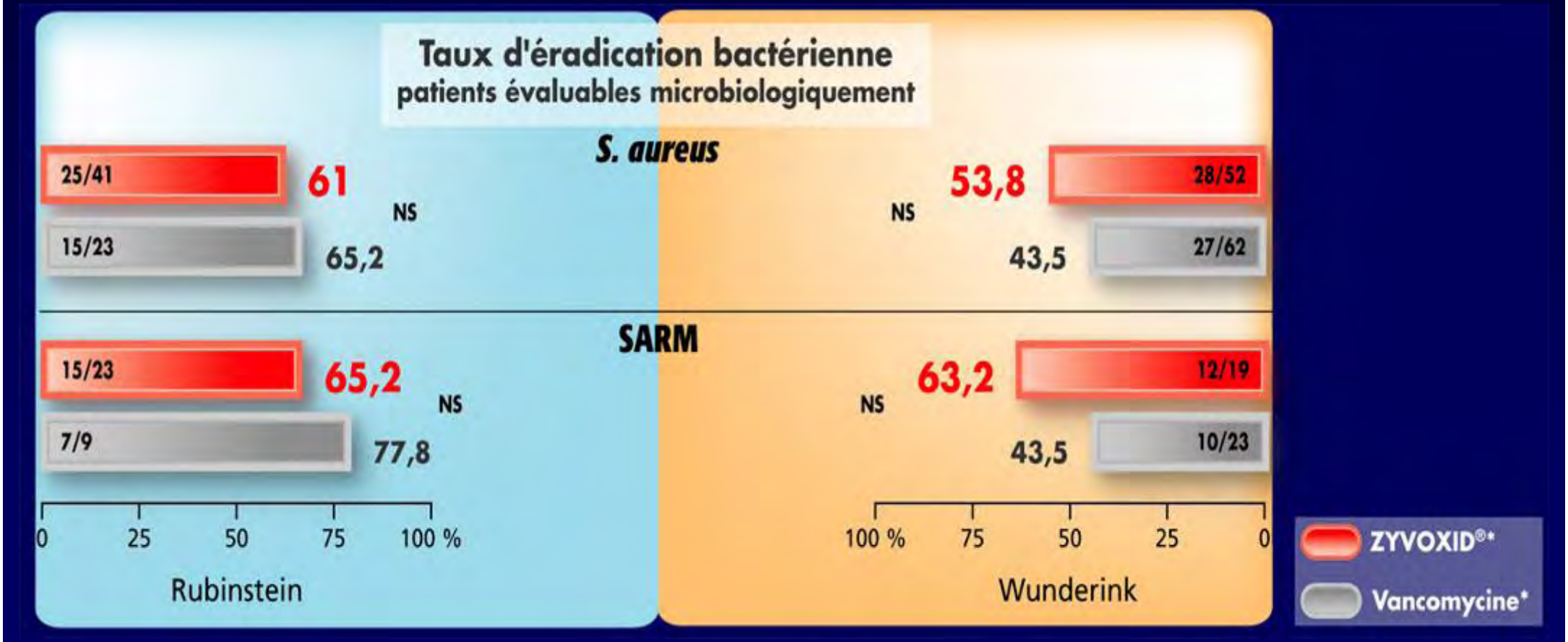


** + aztréonam 1-2 g/8 h si bacille à Gram - documenté ou suspecté.

1) Rubinstein E et al. *CID* 2001. 2) Wunderink RG et al. *Clin Ther* 2003.

Linézolide : études de phase III

- Taux d'éradication bactériologique du staphylocoque chez les patients évaluables microbiologiquement



* + aztréonam 1-2 g/8 h si bacille à Gram - documenté ou suspecté.

1) Rubinstein E et al. *CID* 2001. 2) Wunderink RG et al. *Clin Ther* 2003.

Early Experience with Tigecycline for Ventilator-Associated Pneumonia and Bacteremia Caused by Multidrug-Resistant *Acinetobacter baumannii*

Jason J. Schafer, Pharm.D., Debra A. Goff, Pharm.D., FCCP, Kurt B. Stevenson, M.D., M.P.H., and Julie E. Mangino, M.D.

Study Objective. To evaluate early experience with tigecycline alone or in combination with other antimicrobials for treatment of ventilator-associated pneumonia (VAP) and/or bacteremia caused by multidrug-resistant *Acinetobacter baumannii*.

Design. Retrospective case series.

Setting. University-affiliated medical center.

Patients. Twenty-five patients with multidrug-resistant *A. baumannii* who received tigecycline for VAP (19 patients), bacteremia (3), or VAP plus bacteremia (3) between September 1, 2005, and May 31, 2006. Five patients were treated with tigecycline alone.

Measurements and Main Results. Primary outcomes were resolution of clinical signs and symptoms of the infection and documented microbial eradication of *A. baumannii* with tigecycline. Overall, 21 (84%) of the 25 patients had clinical resolution. Four had clinical failure: three with VAP and one with VAP plus bacteremia that developed resistance to tigecycline during therapy. Microbial eradication was demonstrated in 12 (80%) of 15 patients in whom repeat cultures were obtained. Three patients with VAP had a recurrence of infection: one patient had two recurrences, and two patients had one recurrence each. All four recurrent episodes led to clinical resolution and microbial eradication. No patients discontinued tigecycline because of adverse events.

Conclusion. Tigecycline was effective in most of these 25 patients when used alone or in combination with other antimicrobials for VAP and/or bacteremia caused by multidrug-resistant *A. baumannii*. The emergence of a resistant strain while one patient was receiving therapy, however, is concerning.

Key Words: tigecycline, multidrug-resistant *Acinetobacter baumannii*, ventilator-associated pneumonia, VAP, bacteremia.

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JAC

Administration of antimicrobials via the respiratory tract for the treatment of patients with nosocomial pneumonia: a meta-analysis

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***Background*: Aerosolized antibiotics are a widely recognized treatment for patients with cystic fibrosis (CF). We sought to clarify their role in the treatment of non-CF patients with nosocomial pneumonia by performing a meta-analysis of randomized controlled trials (RCTs) that compared administration of antimicrobials via the respiratory tract (with or without concurrent usage of systemic antibiotics) with control treatment.**

***Methods*: An extensive search of PubMed, Scopus, Cochrane Central Register of Controlled Trials, Current Contents and bibliographies from retrieved publications was made.**

***Results*: Five RCTs were included in the meta-analysis. Administration of antimicrobials via respiratory tract (either inhaled or endotracheally instilled) as opposed to control was associated with better treatment success in intention-to-treat [fixed effect model: odds ratio (OR) = 2.39, 95% confidence interval (CI) 1.29–4.44; random effects model: OR = 2.75, 95% CI 1.06–7.17] and in clinically evaluable patients (fixed effect model: OR = 3.14, 95% CI 1.48–6.70; random effects model: OR = 3.07, 95% CI 1.15–8.19). There were no statistically significant differences between therapeutic regimens regarding all-cause mortality (fixed effect model: OR = 0.84, 95% CI 0.43–1.64; random effects model: OR = 0.71, 95% CI 0.27–1.88), microbiological success (fixed effect model: OR = 2.06, 95% CI 0.91–4.68; random effects model: OR = 2.23, 95% CI 0.64–7.71) and toxicity (fixed effect model: OR = 0.34, 95% CI 0.04–2.55; random effects model: OR = 0.36, 95% CI 0.04–3.16).**

***Conclusions*: The limited available evidence seems not to preclude a benefit from the administration of antimicrobial agents via the respiratory tract for treating nosocomial pneumonia.**

Pneumonies nosocomiales à *Candida*

- **Patients de réanimation décédés**
- **Patients non-neutropéniques**
- **Biopsies pulmonaires et prélèvements bronchiques**

Candida	
Retrouvés à la biopsie	40% des patients
% germes isolés	9%
Responsable de la pneumonie	8 %

El-Ebiary et coll AJRCCM 1997, 156, 583-590.

Bactéries anaérobies

- Patients de réanimation ventilés
- Brossage
- Recherche systématique sur milieux adaptés
- Anaérobies retrouvés dans 23% des pneumonies
  - *Prevotella melaninogenica* 36%
  - *Fusobacterium nucleatum* 17%
  - *Veillonella parvula* 12%
- Surtout avant le 5ème jour chez les patients intubés par la bouche

Dore et coll AJRCCM 1996, 153, 1292-1298.

Bactéries anaérobies

- Patients de réanimation ventilés (143)
- 185 épisodes de pneumonies
- 25 patients avec pneumonie d'inhalation

➔ 1/210 prélèvements avec une bactérie anaérobie !!!

Marik et coll, Chest 1999, 115, 178-183

Antibiothérapie probabiliste

Contrat avec le patient :

- Proposer l ′antibiothérapie la plus efficace possible.

Contrat avec la communauté :

Dès que possible retourner vers une antibiothérapie

. à spectre étroit

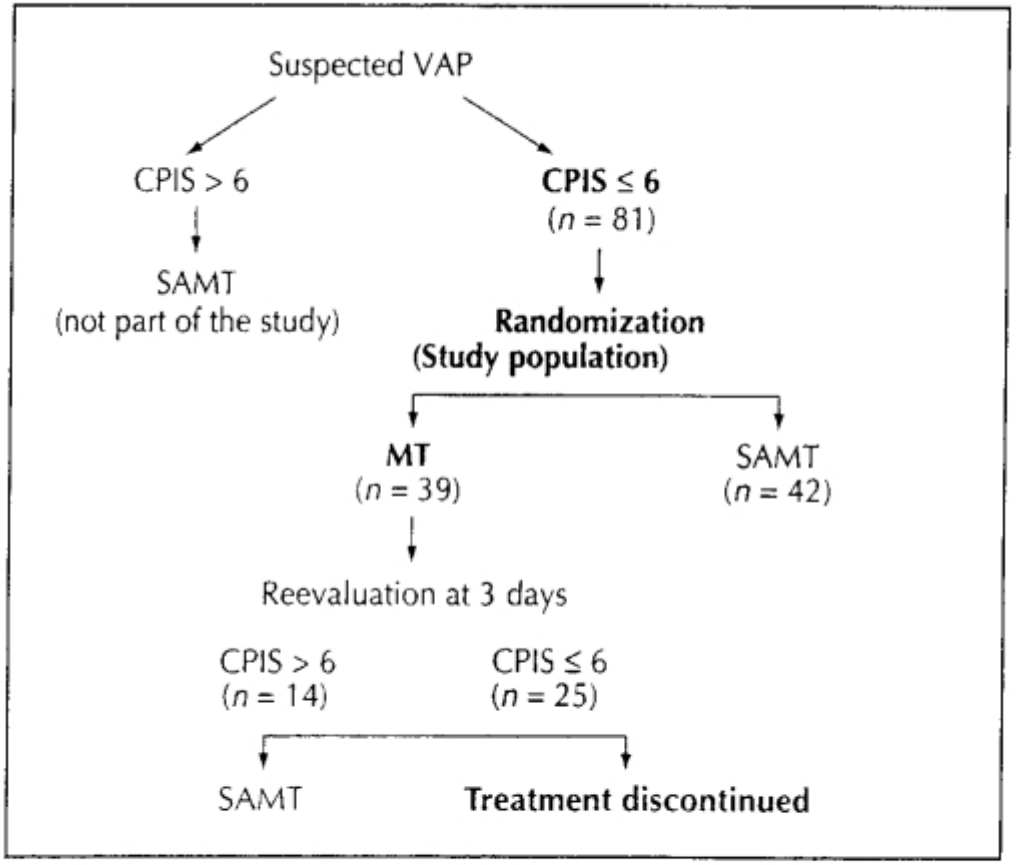
. moins cher

. avec le minimum d ′impact sur l ′écologie bactérienne.

… ou arrêter le traitement antibiotique … !!!

Singh et coll, AJRCCM 2000, 162, 505-511

Figure 1. Study design



Design of the study by Singh *et al.* [75]. CPIS, clinical pulmonary infection score according to Pugin *et al.* [76]; SAMT, standard antimicrobial treatment (length and choice of antimicrobial regimen at the discretion of the attending physician); MT, monotherapy with ciprofloxacin.

SAMT:Standart antimicrobial therapy
MT:Monotherapy with Ciprofloxacine

Durée du traitement

Singh et coll, AJRCCM 2000, 162, 505-511

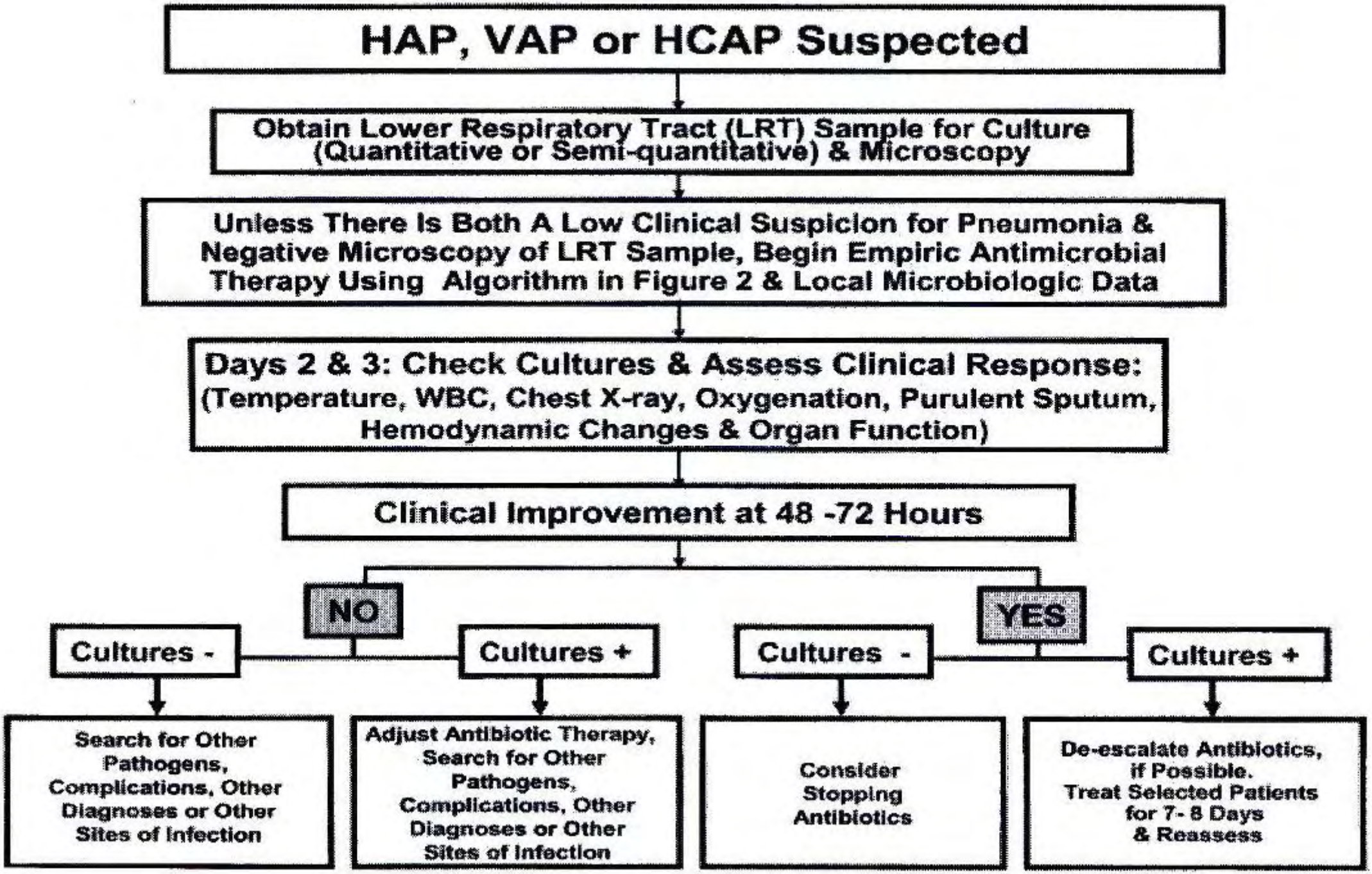
10 à 21 jours à la discrétion du réanimateur ou 3 jours de ciprofloxacine (si score de Pugin ≤ 6)

	Traitement standard n = 42	Traitement court n = 39	P
Traitement > 3 jours	97%	28%	0,0001
Infections extrapulmonaires	15%	18%	NS
↗Résistance ou surinfections	38%	14%	0,017
Séjour en réa	14,7j	9,4j	0,04
Mortalité 3 jours 30 jours	 7% 31%	 0% 13%	 NS NS
Durée du traitement	9,8j	3j	0,0001
Coût	$ 640	$ 259	0,0001

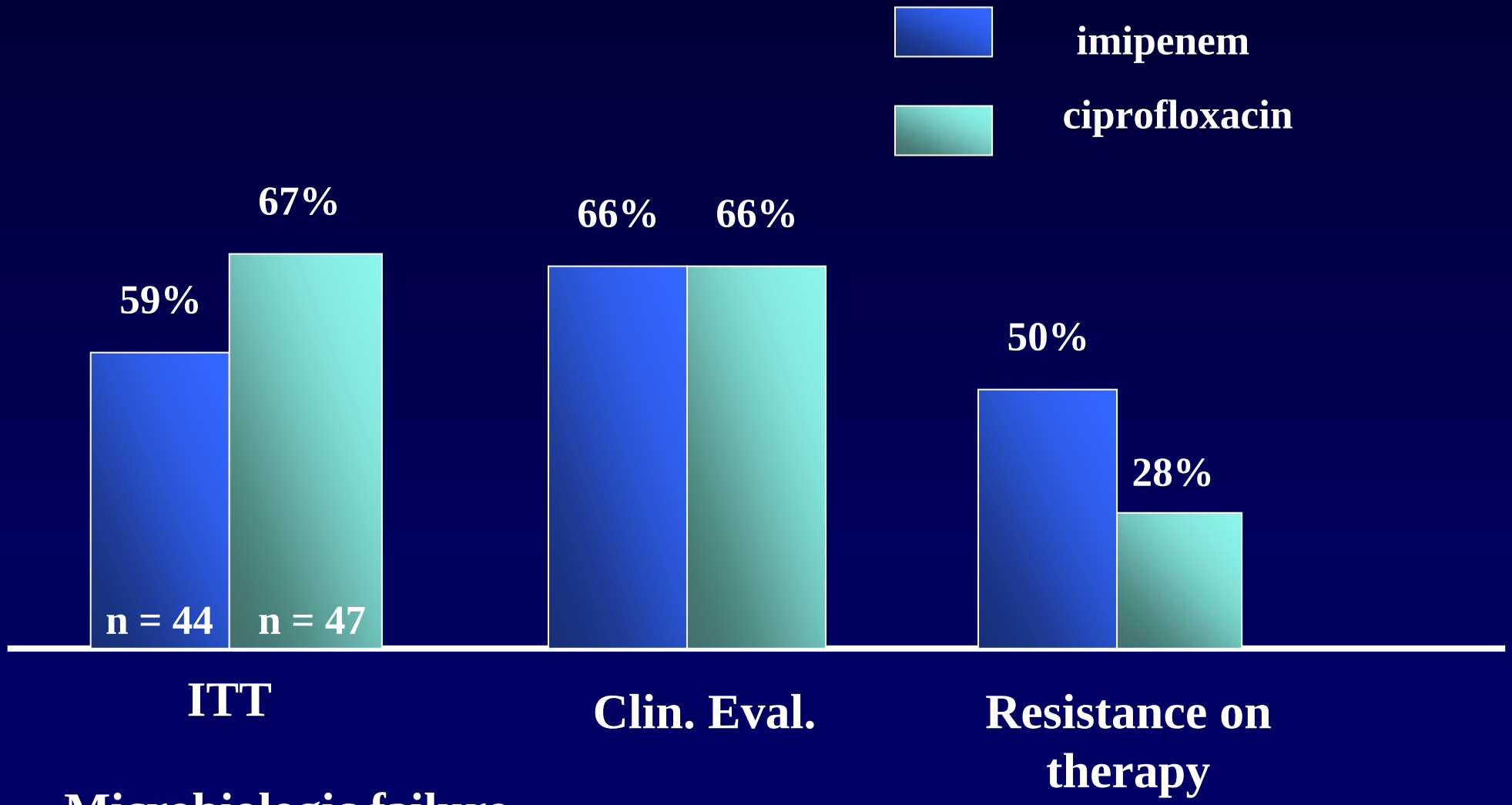
Durée de traitement

Parametres	8 jours TT (n=197)	15 jours TT (n=204)	P
Age	63	65	NS
SAPS 2	45	44	NS
VM > 6 jours	81%	80%	NS
SARM	11,2%	11,8%	NS
GNB non fermentants	32,5%	30,9%	NS
Jours vivants sans ATB	15	12	<0,001
Mortalité J28	18,8%	18,2%	NS
Echecs microbiologiques	29,4%	26%	NS
Echecs cliniques	45,7%	43,1%	NS
DMS en réa (j)	24	23	NS
Emergence de BMR	35,5%	32,8%	NS
Mortalité J60	25,4%	27,9%	NS

Chastre J. JAMA 2003; 290:2588


HAP, VAP or HCAP Suspected
Obtain Lower Respiratory Tract (LRT) Sample for Culture (Quantitative or Semi-quantitative) & Microscopy
Unless There Is Both A Low Clinical Suspicion for Pneumonia & Negative Microscopy of LRT Sample, Begin Empiric Antimicrobial Therapy Using Algorithm in Figure 2 & Local Microbiologic Data
Days 2 & 3: Check Cultures & Assess Clinical Response: (Temperature, WBC, Chest X-ray, Oxygenation, Purulent Sputum, Hemodynamic Changes & Organ Function)
Clinical Improvement at 48 -72 Hours
NO
YES
Cultures -
Cultures +
Cultures -
Cultures +
Search for Other Pathogens, Complications, Other Diagnoses or Other Sites of Infection
Adjust Antibiotic Therapy, Search for Other Pathogens, Complications, Other Diagnoses or Other Sites of Infection
Consider Stopping Antibiotics
De-escalate Antibiotics, if Possible. Treat Selected Patients for 7- 8 Days & Reassess

Pseudomonas : Monotherapy ?



Traitement des pneumonies nosocomiales

- **124 patients de réanimation**
- **APACHE II : 16**

	Pip/Tazo + AMK (2 doses)	**CAZ + AMK (2 doses)**
Guéris/améliorés	63,9%	61,5%
Eradication bactérienne	59%	61%
Effets secondaires	23,9%	16,7%

Alvarez-Lerma Int Care Med 2001, 27,492-502

Traitement des pneumonies nosocomiales

	Ciprofloxacine (800 – 1200 mg/j)	**Imipénem (2 – 4g/j)**
Succès	71%	79%
Eradication bactérienne	49%	50%
Mortalité	16%	24%
Succès sur *P. aeruginosa*	71%	67%
Eradication *P. aeruginosa*	50%	25%
Emergence de Pyo résistants	7%	33%

Torres et coll, Thorax 2000, 55, 1033-1039.

Avantages et inconvénients d'une monothérapie et d'une bithérapie pour le traitement d'une infection bactérienne

Avantages (incontestables) d'une monothérapie	Avantage incontestable d'une bithérapie
. Réduction du coût . Absence d'interaction entre les antibiotiques	. élargissement du spectre d'activité
. Absence de compétition aux sites d'élimination	Avantages théoriques* d'une bithérapie
. Réduction des effets indésirables . Efficacité documentée dans des études de qualité	. accélération de la vitesse de bactéricidie . prévention de l'émergence de souches résistantes.
Facteurs de choix d'une association d'antibiotique . maladie sous jacente . virulence des bactéries (*P. aeurignosa*) . sévérité de l'infection : dysfonction d'organes)	

*** Absence de démonstration pour le traitement des infections nosocomiales chez des sujets hospitalisés en réanimation**

NEWER QUINOLONE AND PENICILLIN-

RESISTANT S. pneumoniae

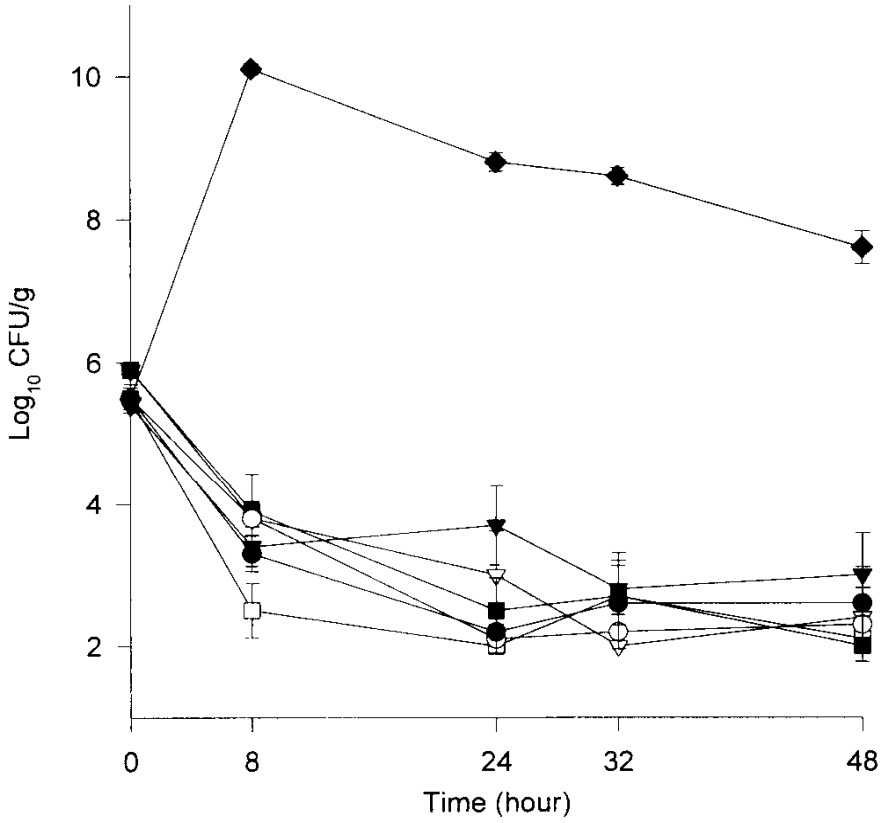


FIG. 1. Activities of trovafloxacin (○), gatifloxacin (●), clinafloxacin (□), sparfloxacin (■), levofloxacin (▽), and ciprofloxacin (▼) against *S. pneumoniae* isolate 68. ◆, growth control. Error bars indicate standard deviations.

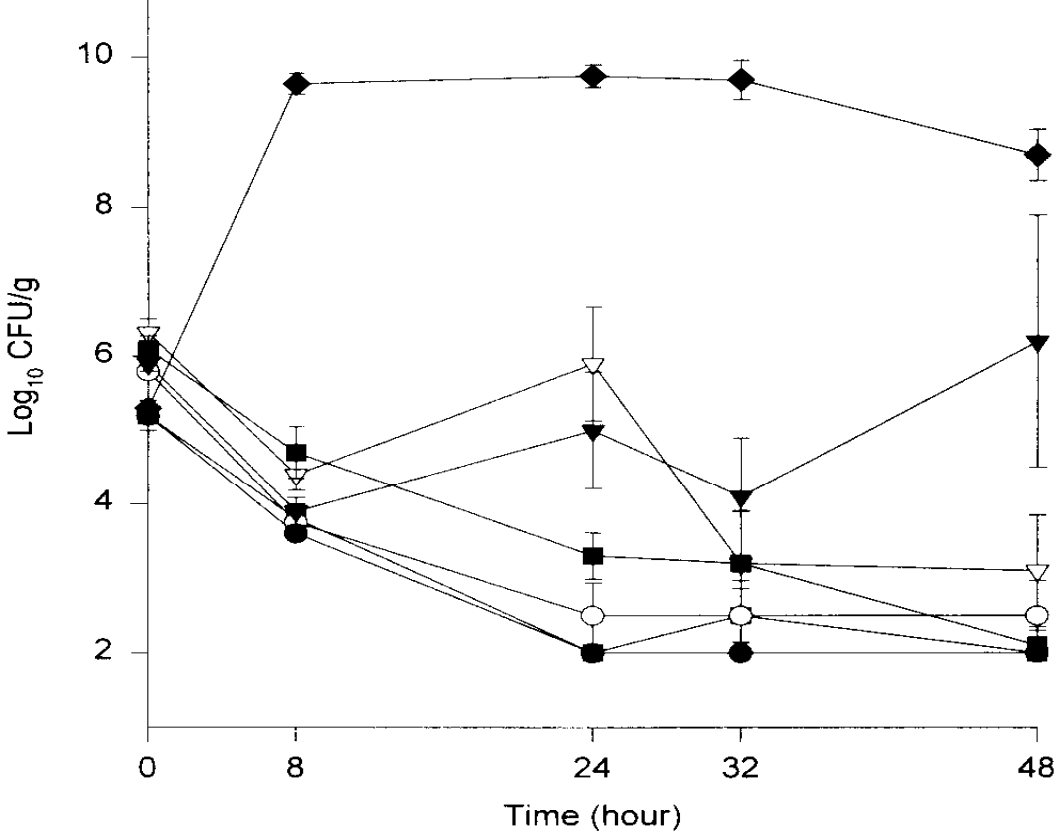


FIG. 2. Activities of trovafloxacin (○), gatifloxacin (●), clinafloxacin (□), sparfloxacin (■), levofloxacin (▽), and ciprofloxacin (▼) against *S. pneumoniae* isolate 79. ◆, growth control. Error bars indicate standard deviations.

F. Hershberger AAC 2000, 44, 598

Facteurs de risques particuliers favorisant une étiologie bactérienne donnée (2)

Facteurs de risques	Bactéries
Séjour hospitalier prolongé (réanimation, services de médecine ou de chirurgie, centre de long séjour), ventilation mécanique, corticothérapie, antibiothérapie, maladie structurale du poumon (bronchectasie, musoviscidose…), malnutration sévère.	*Staphylococcus aureus* méticilline résistant *Pseudomonas aeruginosa* *Enterobacter spp* *Acinetobacter spp*

Facteurs de risques particuliers favorisant une étiologie bactérienne donnée

Facteurs de risques	Bactéries
Chirurgie digestive ou thoracique ,inhalation documentée ou fortement suspectée	Bactéries anaérobies (dont la fréquence est mal connue mais peut dépasser 30%)
Coma traumatisme crânien, diabète sucré, insuffisance rénale chronique, grippe récente.	*Staphylococcus aureus* dont la méticilline-résistance doit être discutée en fonction du contexte* (exceptionnel par exemple en cas de traumatisme récent)
Corticothérapie (surtout à haute dose)	*Legionella* *Pseudomonas aeruginosa*

* Par exemple un contexte épidémiologique avec une forte prévalence de *Staphylococcus aureus* méticilline-résistant, ou une antibiothérapie antérieure.

Un traitement correct des pneumonies peut améliorer la survie

Variable	Catégorie	Odds-ratio	P
Maladie sous-jacente	rapidement fatale	8.84	0.0018
Aggravation de la symptomatologie	oui	11.94	0.0096
Etat de choc	oui	2.83	0.016
Traitement antibiotique	inapproprié	5.81	0.02

Torres et coll ARRD 1990, 142, 523

Indications (raisonnables ?) d 'une association d 'antibiotique

. Lors de la mise en route du traitement probabiliste

. Sepsis sévère , choc septique

. *P. aeruginosa* prouvé ou suspecté

. Etiologie plurimicrobienne

- inhalation

- BGN + SAMR

PROTOCOLE I

PROTOCOLE II

Changing Initial Empiric Therapy of ICU-Acquired Pneumonia

Reason for changing	1 ATB (n = 50)	2 ATB (n = 139)	3 ATB (n = 25)
Poor response	52%	32%	28%
Microorganism not covered	58%	69%	32%
Resistance during treatment	1/50 (2%)	11/139 (8%)	2/25 (4%)

Alvarez-Lerma et al Int. Care Med 1996, 22, 387-394

Adequate Antibiotic Therapy of Pneumonia and Survival

Variable	Category	Odds-ratio	p
Underlying disease	Rapidly fatal	8-84	0.0018
Aggravation of clinical signs	Yes	11-94	0.0096
Shock state	Yes	2.83	0.016
Antibiotic	Appropriate	5.81	0.02

Torres et al ARRD 1990, 142, 523

Pneumonia and Head-Trauma

Bacteria (%)	Pneumonia early (≤ 5d)	Pneumonia Late (> 5d)
H. influenzae	65	27
MSSA	17	16
S. pneumoniae	12	3
Enterobacteriaceae	6	13
P. aeruginosa	0	14
MRSA	0	3

C. Martin et al ATS, 1998

Situations prédisposant à certaines étiologies

Situations	Etiologies
DDS	Enterococcus -SAMR
coma	SAMS
neurochirurgie	SAMS
traumatisme crânien	*H. influenzae* - SAMS
phlébite septique	BGN-SCN

Situations prédisposant à certaines étiologies

Situations	Etiologies
Antibiothérapie antérieure	**SAMR** ***P. aeruginosa*** ***Acinetobacter*** ***Serratia*** **Champignons**
BCPO	**SAMR** ***P. aeruginosa***
Ventilation mécanique prolongée	**SAMR** ***P. aeruginosa***

Situations prédisposant à certaines étiologies

Situations	Etiologies
Dénutrition	*P. aeruginosa*
Nébuliseurs ou bronchoscopes contaminés	*P. aeruginosa*
Inhalation	Anaérobies
Corticothérapie	Champignons

Gravité faible à modérée chez des patients sans facteur de risques particuliers, début précoce ou tardif
Gravité importe chez des patients sans facteur de risques particuliers, début précoce.

Bactéries	Antibiotiques
. *Enterobacter spp** . *Escherichia coli* . *Klebsiella spp* . *Proteus* . *Serratia spp* . *Haemophilus influenzae*	. Céphalosporine de 2ème**, ou de 3ème génération sans action sur *P. aeruginosa**** association aminopénicilline (ou ticarcilline) + inhibiteur
. *Staphylococcus aureus* (méticiline sensible) . *Streptococcus pneumoniae*	. Allergie aux bétalactamines : ciprofloxacine***** (+ aminoside) ou clindamycine + aminoside ou ciprofloxacine.

* bithérapie recommandée (+ aminoside ou + quinolone) ** céfuroxine, céfamandole,
*** ceftriaxone, céfotaxime **** sauf si suspicion de *S. pneumoniae*

Pneumonie nosocomiale, de gravité faible à modérée chez des patients présentant des facteurs de risques particuliers, début précoce ou tardif

Bactéries	Antibiotiques
Bactéries du tableau précédent, plus :	Antibiotiques du tableau précédent, plus :
Bactéries anaérobies	Métronidazole ou clindamycine ou aminopénicilline (carboxypénicilline) + Inhibiteur
Staphylococcus aureus	Si on suspecte une résistance à la méticilline : vancomycine (jusqu'au résultats des cultures)
Legionella	Erythromycine
Pseudomonas aeruginosa *Enterobacter spp* *Acinetobacter spp*	Aminoside ou ciprofloxacine plus* : ceftazidime ou pénicilline antipseudomonas (± inhibiteur) ou imipénème

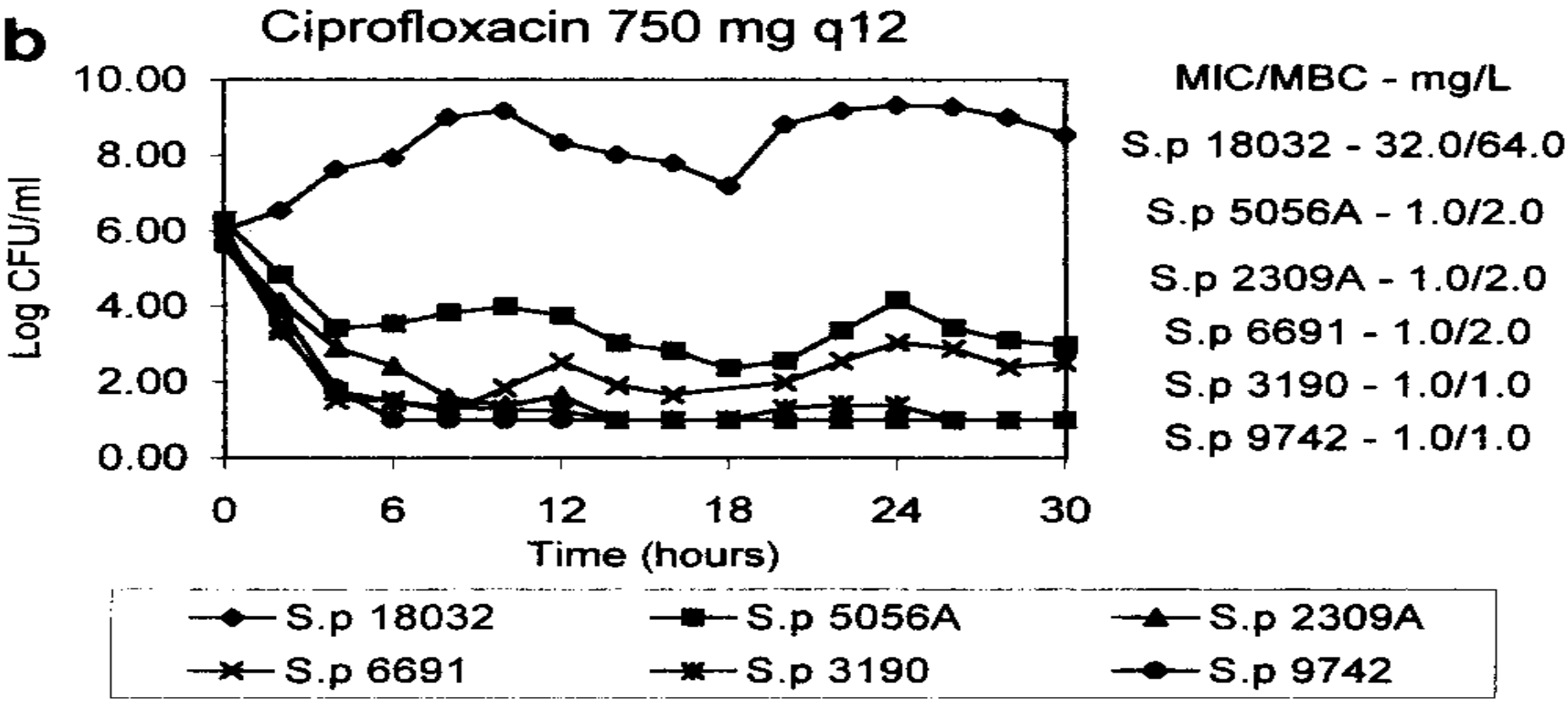
Pneumonie nosocomiale, de gravité importante chez des patients présentant certains facteurs de risques particuliers, début précoce.
Pneumonie de gravité importante, début tardif.

Bactéries du tableau précédent, plus :	Antibiotiques
Pseudomonas aeruginosa	Aminoside ou ciprofloxacine plus* :
Acinetobacter spp	Ceftazidime ou péniciline antipseudomonas (+ inhibiteur) ou imipénème.
Staphylococcus aureus potentiellement méticilline-résistant	Plus ou moins vancomycine.

*** la nécessité de maintenir une association d ′antibiotiques doit être réévaluée au 3ème jour du traitement**

CIPROFLOXACIN AND S. PNEUMONIAE

Simulated dose : 750mg bid oral



S.H. Zinner et al AAC 2000, 44, 773

Groupe 2 ATS: pneumonie nosocomiale avec facteurs de risque . Survenue à tout moment .

. Anaérobies
(chirurgie de l ’abdomen récente, inhalation bronchique visualisée)

. *Staphylococcus aureus*
(coma, traumatisme crânien, diabète sucré, insuffisance rénale)

. *Legionella*
(forte dose de stéroïdes)

. *P. aeruginosa*
(séjours prolongés en unités de soins intensifs, stéroïdes, antibiotiques, maladie de structure du poumon)

Clindamycine
ou β-lactamine/ inhibiteur β-lactamase (seul)

Vancomycine

Erythromycine ± rifampine

Traitement identique à celui des pneumonies nosocomiales sévères (groupe 3)