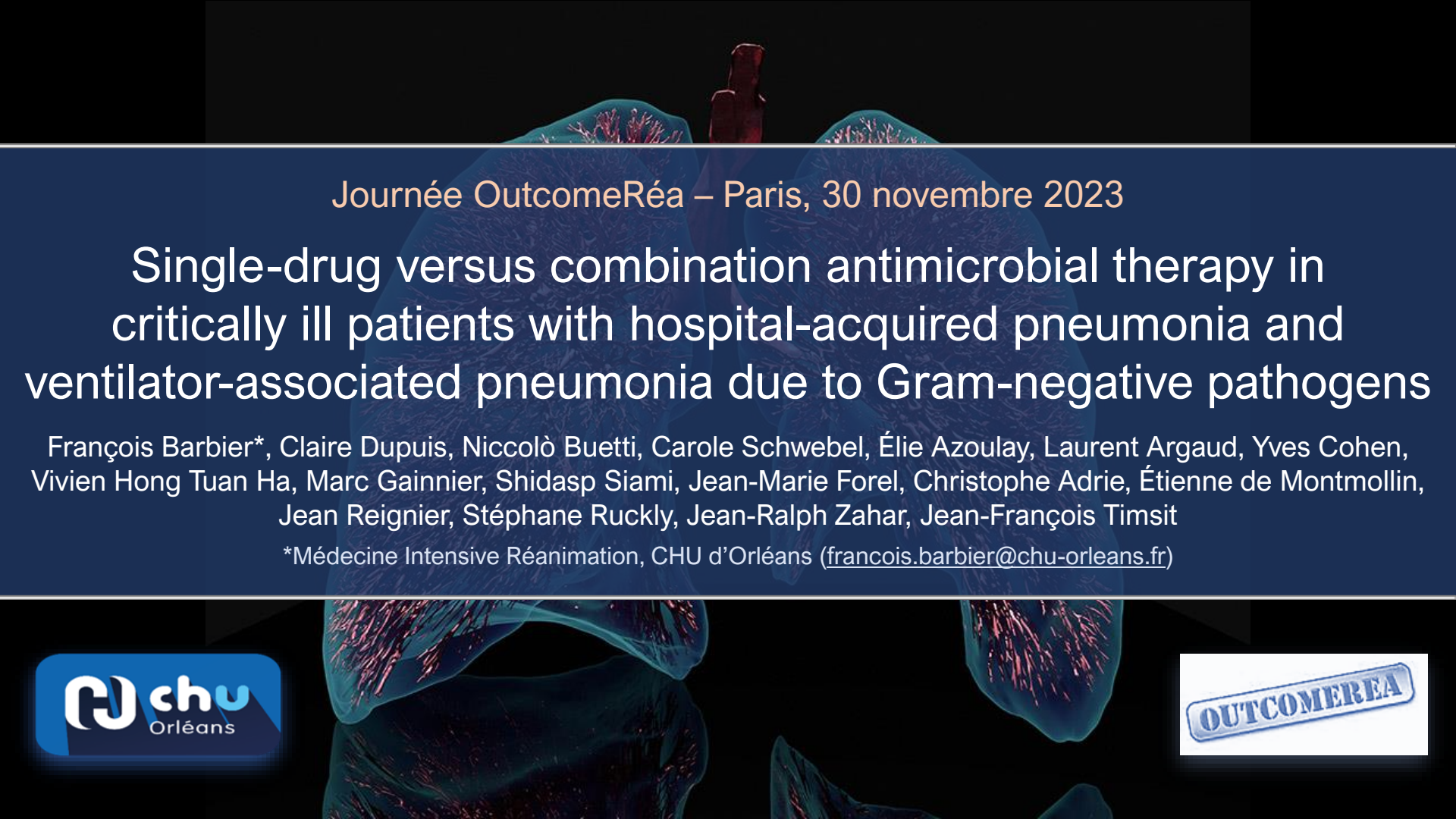


Journée OutcomeRéa – Paris, 30 novembre 2023

Single-drug versus combination antimicrobial therapy in critically ill patients with hospital-acquired pneumonia and ventilator-associated pneumonia due to Gram-negative pathogens

François Barbier*, Claire Dupuis, Niccolò Buetti, Carole Schwebel, Élie Azoulay, Laurent Argaud, Yves Cohen, Vivien Hong Tuan Ha, Marc Gainnier, Shidasp Siami, Jean-Marie Forel, Christophe Adrie, Étienne de Montmollin, Jean Reignier, Stéphane Ruckly, Jean-Ralph Zahar, Jean-François Timsit

*Médecine Intensive Réanimation, CHU d'Orléans (francois.barbier@chu-orleans.fr)

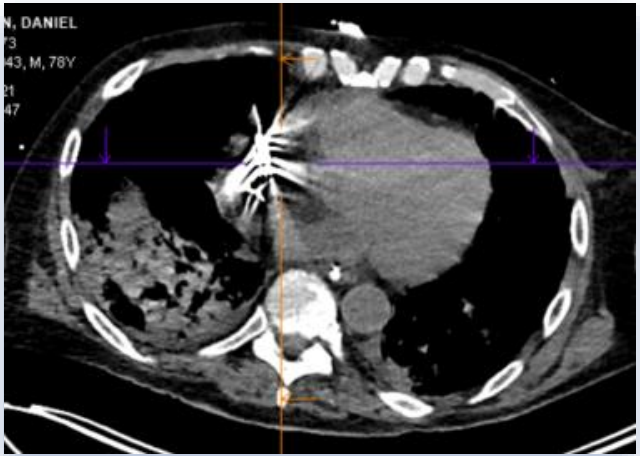
Conflits d’intérêt potentiels (2019-2023)

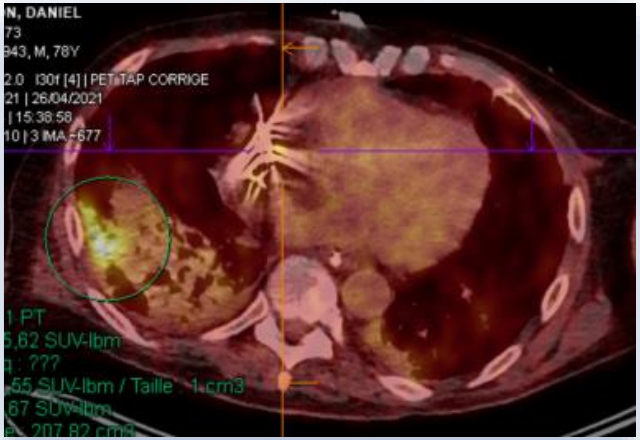
MSD

BioMérieux

Financement du projet

MSD (grant number #59746)





PAVM

Infection acquise en réanimation la plus fréquente chez les patients sous VM invasive >48h

Incidence globale (1er épisode) : 5-40% (2-16 pour 1000 jours-VM)

Mortalité: globale 30-50%, attribuable 1-13%

Durée de VM +7 à 11 jours

Burden médico-économique (+25 à 40 kE)

Principal vecteur nosocomial de consommation d'antibiotiques en réanimation

Papazian et al. *Intensive Care Med* 2020; 46: 888-906

Melsen et al. *Lancet Infect Dis* 2013; 13: 665-71

Bekaert et al. *Am J Respir Crit Care Med* 2011; 184: 1133-1139

Zimlichman et al. *JAMA Intern Med*. 2013;173(22): 2039-2046

SURVEILLANCE DES PNEUMONIES ACQUISES SOUS VM

Résultats 2020

Santé publique France

RéPias Réseau de Prévention des Infections Associées aux Soins SPIADI

936 PAVM - Distribution des pathogènes (n = 1033)

***S. aureus* : 10% des PAVM**

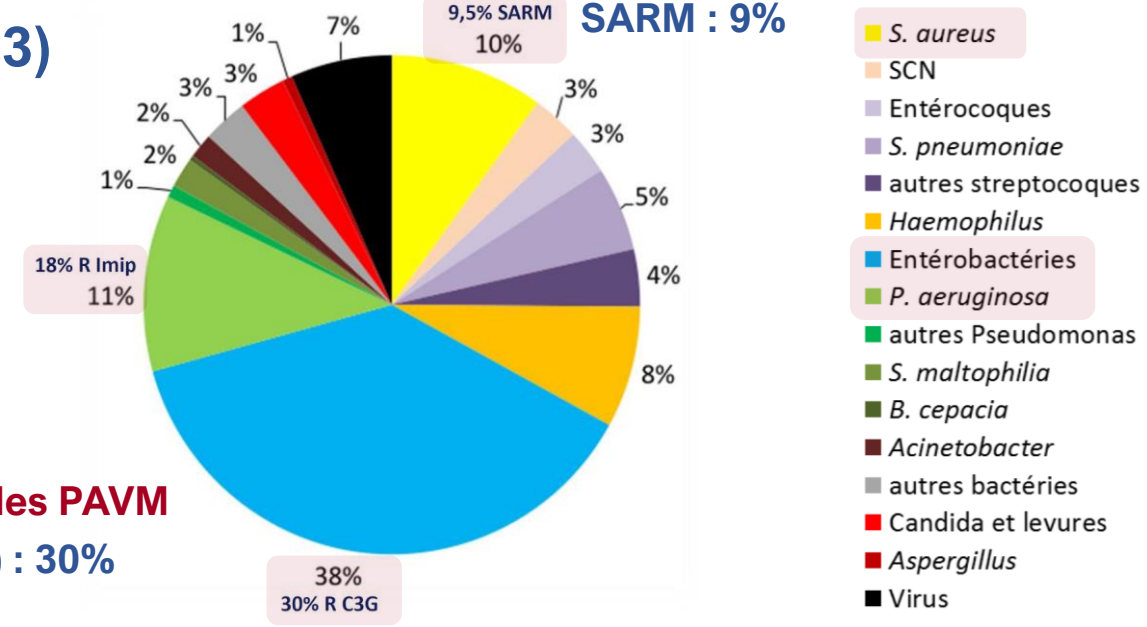
SARM : 9%

***P. aeruginosa* : 11% des PAVM**

Carbapénème-R : 18%

Entérobactéries : 38% des PAVM

C3G-R (BLSE/AmpC) : 30%



A Comparison of the Mortality Risk Associated With Ventilator-Acquired Bacterial Pneumonia and Nonventilator ICU-Acquired Bacterial Pneumonia*

OUTCOMEREA

Critical Care Medicine®

Ibn Saied et al. *Crit Care Med* 2019; 47: 345-352

19 561 patients in the **OUTCOMEREA** database

5 349 patients excluded (hospitalization less than 48 hours in ICU)

14 212 patients admitted in ICU

PAVM

Mortalité globale à J30 : 28%

Hazard ratio/décès à J30 1,38; IC 95%1,24-1,52; *P* <0,0001

PN acquise en réanimation hors VM

Mortalité globale à J30 : 24% (si intubation pour PN : 32%)

Hazard ratio/décès à J30 1,82; IC 95% 1,35-2,45; *P* <0,0001

6 574 (85%) patients without VAP

1 161 (15%) patients with VAP

-173 patients with 2 episodes
-21 patients with 3 episodes

9 571 (98%) patients without ICU-HAP

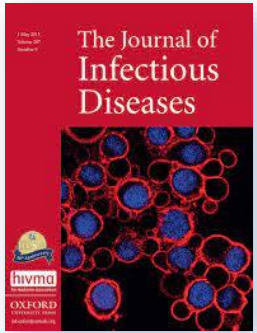
176 (2%) patients with ICU-HAP

-9 patients with 2 episodes

Evidence-Based Study Design for Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia

George H. Talbot,[1] Anita Das,[2] Stephanie Cush,[3] Aaron Dane,[4] Michele Wible,[5] Roger Echols,[6] Antoni Torres,[7] Sue Cammarata,[8] John H. Rex,[9] John H. Powers,[10] Thomas Fleming,[11] Jeffrey Loutit,[12] and Steve Hoffmann[3]; for the Foundation for the National Institutes of Health Biomarkers Consortium HABP/VABP Project Team[a]

The Journal of Infectious Diseases® 2019;219:1536–44



All-cause mortality rates differed notably between HAP, **vHAP** and VAP in assessed studies: HAP 9.8-18.8%, **vHAP 15.2-30.2%**, VAP 12.6-26.3%

OUTCOMEREA

A Comparison of the Mortality Risk Associated With Ventilator-Acquired Bacterial Pneumonia and Nonventilator ICU-Acquired Bacterial Pneumonia*

Critical Care Medicine®

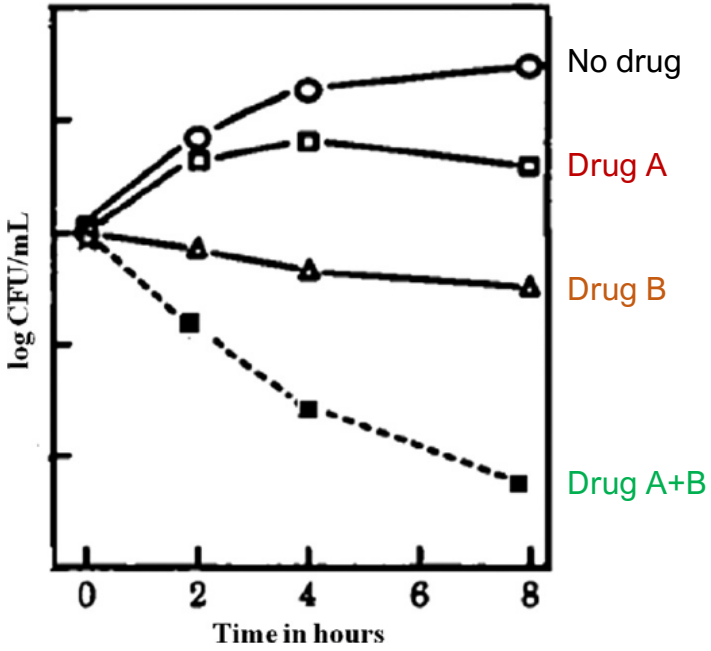
Ibn Saied et al. *Crit Care Med* 2019; 47: 345-352

Microorganisms, n (%)	Ventilator-Associated Pneumonia (*n* = 1,355)	ICU–Hospital-Acquired Pneumonia (*n* = 185)
Gram positive		
Streptococcus pneumoniae	66 (4.9)	5 (2.7)
Other Streptococci	61 (4.5)	7 (3.8)
Staphylococcus aureus	258 (19)	34 (18)
Methicillin susceptible	158 (11.7)	23 (12.4)
Methicillin resistant	100 (7.4)	11 (5.6)
Enterococcus	25 (1.8)	5 (2.7)
S. epidermidis	58(4.3)	21 (11.1)
Other Gram-positive microorganisms	11 (0.8)	3 (1.6)
Gram negative		
Enterobacteriaceae	438 (32.3)	51 (27.6)
Susceptible to third generation cephalosporin	340 (25.1)	39 (21.1)
Resistant to third generation cephalosporin	98 (7.2)	12 (6.5)
Pseudomonas aeruginosa	454 (33.5)	62 (33.5)
Susceptible	312 (23)	29 (15.7)
Resistant to ticarcillin, ceftazidime or penems	142 (10.5)	33 (17.8)
Stenotrophomonas maltophilia	64 (4.7)	4 (2.2)

Combination Therapy for Treatment of Infections with Gram-Negative Bacteria

Pranita D. Tamma,[a] Sara E. Cosgrove,[b] and Lisa L. Maragakis[b]

July 2012 Volume 25 Number 3



Traitement probabiliste

Optimiser la probabilité d'administrer au moins une molécule active

Infection documentée
(pathogènes et sensibilité)

NA

Accélérer la clairance bactérienne (synergie)

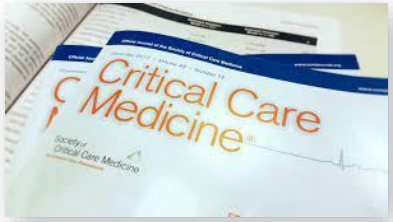
Prévenir l'émergence de résistances au site de l'infection

Améliorer le pronostic des patients (?)

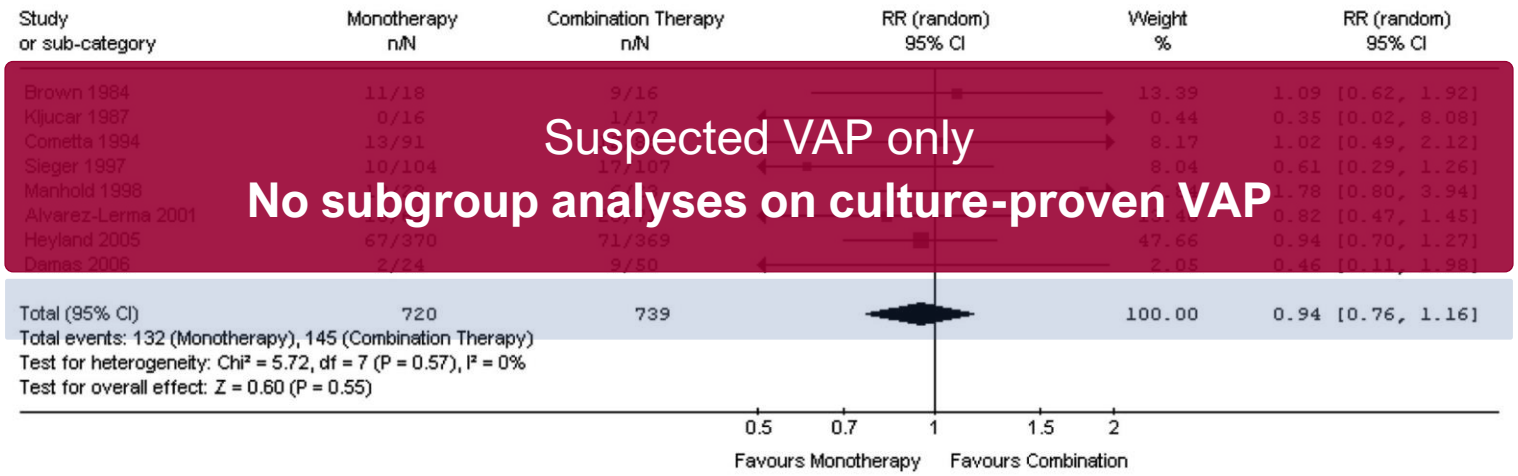
Empiric antibiotic therapy for suspected ventilator-associated pneumonia: A systematic review and meta-analysis of randomized trials

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

Crit Care Med 2008 Vol. 36, No. 1

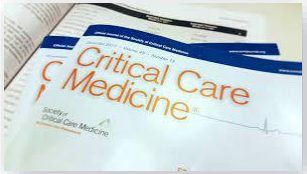


Mortality with single-drug versus combination therapy: RR 0.94, 95% CI 0.76-1.16



Suspected VAP only

No subgroup analyses on culture-proven VAP



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

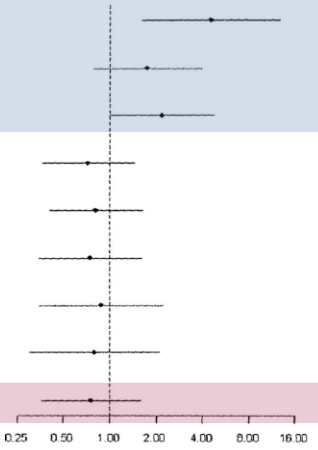
Crit Care Med 2008 Vol. 36, No. 3

- 740 patients with <u>suspected</u> VAP
- **Non-inclusion:** colonization with *P. aeruginosa* and/or MRSA, ID
- Meropenem (1 g q8h) plus ciprofloxacin (400 mg q12h) vs meropenem alone
- **Culture-proven VAP due to high-risk pathogens (*Pa*, *Ab*, MDR Enterobacterales, MRSA): n = 59 (16%)**

Subgroup analysis: VAP due to high-risk GNB

Combination (n = 39) versus single-drug (n = 17)

	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)	



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

Crit Care Med 2007 Vol. 35, No. 8

Retrospective study, 5 ICUs, 183 patients with VAP due to *P. aeruginosa*

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

Effect of Empirical Treatment With Moxifloxacin and Meropenem vs Meropenem on Sepsis-Related Organ Dysfunction in Patients With Severe Sepsis

A Randomized Trial

Brunkhorst et al. *JAMA* 2012; 307(22): 2390-2399

RCT, 44 réanimations (Allemagne), 2007-2010

Antibiothérapie probabiliste :
méropénème (1 gr/8h) + moxifloxacine (400 mg/24h) versus méropénème seul

551 patients randomisés (pneumonies 41%, IIA 38%)

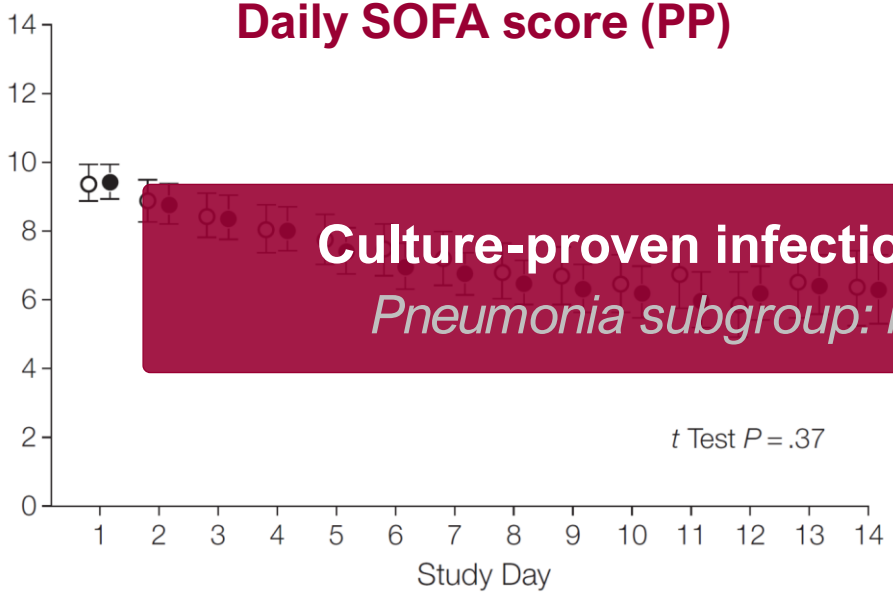
BGN (49%) : principalement entérobactéries (35%, méropénème-S 99%)
et *P. aeruginosa* (8%, méropénème-S 86%)

Effect of Empirical Treatment With Moxifloxacin and Meropenem vs Meropenem on Sepsis-Related Organ Dysfunction in Patients With Severe Sepsis

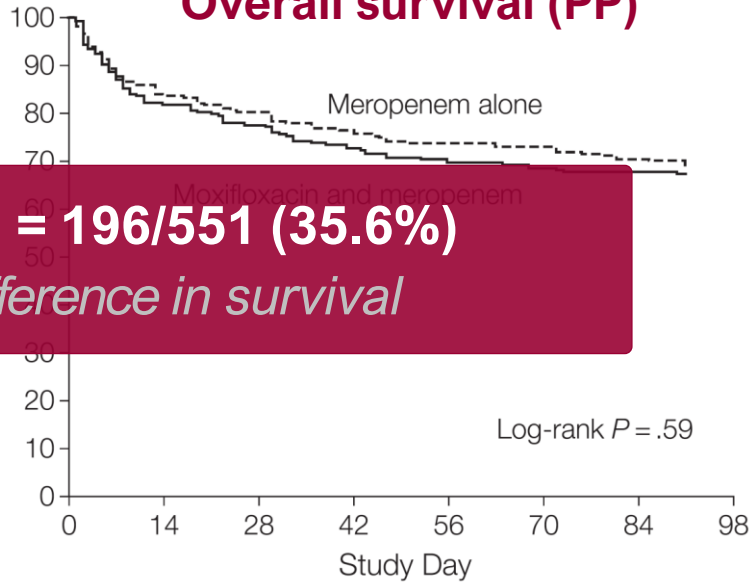
A Randomized Trial

Brunkhorst et al. *JAMA* 2012; 307(22): 2390-2399

Daily SOFA score (PP)



Overall survival (PP)



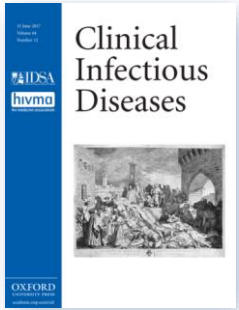
Culture-proven infections: n = 196/551 (35.6%)

Pneumonia subgroup: no difference in survival

Short-Course Adjunctive Gentamicin as Empirical Therapy in Patients With Severe Sepsis and Septic Shock: A Prospective Observational Cohort Study

David S. Y. Ong,[1,2] Jos F. Frencken,[2,3] Peter M. C. Klein Klouwenberg,[1,2] Nicole Juffermans,[4] Tom van der Poll,[5] Marc J. M. Bonten,[1,3] and Olaf L. Cremer[2]; for the MARS consortium[a]

Clinical Infectious Diseases® 2017;64(12):1731–6



Pays-Bas, 2 réanimations, 2011-2015

Antibiothérapie probabiliste protocolisée

ICU A : β-lactamine (C3G 84%) + gentamicine (5 mg/kg/24h, 24h-72h)

ICU B : β-lactamine seule (C3G 82%) (ICU B)

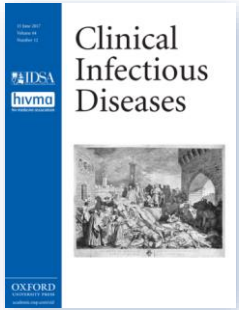
N = 648 patients

Infections intra-abdominales 49%, infections urinaires 16%

Short-Course Adjunctive Gentamicin as Empirical Therapy in Patients With Severe Sepsis and Septic Shock: A Prospective Observational Cohort Study

David S. Y. Ong,[1,2] Jos F. Frencken,[2,3] Peter M. C. Klein Klouwenberg,[1,2] Nicole Juffermans,[4] Tom van der Poll,[5] Marc J. M. Bonten,[1,3] and Olaf L. Cremer[2]; for the MARS consortium[a]

Clinical Infectious Diseases® 2017;64(12):1731–6



Traitement empirique inadéquate :

5% (A) vs 4% (B), *P* = 0,66

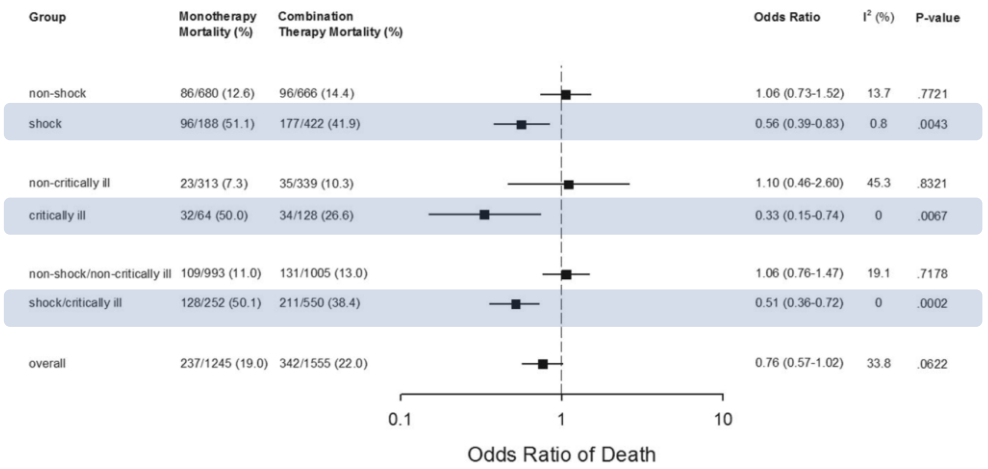
Table 4. Associations of Gentamicin Use With Renal Failure–Free Days, Shock-Free Days, and Death Before Day 14

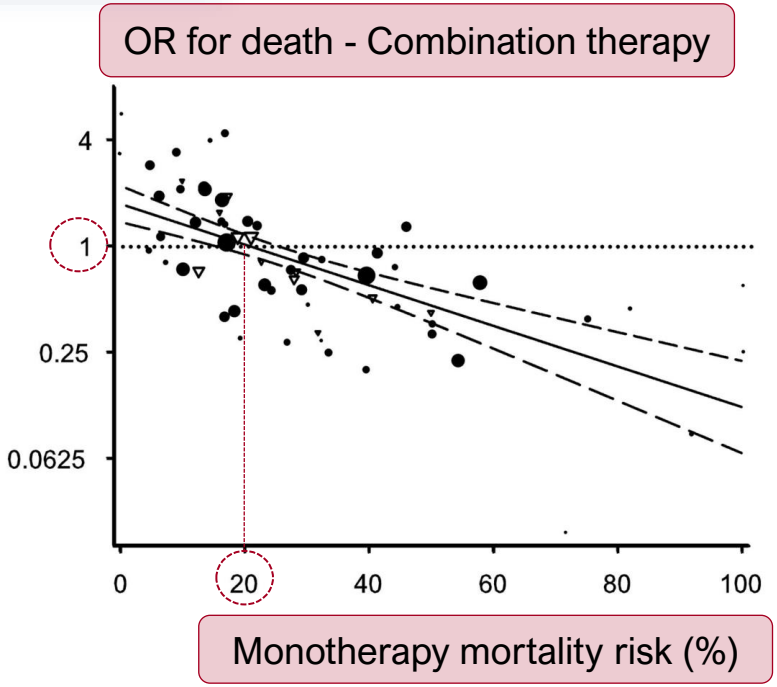
Model	Primary Outcome	Secondary Outcome	
	Renal Failure–Free Days	Shock-Free Days	Death Before Day 14
Per protocol (primary) analysis			
Crude	1.35 (1.00–1.82)	1.30 (0.96–1.77)	1.41 (0.98 – 2.02)
Adjusted[a]	1.39 (1.00–1.94)	1.34 (0.96–1.86)	1.41 (0.94 – 2.12)
Intention-to-treat (sensitivity) analysis			
Crude	1.39 (1.04–1.86)	1.17 (0.87–1.57)	1.47 (1.03 – 2.10)
Adjusted[a]	1.70 (1.22–2.36)	1.28 (0.93–1.77)	1.76 (1.17 – 2.64)

A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: A meta-analytic/meta-regression study

Anand Kumar, MD; Nasia Safdar, MD; Shravan Kethireddy, MD; Dan Chateau, PhD

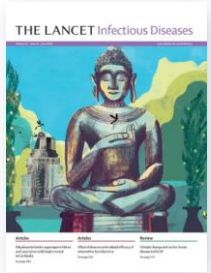
Crit Care Med 2010 Vol. 38, No. 8





Effect of appropriate combination therapy on mortality of patients with bloodstream infections due to carbapenemase-producing Enterobacteriaceae (INCREMENT): a retrospective cohort study

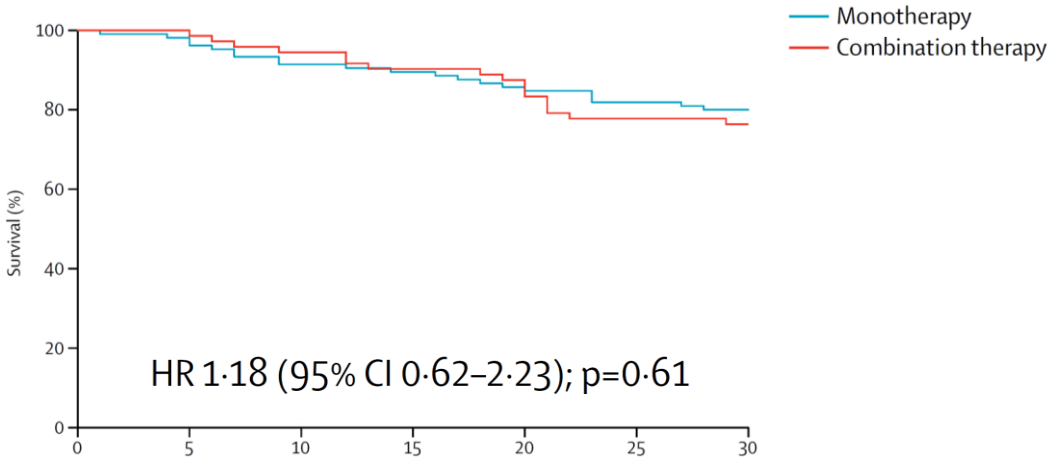
Lancet Infect Dis 2017; 17: 726–34



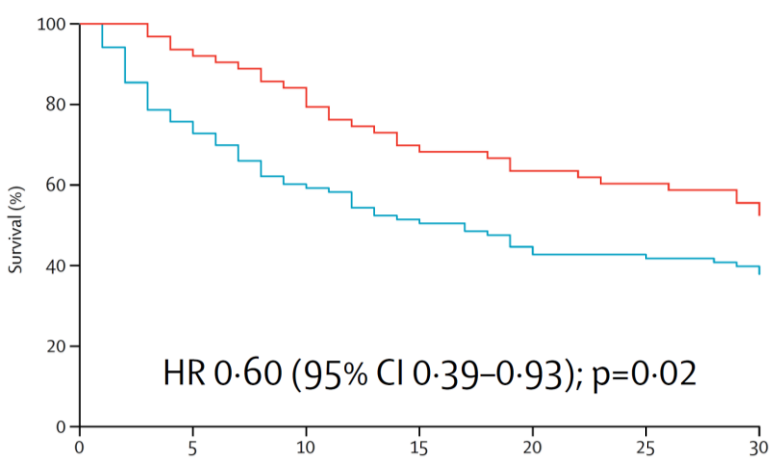
44 centres (26 pays), 2004-2013, 437 patients avec bactériémie à EPC (*K. pneumoniae* KPC, 75%)

Traitement adéquate (sensibilité *in vitro*) : 343 patients (monothérapie 61%, combo 39%)

Low probability of death



High probability of death



Empirical mono- versus combination antibiotic therapy in adult intensive care patients with severe sepsis: a systematic review with meta-analysis and trial sequential analysis

Fredrik Sjövall, Anders Perner, Morten Hylander Møller

Journal of Infection 2017; 74: 331-344

All-cause mortality : RR 1.11, 95% CI 0.95-1.29

«The quantity and quality of data was low without firm evidence for benefit or harm of combination therapy. »

« The QoE on emergence of resistant bacteria was low due to imprecision and risk of bias. »

Risk of bias summary

CONFERENCE REPORTS AND EXPERT PANEL

Surviving sepsis campaign: research priorities for sepsis and septic shock

Craig M. Coopersmith[1], Daniel De Backer[2*], Clifford S. Deutschman[3,4], Ricard Ferrer[5,6], Ishaq Lat[7], Flavia R. Machado[8], Greg S. Martin[9], Ignacio Martin-Loeches[10], Mark E. Nunnally[11], Massimo Antonelli[12], Laura E. Evans[13], Judith Hellman[14], Sameer Jog[15], Jozef Kesecioglu[16], Mitchell M. Levy[17] and Andrew Rhodes[18]

Intensive Care Med (2018) 44:1400–1426

Surviving Sepsis Campaign

Table 1 Top research priorities

Can targeted/personalized/precision medicine approaches determine which therapies will work for which patients at which times?
Should empiric antibiotic combination therapy be used in sepsis or septic shock?
What are the predictors of sepsis long-term morbidity and mortality?
What information identifies organ dysfunction?

Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society

Table 3. Suggested Empiric Treatment Options for Clinically Suspected Ventilator-Associated Pneumonia in Units Where Empiric Methicillin-Resistant *Staphylococcus aureus* Coverage and Double Antipseudomonal/Gram-Negative Coverage Are Appropriate

A. Gram-Positive Antibiotics With MRSA Activity	B. Gram-Negative Antibiotics With Antipseudomonal Activity: β-Lactam–Based Agents	C. Gram-Negative Antibiotics With Antipseudomonal Activity: Non-β-Lactam–Based Agents
Glycopeptides[a]	Antipseudomonal penicillins[b]	Fluoroquinolones
Vancomycin 15 mg/kg IV q8–12h (con… mg/kg × 1 for severe illness)	Piperacillin-tazobactam 4.5 g IV q6h[b]	Ciprofloxacin 400 mg IV q8h
OR	OR	
Oxazolidinones	Cephalosporins[b]	Aminoglycosides[a,c]
Linezolid 600 mg IV q12h	Ceftazidime 2 g IV q8h	Gentamicin 5–7 mg/kg IV q24h
	OR	OR
	Carbapenems[b]	Polymyxins[a,e]
	Meropenem 1 g IV q8h	Colistin 2.5–5 mg × (1.5 × CrCl + 30) IV q12h (maintenance dose) [135]
		Polymyxin B 2.5–3.0 mg/kg/d divided in 2 daily IV doses
	OR	
	Monobactams[f]	
	Aztreonam 2 g IV q8h	

Inclusion systématique dans le spectre de l'antibiothérapie probabiliste : *S. aureus*, *P. aeruginosa*, « autres BGN »

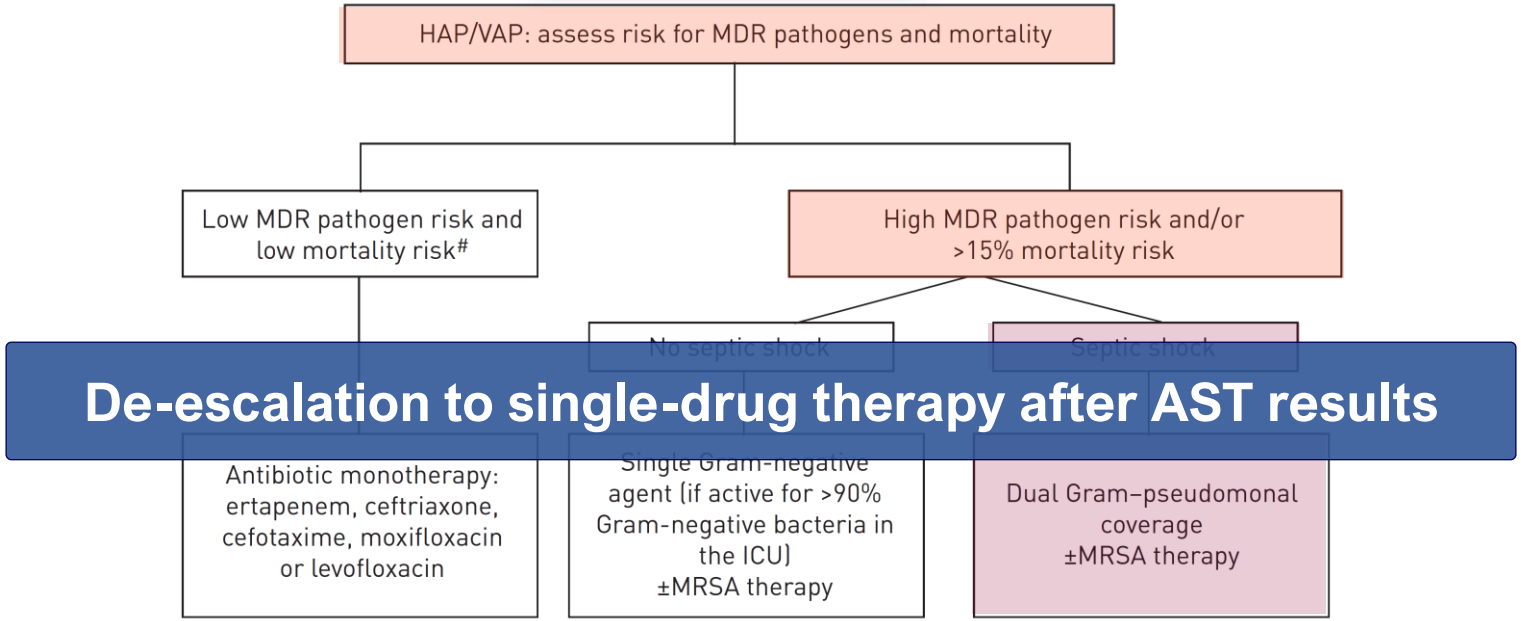
≥ 1 facteur de risque de BMR : bithérapie probabiliste

+/- traitement anti-SARM si endémicité locale

Réévaluation: poursuite d'une bithérapie active si choc septique

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

Eur Respir J 2017; 50: 1700582



Implementation of French Recommendations for the Prevention and the Treatment of Hospital-acquired Pneumonia: A Cluster-randomized Trial

Clinical Infectious Diseases® 2021;73(7):e1601–10

35 ICUs in France (SFAR research network), 1856 patients with ICU LOS ≥3 days

- Monotherapy for empirical treatment in the absence of risk for MDRB
- De-escalation of empirical antibiotherapy

Association between combination antibiotic therapy as opposed as monotherapy and outcomes of ICU patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia: an ancillary study of the iDIAPASON trial

Foucrier et al. *Critical Care* (2023) 27:211

169 patients with Pa-VAP

Dual-active empiral regimen: n = 113 (66.9%) / Dual-active definite regimen: n = 75 (44.4%)

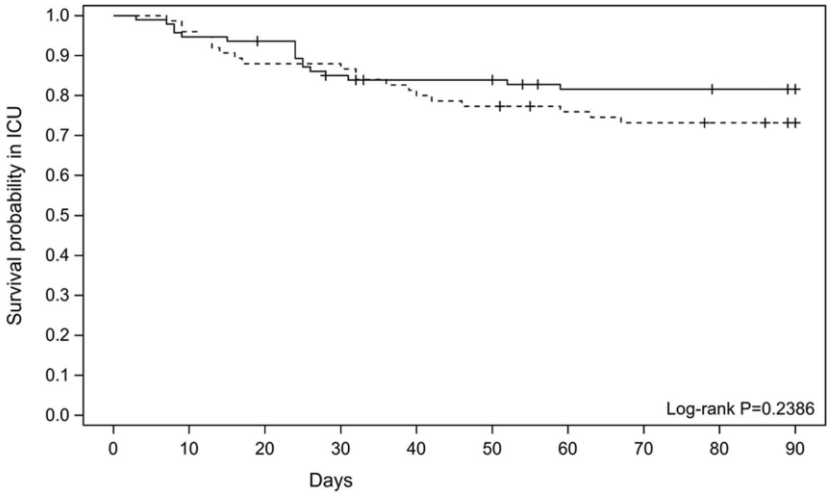
Total treatment duration: single-drug = 10.5 (8-15) days, combination = 15.0 (9-16) days

Table 2 Summary of the results of the comparative analyses between adapted monotherapy and combination therapy

	Monotherapy $N=94$	Combination therapy $N=75$	*P*-value
ICU mortality	17 (18.1)	20 (26.7)	0.1801
Recurrence of VAP	15 (16.0)	8 (10.7)	0.3190
Number of days under mechanical ventilation[a]	23.0 [12.0; 34.0]	28.0 [16.5; 50.0]	0.0243
Length of stay in intensive care unit (days)	33.0 [21.0; 51.0]	38.0 [25.0; 60.0]	0.0654
Number of extra pulmonary infections during ICU stay[b]	1.0 [0.0; 2.0]	0.0 [0.0; 2.0]	0.8971
MDR pathogens acquired during ICU stay[c]	18 (19.8)	16 (21.9)	0.7372

Association between combination antibiotic therapy as opposed as monotherapy and outcomes of ICU patients with *Pseudomonas aeruginosa* ventilator-associated pneumonia: an ancillary study of the iDIAPASON trial

Foucrier et al. *Critical Care* (2023) 27:211



aOR and 95% CI for combination (versus single-drug) therapy

	Adjusted model*	Propensity score stratified model
ICU mortality	1.66 (0.80-3.47)	1.66 (0.73-3.76)
Recurrence of VAP	0.64 (0.25-1.61)	0.86 (0.30-2.50)
MV duration (days)	0.27 (0.03-0.51)	-
ICU LOS (days)	0.17 (-0.03-0.37)	-
ICU-acquired MDRB	1.13 (0.53-2.41)	-

* Adjustment on randomization arm and SOFA at inclusion

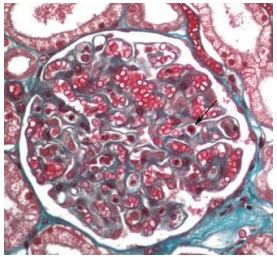
Study design & objectives

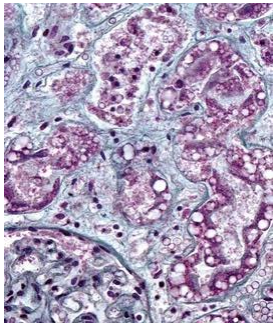
- **Design:** retrospective cohort study based on prospectively collected data (OutcomeRéa database, 2008-2019)
- **Primary objective:** to investigate the effect of initial adequate combination therapy compared to initial adequate single-drug therapy on Day-28 all-cause mortality in critically ill patients with HAP, vHAP or VAP due to Gram-negative pathogens
- **Secondary objectives:** to appraise the impact of combination therapy on (i) the likelihood of clinical cure rate at Day 14, and (ii) the hazard of treatment-emergent acute kidney injury (AKI) or death at Day 7

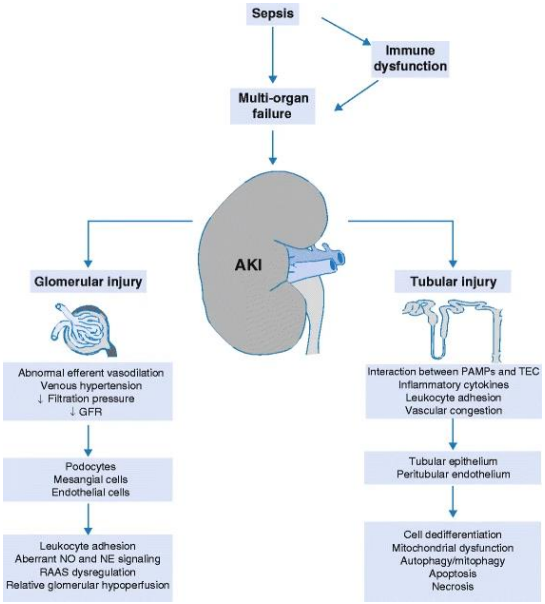
Weiss et al. *Clin Infect Dis* 2019;69 (11): 1912-8
See et al. *Crit Care* 2023; 27 (1): 39

Improvement of composite kidney outcomes by AKI care bundles: a systematic review and meta-analysis

See *et al. Critical Care* (2023) 27:390







Major adverse kidney events (MAKEs) in critically ill patients:

1. Moderate/severe AKI
2. New requirement for RRT
3. Death *(competing risk for 1 & 2)*

Study population & definitions

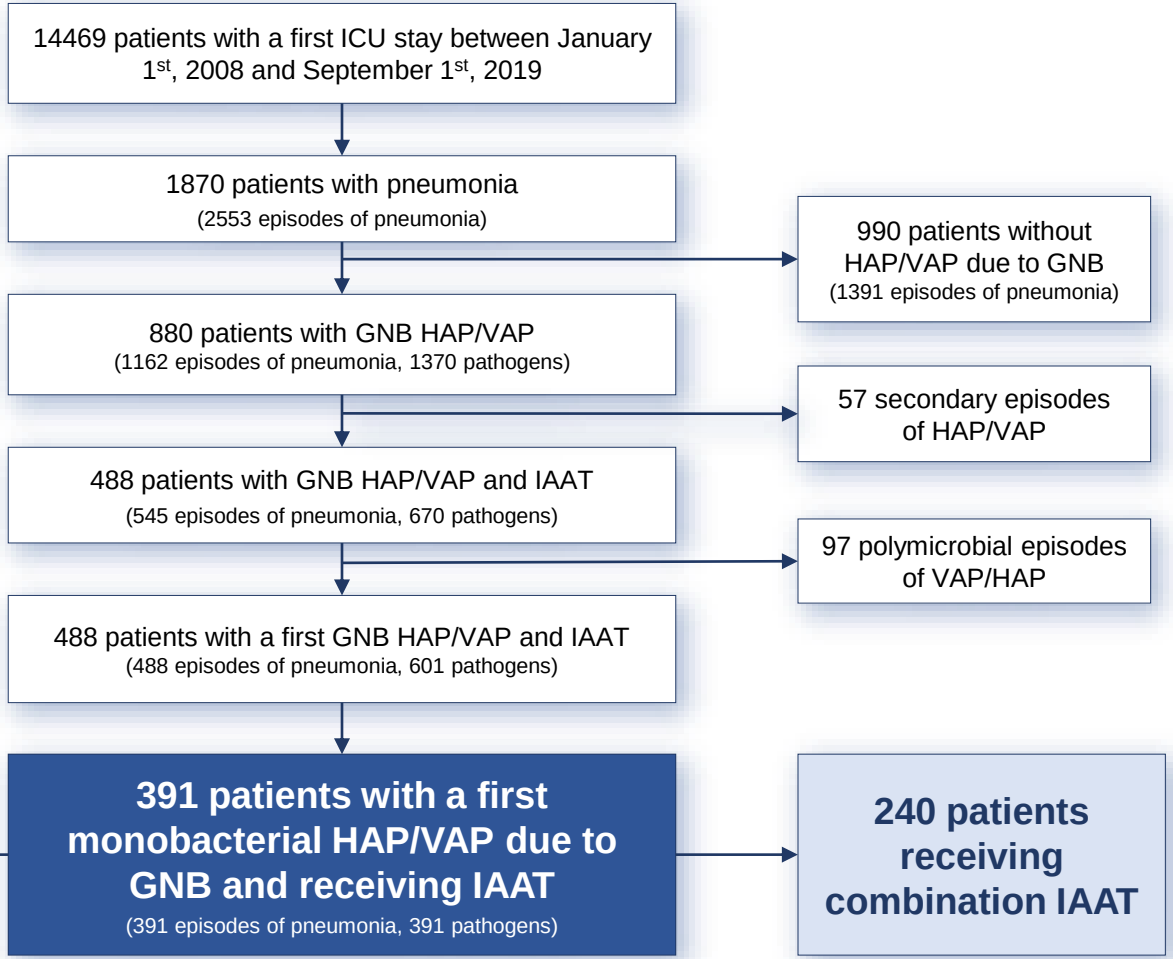
- Patients with a first ICU stay between January 2008 and September 2019
- Monobacterial HAP, vHAP or VAP due to GNB and treated with **adequate single-drug or adequate combination antimicrobial therapy at Day 0 (date of pneumonia diagnosis) and/or Day 1**
- Only the first pneumonia for patients with multiple episodes
- MDR/XDR: CDC/eCDC definitions
- Adequacy of initial antimicrobial therapy assessed through manual reviewing of AST results (CD, NB, JRZ, FB, JFT)

Statistical analyses (SR/JFT)

- Average treatment effect of combination therapy on study endpoints assessed through **(i) IPTW regression** and **(ii) multivariable regression**
- **Propensity score calculation** (i) **/adjustment** (ii) **:** inclusion period, SAPS 2 at admission, prior chronic diseases/ID, prior hospital LOS, pneumonia type, SOFA at pneumonia onset, plus colonization with MDRB (for clinical cure at Day 14) and diabetes mellitus, prior contrast-enhanced CT/angiography, and prior aminoglycoside and/or glycopeptide exposure (for MAKE)
- **Subgroup analyses:** MDR pathogens, NF-GNB, pivotal β-lactam class (carbapenems or others), companion drug class (AMG or others), duration of combination therapy, SOFA at pneumonia onset, pneumonia-related BSI, septic shock at pneumonia onset

Study flow-chart

IAAT: initial adequate antimicrobial therapy



Main characteristics of the study population (1/2)

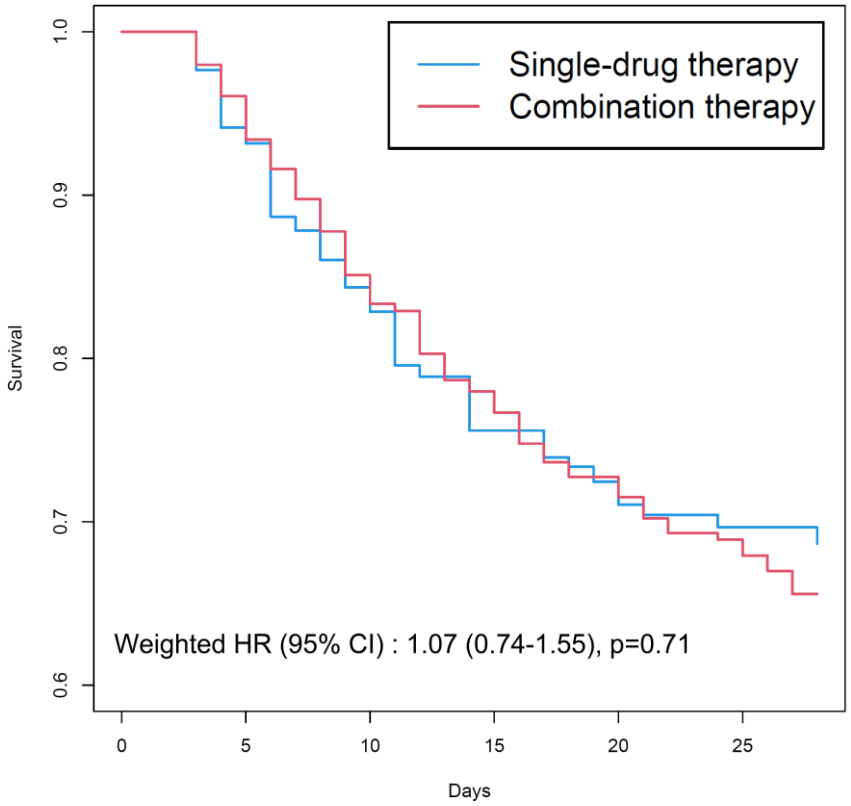
Variables – n (%) or median (IQR)	**All patients** (n = 391)	**Single-drug IAAT** (n = 151)	**Combination IAAT** (n = 240)	*P*-value
Male sex	281 (71.9)	103 (68.2)	178 (74.2)	0.20
Age, years	65 (54-73)	63 (53-73)	66 (55-73)	0.89
BMI, $kg.m^{-2}$	24.9 (21.5-29.7)	25.1 (22.5-30)	24.8 (21.4-29.1)	0.51
Any chronic disease except ID	163 (41.7)	60 (39.7)	103 (42.9)	0.53
Immune deficiency	93 (23.8)	35 (23.2)	58 (24.2)	0.82
SAPS 2 at ICU admission	50 (37-64)	53 (38-64)	48 (35-64)	0.35
VAP	263 (67.3)	105 (69.5)	158 (65.8)	0.15
vHAP	64 (16.4)	18 (11.9)	46 (19.2)	
HAP	64 (16.4)	28 (18.6)	36 (15.0)	
Time from hospital admission to Day 0	12 (7-22)	10 (6-20)	14 (7-23)	0.02
Sepsis / Septic shock at Day 0/Day 1	312 (79.8) / 99 (25.3)	112 (74.2) / 30 (19.9)	200 (83.3) / 69 (28.8)	0.03 / 0.05
SOFA at Day 0/Day 1	7 (4-9)	6 (4-9)	7 (4-9)	0.16
GNB responsible for pneumonia				
Enterobacterales	207 (52.9)	91 (60.3)	116 (48.3)	0.02
NF-GNB (all)	170 (43.5)	52 (34.4)	118 (49.2)	0.005
Pseudomonas aeruginosa	150 (38.4)	44 (29.2)	106 (44.2)	0.003
MDR / XDR/PDR	76 (19.5) / 8 (2.1)	24 (15.9) / 3 (2.0)	52 (21.7) / 5 (2.1)	0.19 / 1

Main characteristics of the study population (2/2)

Variables – n (%) or median (IQR)	**All patients** (n = 391)	**Single-drug IAAT** (n = 151)	**Combination IAAT** (n = 240)	*P*-value
Duration of antimicrobial therapy, overall, days	8 (6-12)	7 (5-10)	8.5 (6-13)	0.04
Duration of combination therapy, days	-	-	3 (2-5)	-
Pivotal antimicrobial agent				
Anti-Pa penicillins ± BLI	137 (35.0)	47 (31.1)	90 (37.5)	<0.0001
Anti-Pa carbapenems	104 (26.6)	32 (21.2)	72 (30.0)	
Anti-Pa cephalosporins	76 (19.5)	25 (16.6)	51 (21.2)	
Non-anti-Pa beta-lactams	55 (14.1)	37 (24.5)	18 (7.5)	
Others	19 (5.3)	10 (6.7)	9 (3.7)	
Companion antimicrobial agent				
Aminoglycosides	-	-	174 (72.5)	-
Fluoroquinolones	-	-	51 (21.3)	
Others	-	-	15 (6.3)	
Organ support during the ICU stay				
MV	376 (96.2)	141 (93.4)	235 (97.9)	0.03
Vasopressors	308 (78.8)	106 (70.2)	202 (84.2)	0.001
RRT	144 (36.8)	56 (37.1)	88 (36.7)	0.93
ECMO	25 (6.4)	9 (6.0)	16 (6.7)	0.78

Antimicrobial agents	Maximal daily doses at Day 0 / Day 1 (mg.kg^{-1} per 24 hours)				
	All patients	KDIGO 0	KDIGO 1	KDIGO 2	KDIGO 3
Ceftriaxone	17.5 (13.6-24.1)	22.7 (16.2-28.1)	12.9 (11.4-18.5)	12.0 & 13.7 -	17.5 (15.7-24.1)
Piperacillin-tazobactam	157.9 (130.4-205.1)	178.4 (145.6-225.5)	170.2 (146.7-214.5)	172.7 (154.8-200.0)	133.3 (95.9-162.2)
Ceftazidime	68.1 (53.7-85.1)	63.5 (53.7-94.1)	58.5 (36.7-87.2)	-	71.8 (60.5-82.4)
Cefepime	62.7 (44.4-80.4)	70.6 (44.4-85.1)	46.5 & 48.5	72.1 (59.0-83.7)	52 (40.3-78.9)
Imipenem	32.2 (22.0-46.2)	35.0 (28.0-46.2)	37.2 (20.3-43.5)	34.1 (25.0-45.9)	19.6 (12.1-31.9)
Meropenem	41.7 (29.1-60.3)	45.2 (41.7-71.9)	56.1 & 60.3 -	23.7 -	40.2 (11.3-44.7)
Amikacin	22.9 (19.4-25.8)	21.3 (19.3-25.6)	23.7 (17.8-28.1)	20.7 (15.0-25.7)	25.1 (22.5-28.2)
Ciprofloxacin	12.5 (8.9-15.7)	12.3 (7.9-15.7)	14.1 (11.4-17.7)	5.2 -	11.5 (8.9-15.7)

Primary study endpoint



All-cause mortality rates at Day 28

28.5% in the single-drug IAAT group versus 32.9% in the combination IAAT group, *P* = 0.36

Cumulative survival overtime

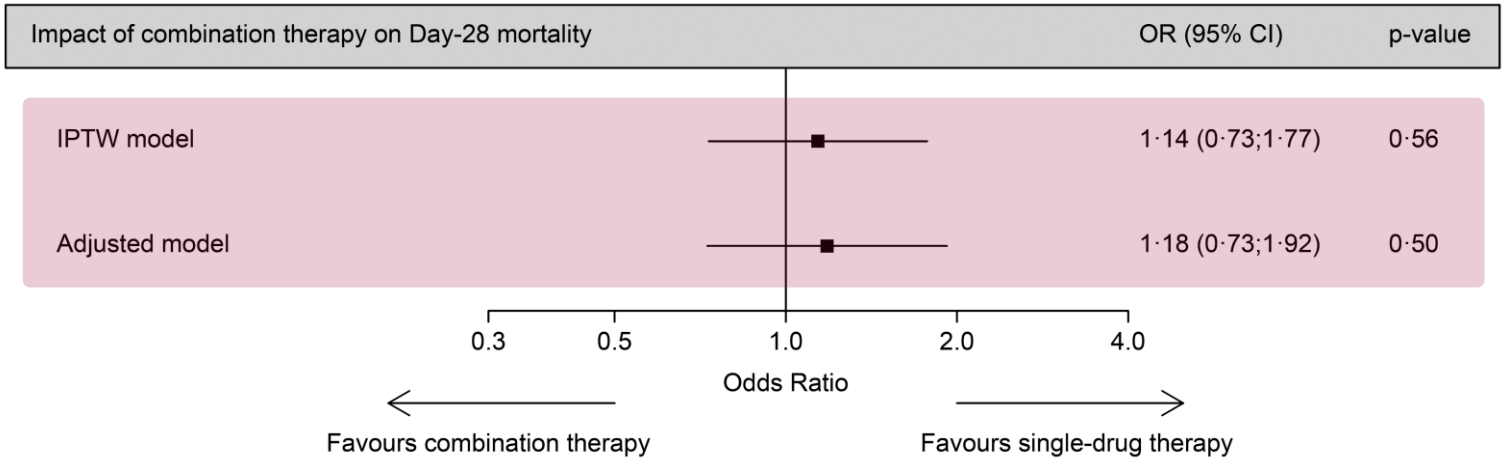
IPT-weighted hazard ratio 1.07, 95% CI 0.74-1.55, *P* = 0.71

Primary study endpoint

No independent association between combination IAAT (vs single-drug IAAT) and the likelihood of all-cause death at Day 28

IPTW: aOR 1.14, 95% CI 0.73-1.77, *P* = 0.56

Multivariable regression: aOR 1.18, 95% CI 0.73-1.92, *P* = 0.50

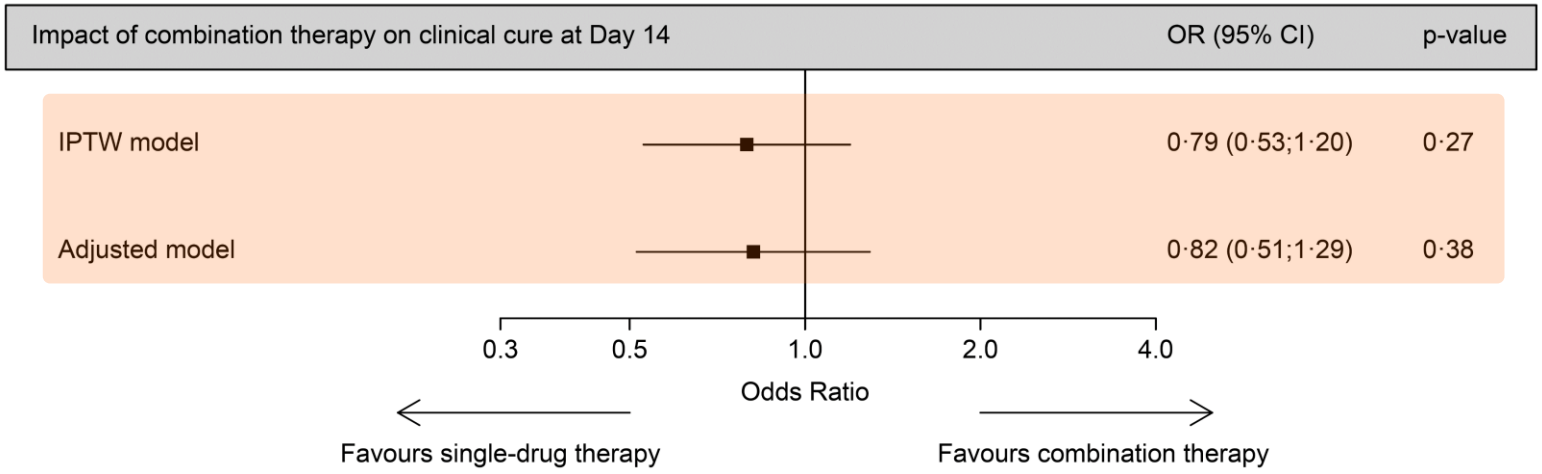


Secondary study endpoint – *clinical cure*

Clinical cure rate at Day 14

49.7% with single-drug IAAT vs 40.0% with combination IAAT, *P* = 0.06

No independent association between combination IAAT (vs single-drug IAAT) and the likelihood of clinical cure at Day 14



Secondary study endpoint – *MAKE*

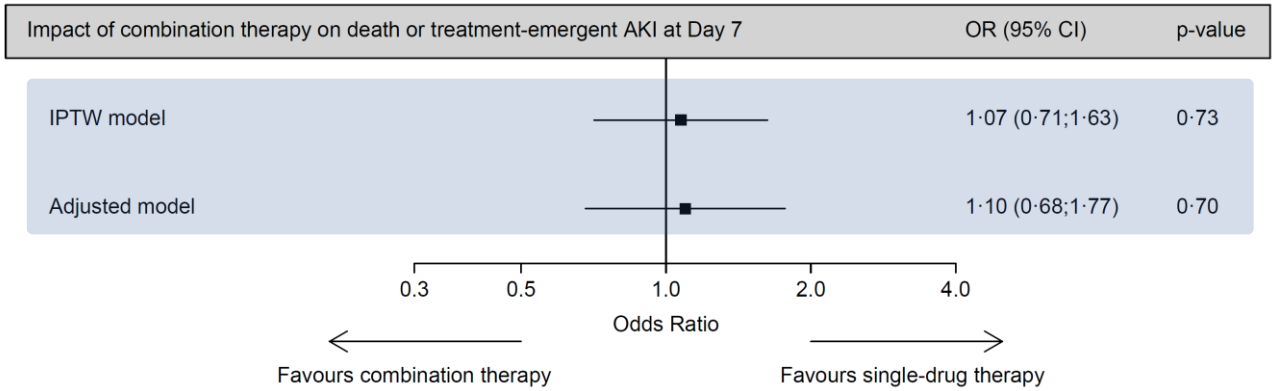
Treatment-emergent AKI at Day 7 (with or without RRT)

31.1% with single-drug IAAT vs 39.6% with combination IAAT, *P* = 0.09

Combination group: 37.9% with AMG vs 43.9% with other companion drugs, *P* = 0.30

Death at Day 7: 10.6% with single-drug IAAT vs 10.0% with combination IAAT, *P* = 0.85

No independent association between combination IAAT (versus single-drug IAAT) and the likelihood of death or AKI at Day 7



Subgroup analyses

Patient subpopulations	Mortality at Day 28		Clinical cure at Day 14		Death or AKI at Day 7	
	aOR (95% CI)	*P*-value	aOR (95% CI)	*P*-value	aOR (95% CI)	*P*-value
Pneumonia due to MDR GNB	0.88 (0.31-2.53)	0.82	1.52 (0.42-5.41)	0.52	1.82 (0.57-5.77)	0.31
Pneumonia due to non-MDR GNB	1.22 (0.69-2.16)	0.50	0.76 (0.46-1.27)	0.30	0.96 (0.55-1.66)	0.88
Pneumonia due to NF-GNB	0.73 (0.30-1.73)	0.47	1.13 (0.49-2.56)	0.78	1.36 (0.54-3.46)	0.52
Carbapenem-based regimen	1.14 (0.45-2.88)	0.78	0.53 (0.20-1.41)	0.21	1.51 (0.45-5.05)	0.50
Non-carbapenem-based regimen	1.09 (0.60-1.99)	0.77	0.99 (0.57-1.73)	0.98	0.81 (0.46-1.44)	0.48
AMG-containing regimen	1.23 (0.74-2.06)	0.42	0.78 (0.48-1.26)	0.31	1.05 (0.62-1.76)	0.86
Non-AMG-containing regimen	1.01 (0.48-2.12)	0.98	0.76 (0.39-1.47)	0.42	1.26 (0.65-2.46)	0.49
Combination therapy <3 days	1.04 (0.58-1.87)	0.90	1.12 (0.64-1.95)	0.70	1.00 (0.55-1.80)	0.99
Combination therapy ≥3 days	1.34 (0.76-2.39)	0.32	0.59 (0.35-1.01)	0.05	1.18 (0.68-2.05)	0.55
SOFA <7 at Day 0/Day 1	1.43 (0.65-3.12)	0.37	0.79 (0.42-1.50)	0.47	1.11 (0.56-2.18)	0.77
SOFA ≥7 at Day 0/Day 1	1.01 (0.54-1.91)	0.97	0.89 (0.43-1.84)	0.76	1.05 (0.50-2.09)	0.95
Septic shock at Day 0/Day 1	1.40 (0.49-3.99)	0.53	0.60 (0.19-1.88)	0.38	2.22 (0.65-7.62)	0.21
Pneumonia-related BSI	1.49 (0.29-7.74)	0.64	0.50 (0.10-2.43)	0.39	0.80 (0.17-3.77)	0.78

All = NS

Other outcomes

Variables – n (%) or median (IQR)	**All patients** (n = 391)	**Single-drug IAAT** (n = 151)	**Combination IAAT** (n = 240)	*P*-value
MDRB carriage acquired after pneumonia	57 (14.6)	29 (19.2)	28 (11.7)	0.04
Clostridioides difficile infection after pneumonia	5 (1.3)	4 (2.6)	1 (0.4)	0.10
ICU LOS, days	23 (14-39)	22 (13-37)	26 (15-41)	0.55
Hospital LOS, days	40 (24-69)	40.5 (22.5-70)	40 (26-69)	0.66
In-hospital death				
Day 14	86 (22.0)	34 (22.5)	52 (21.7)	0.84
Overall	195 (49.9)	64 (42.4)	131 (54.6)	0.02

Limits

- Retrospective study (prospectivelly collected data, PS)
- Impact of dosing scheme not assessed
- No data on therapeutic drug monitoring
- Very few XDR/PDR pathogens (no subgroup analyses)
- Antimicrobial-related adverse events other than AKI not assessed
- Patients with HAP managed outside the ICU not included

MAIN MESSAGES

- No impact of combination therapy on day-28 mortality in ICU patients with HAP, vHAP or VAP due to GNB – including in those with septic shock and/or pneumonia due to NFGNB
- No benefit of combination therapy on the likelihood of clinical cure
- No overrisk of AKI with AMG (short duration, once-daily dose, TDM)
- MDRB/*C. difficile* acquisition: no « red flag » with combination therapy
- In HAP/VAP due to XDR GNB?