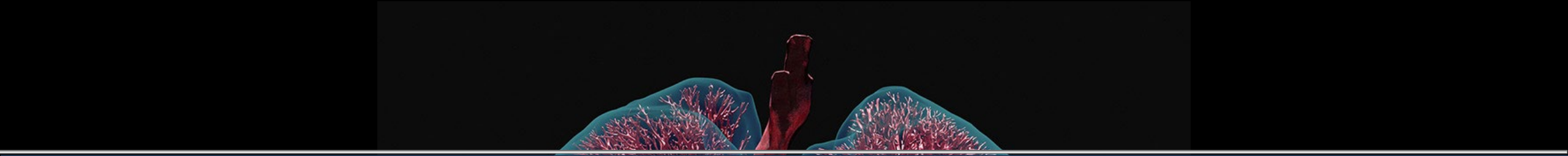

4ème Journée d'Infectiologie de l'IMR – Paris, vendredi 31 janvier 2025

Antibiothérapie des pneumonies acquises sous ventilation mécanique

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CRICS TRIGGERSEP F-CRIN network

PROMISE Professional community network on antimicrobial resistance

Institut Maurice Rapin

Conflits d’intérêt potentiels (2020-2024)

MSD

Pfizer

Shionogi

Advanz Pharma

Antibiothérapie des PAVM

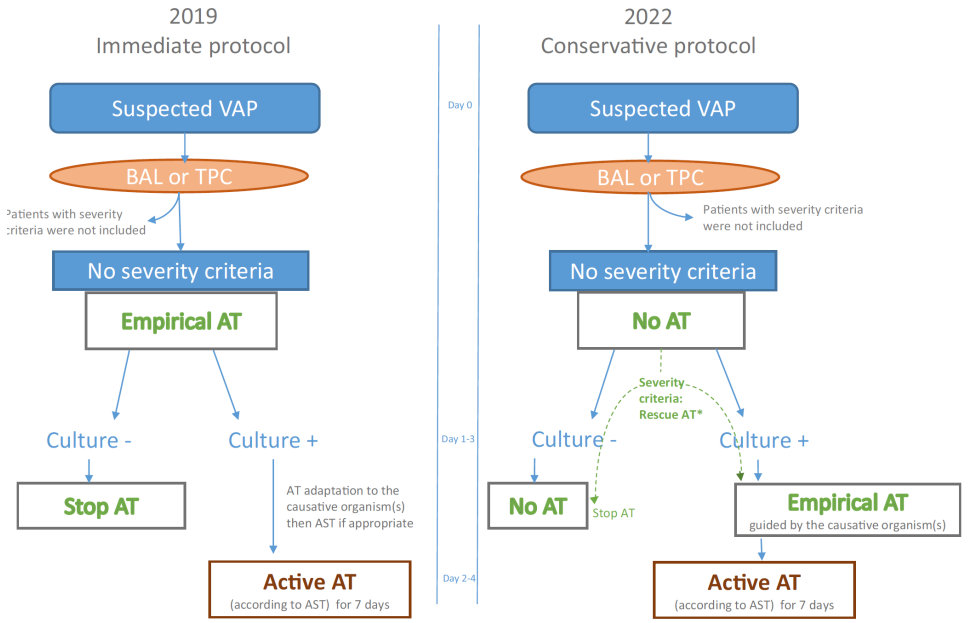
Timing d’introduction ?

Immediate vs. culture-initiated antibiotic therapy in suspected non-severe ventilator-associated pneumonia: a before–after study (DELAVAP)

Maëlle Martin[1*], Solène Forveille[1], Jean-Baptiste Lascarrou[1], Amélie Seguin[1], Emmanuel Canet[1], Jérémie Lemarié[1], Maïté Agbakou[1], Luc Desmedt[1], Gauthier Blonz[1], Olivier Zambon[1], Stéphane Corvec[2], Aurélie Le Thuaut[3] and Jean Reignier[1,4]

Annals of Intensive Care (2024) 14:33

Delayed (culture-based) vs immediate initiation of antimicrobials for VAP (no ARDS, no shock): no significant difference on MV duration or Day-28 mortality



	Immediate n = 44	Conservative n = 43	*p* value
Days alive without AT by day 28, median [IQR]	16.0 [0.0–20.0]	18.0 [0.0–21.0]	0.50
Days alive without broad-spectrum AT by day 28, median [IQR]	23.5 [5.0–26.0]	25.0 [0.0–28.0]	0.53
Days alive without carbapenem by day 28, median [IQR]	28.0 [9.0–28.0]	28.0 [0.0–28.0]	0.65
iMV duration, days, median [95% confidence interval] HR [95%CI]	9.0 [6.0–24.0] 1.1 [0.7–1.8]	9.0 [6.0–19.0]	0.65
Ventilator-free days, median [IQR]	18.5 [0.0–23.0]	16.0 [0.0–22.0]	0.99
ICU stay, days, median [95% confidence interval]	9.0 [6.0–14.0]	13.0 [8.0–17.0]	0.71
Day-28 mortality, n (%) HR [95%CI]	11 (25.0) 0.8 [0.4–2.0]	11 (25.6)	0.71
VAP-related abscess, n (%)	0	2 (4.6)	0.24
VAP-related bacteraemia, n (%)	0	2 (4.6)	0.24
Subsequent VAP, n (%)			
Recurrence[a]	3 (6.8)	2 (4.6)	0.11
Superinfection[a]	2 (4.5)	0 (0)	
First VAP after suspected unconfirmed VAP	0 (0)	4 (9.3)	
MRB[b], n (%)	0	0	-

Prognostic impact of early appropriate antimicrobial therapy in critically ill patients with nosocomial pneumonia due to Gram-negative pathogens: a multicenter cohort study

François Barbier, Niccolò Buetti, (…), Jean-Ralph Zahar, Jean-François Timsit, for the OutcomeRéa study group

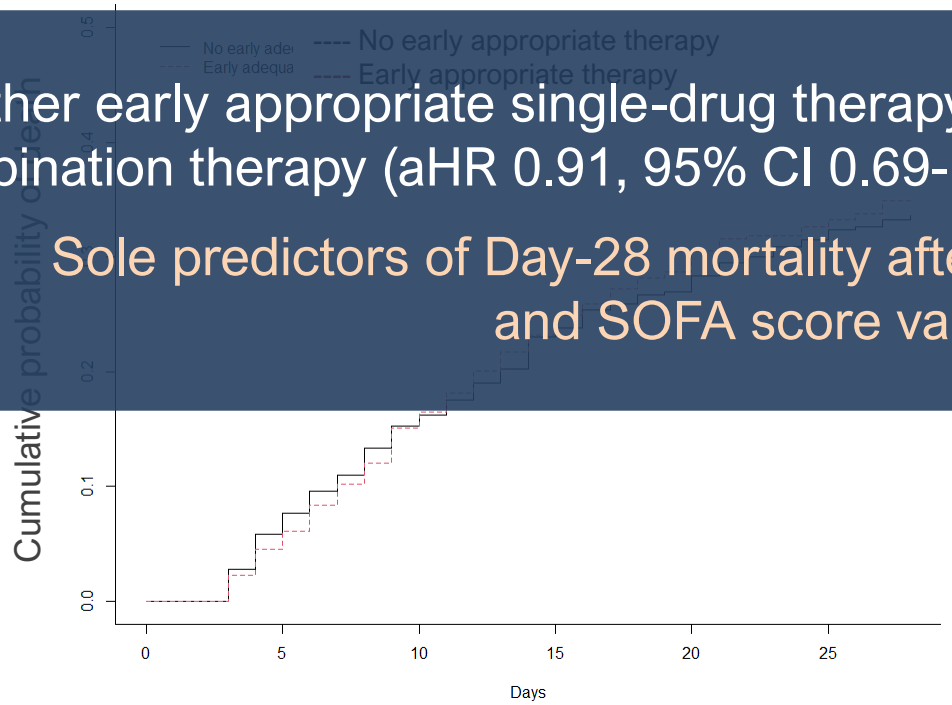
Crit Care Med 2025 (in press)

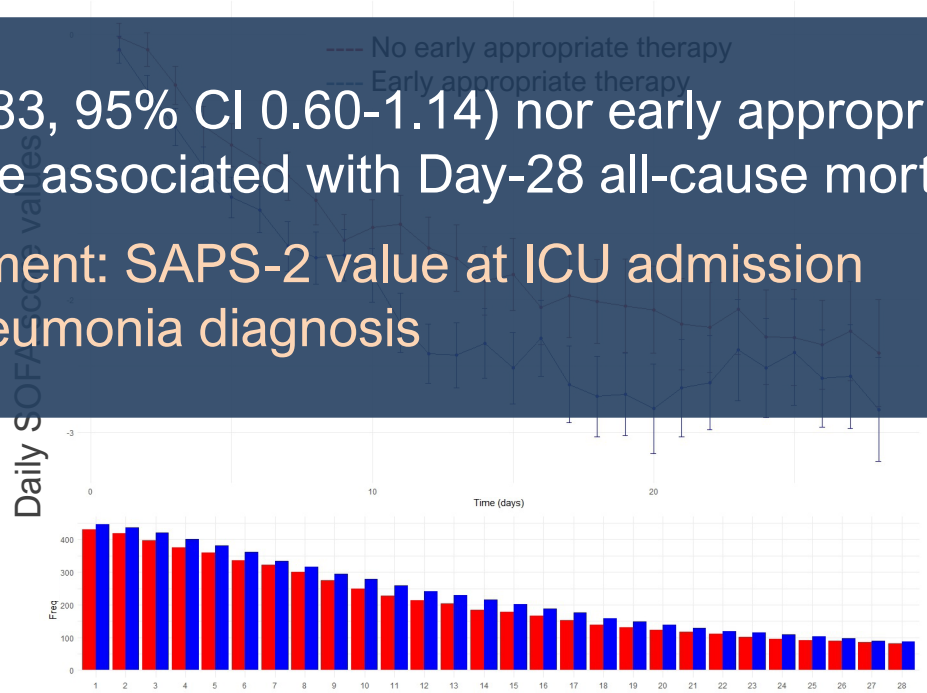
804 patients with HAP/VAP due to GNB

Early appropriate antimicrobial therapy: n = 495 (62%) (single 25%, combo 36%)

Neither early appropriate single-drug therapy (aHR 0.83, 95% CI 0.60-1.14) nor early appropriate combination therapy (aHR 0.91, 95% CI 0.69-1.19) were associated with Day-28 all-cause mortality

Sole predictors of Day-28 mortality after adjustment: SAPS-2 value at ICU admission and SOFA score value at pneumonia diagnosis





Antibiothérapie des PAVM

Apports des mPCR pour le traitement initial?

Fast multiplex bacterial PCR of bronchoalveolar lavage for antibiotic stewardship in hospitalised patients with pneumonia at risk of Gram-negative bacterial infection (Flagship II): a multicentre, randomised controlled trial

Andrei M Darie, Nina Khanna, Kathleen Jahn, Michael Osthoff, Stefano Bassetti, Mirjam Osthoff, Desiree M Schumann, Werner C Albrich, Hans Hirsch, Martin Brutsche, Leticia Grize, Michael Tamm, Daiana Stolz

***Lancet Respir Med* 2022; 10: 877–87**

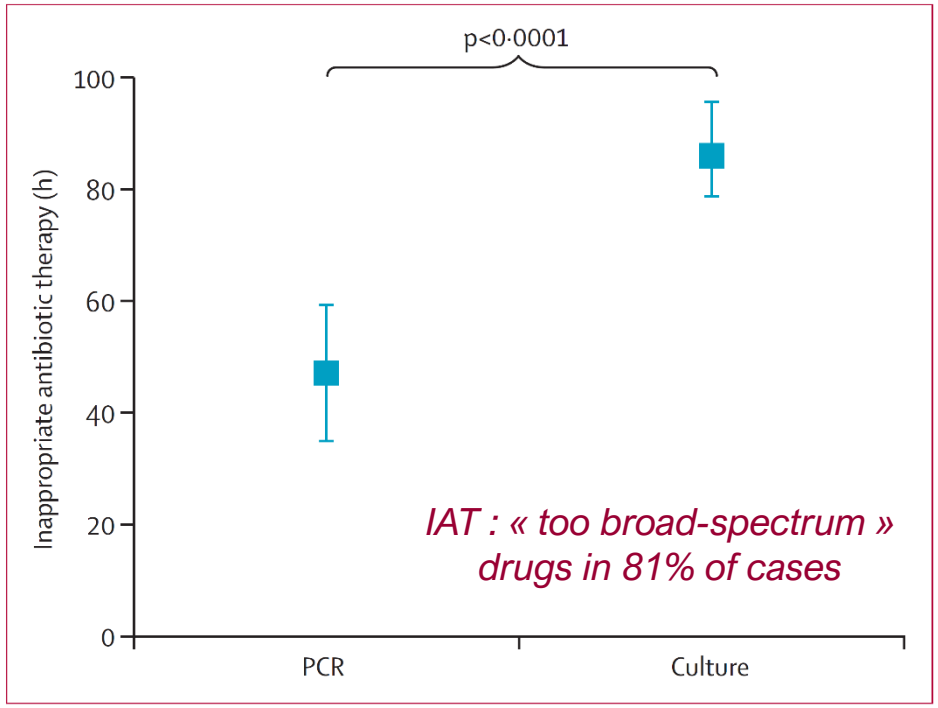


Figure 2: **Duration of inappropriate antibiotic therapy**
Bars indicate 95% CIs.

	Unyvero PCR		Conventional microbiology	
	Control group (n=108)	PCR group (n=100)	Control group (n=107)*	PCR group (n=100)
Citrobacter freundii	1 (<1%)	0	0	0
Escherichia coli	2 (2%)	3 (3%)	1 (<1%)	2 (2%)
Enterobacter cloacae complex	0	2 (2%)	2 (2%)	4 (4%)
Enterobacter aerogenes	1 (<1%)	0	0	2 (2%)
Proteus spp	1 (<1%)	2 (2%)	2 (2%)	2 (2%)
Klebsiella pneumoniae	1 (<1%)	1 (1%)	2 (2%)	0
Klebsiella oxytoca	0	0	0	0
Klebsiella variicola	0	0	1 (<1%)	0
Serratia marcescens	1 (<1%)	0	1 (<1%)	1 (1%)
Morganella morganii	0	2 (2%)	0	1 (1%)
Moraxella catarrhalis	1 (<1%)	1 (1%)	1 (<1%)	0
Pseudomonas aeruginosa	5 (5%)	4 (4%)	5 (5%)	0
Acinetobacter baumannii complex	0	0	0	1 (1%)
Stenotrophomonas maltophilia	2 (2%)	0	0	0
Haemophilus influenzae	10 (9%)	5 (5%)	4 (4%)	0

Rapid multiplex PCR panels for the management of ventilator-associated pneumonia: pondering strengths and weaknesses

Mara Tomasello[1,2], Davide Mangioni[1*], Mauro Panigada[3], Caterina Matinato[4] and Alessandra Bandera[1,2]

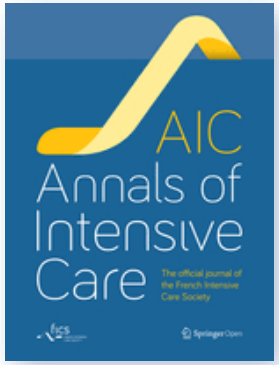
Intensive Care Med (2024) 50:789–791

N = 49 COVID-19 patients

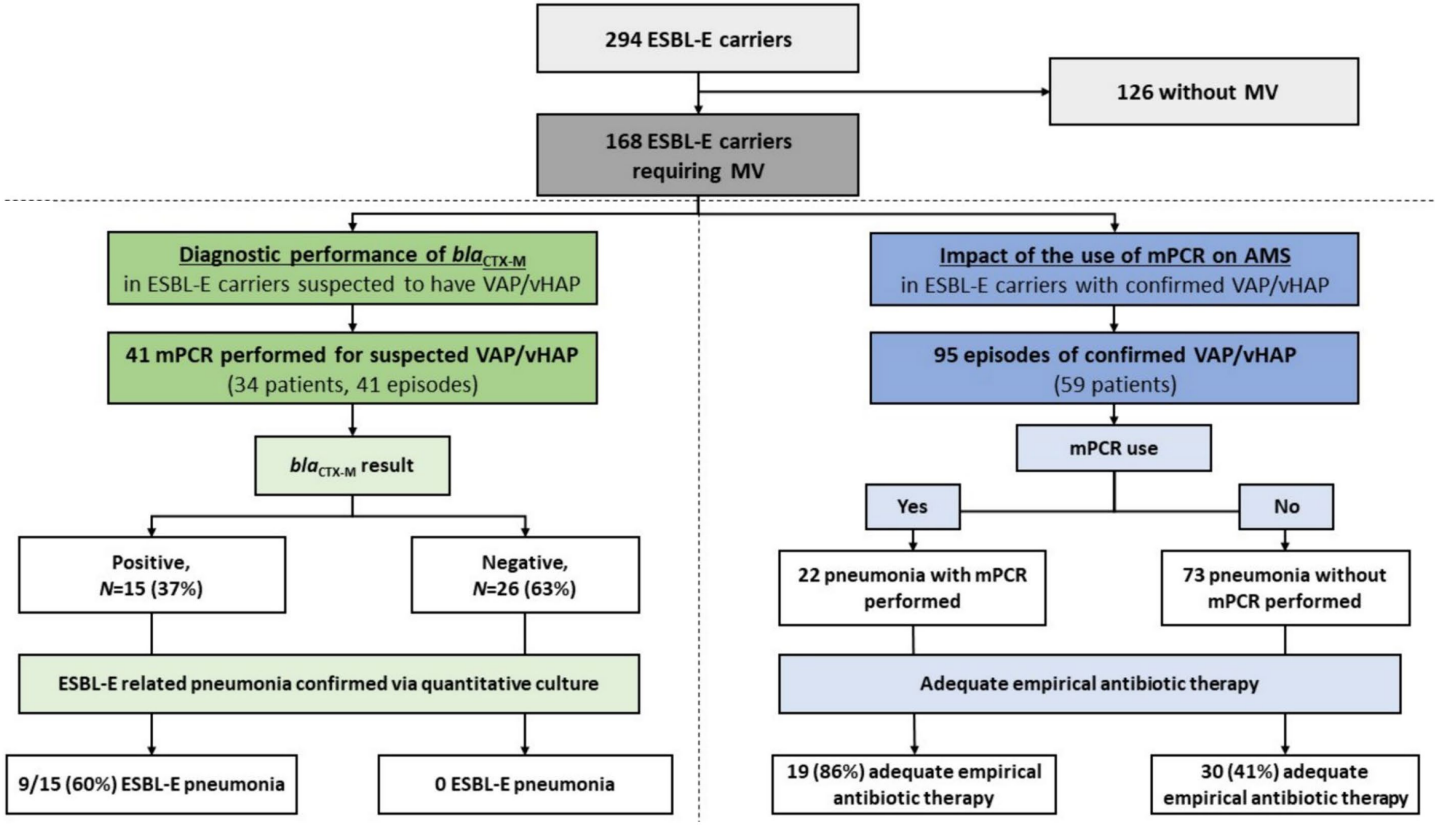
Therapeutic choice	ANTIBIOTIC START	ANTIBIOTIC MODIFICATION*	CONFIRMATION OF ONGOING ANTIBIOTIC*	CONFIRMATION OF NO ANTIBIOTIC*
Bases on BAL_{FAPPP}	15/49 (30.6%)	3/49 (6.1%)	13/49 (26.6%)	18/49 (36.7%)
Based on BAL_{CX}**	6/49 (12.2%)	3/49 (6.1%)	28/49 (57.2%)	12/49 (24.5%)
Definitive choice NOT in line with BAL_{FAPPP}	9/49 (18.4%)			
Definitive choice in line with BAL_{FAPPP}			40/49 (81.6%)	

Fig. 1 Therapeutic choices based on BAL_{FAPPP} and BAL_{CX} in patients with suspected VAP of the CoV-AP study. *16/49 patients (32.6%) were already on antimicrobial therapy at the time of BAL acquisition. **Therapeutic choices based on BAL_{CX} considered decisions guided by BAL_{FAPPP} as baseline

Performance and impact of rapid multiplex PCR on diagnosis and treatment of ventilated hospital-acquired pneumonia in patients with extended-spectrum β-lactamase-producing *Enterobacterales* rectal carriage



Bay *et al. Annals of Intensive Care* (2024) 14:118



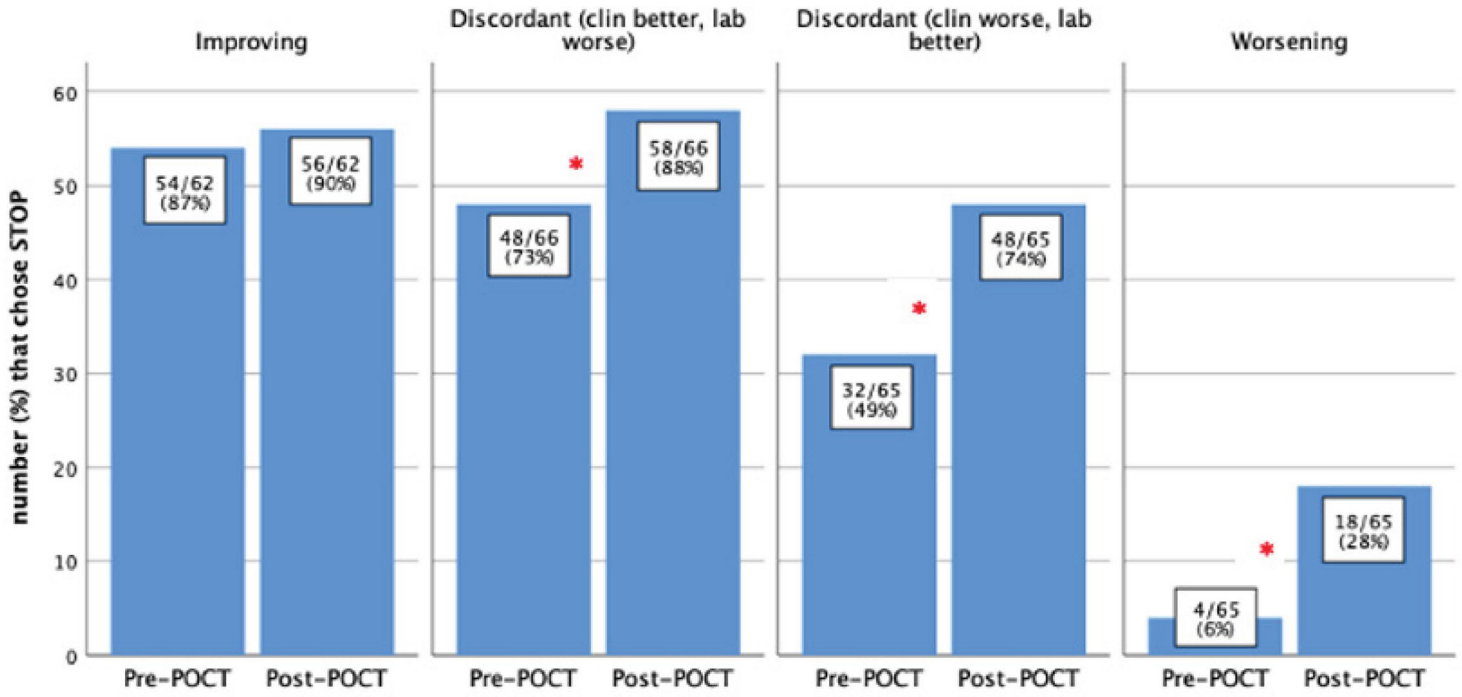
- 168 ESBLE carriers under MV
- mPCR in suspected 41 VAP/Vhap
- *bla*$_{CTX-M}$ gene detected in 15/41 (37%) episodes: 9/15 (60%) were confirmed ESBLE pneumonia
- **All episodes with a negative *bla*$_{CTX-M}$ PCR (n = 26): culture negative for ESBLE**

WHY STOP? A prospective observational vignette-based study to determine the cognitive-behavioural effects of rapid diagnostic PCR-based point-of-care test results on antibiotic cessation in ICU infections

Suveer Singh [1,2] Martine Nurek [3] Sonia Mason,[4] Luke SP Moore [5,6] Nabeela Mughal,[5,6] Marcela P Vizcaychipi [7,8]

BMJ Journals
BMJ Open

BMJ Open 2023;**13**:e073577.



- Observational cohort simulation study
- 70 ICU physicians (UK)
- 4 case vignettes describing patients who had completed a course of antibiotics for pneumonia (clinical and biological data [WBC and CRP])
- Decision to stop or not antimicrobials before then after a **negative point-of-care mPCR result**

Antibiothérapie des PAVM

Monothérapie ou bithérapie ?

D-PRISM: a global survey-based study to assess diagnostic and treatment approaches in pneumonia managed in intensive care

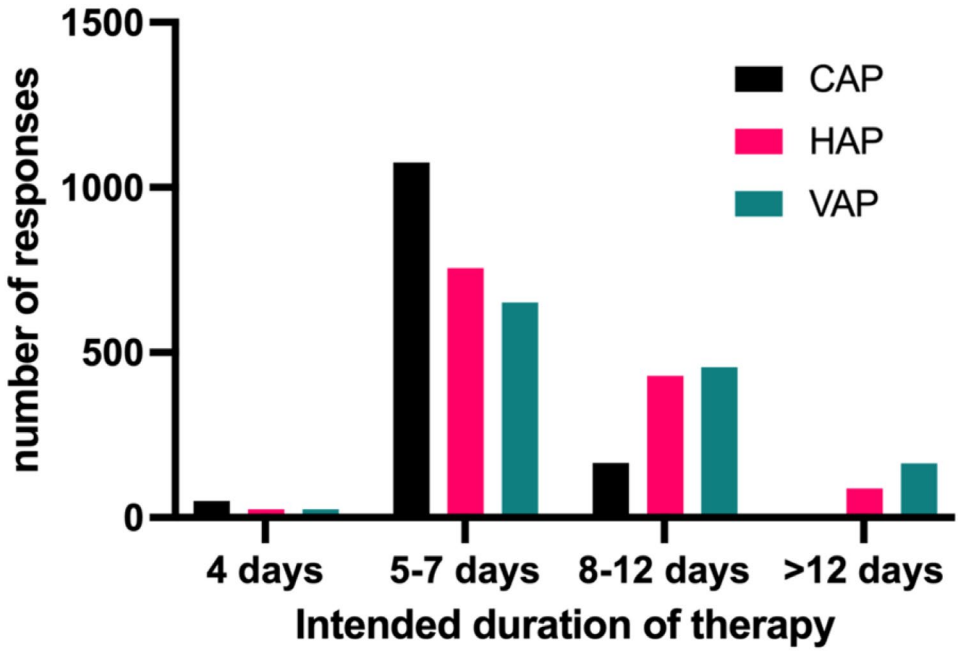
Reyes *et al. Critical Care* (2024) 28:381

CRITICAL CARE

On-line survey (2022) - 1296 ICU physicians from 72 countries (LMIC 51%, HIC 49%)

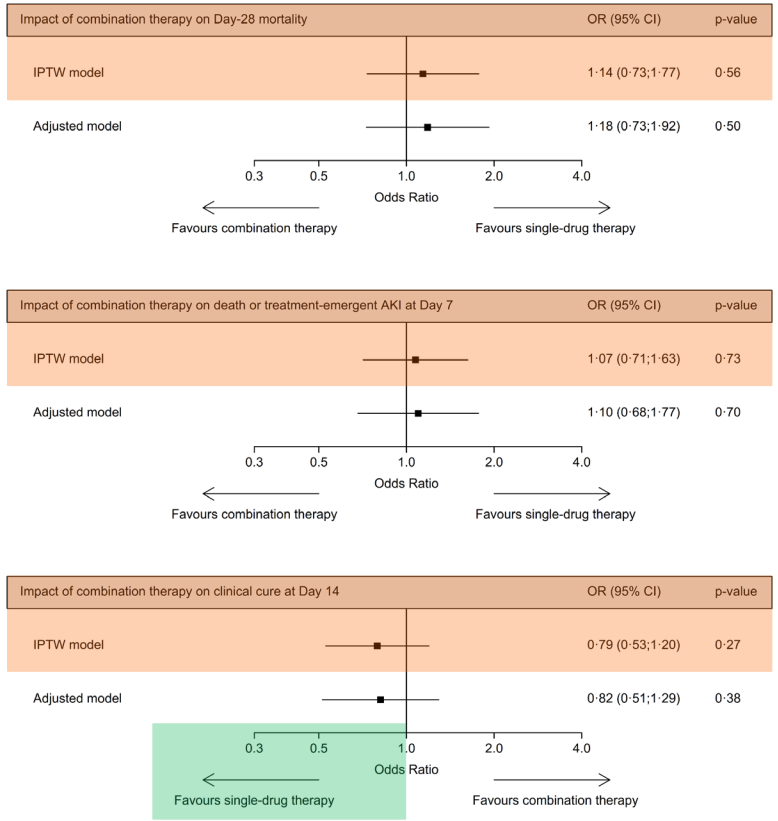
Antibiotic regimen	VAP = 1296
Monotherapy for all patients	163 (12.5%)
Monotherapy for low risk of resistant organisms	511 (39.4%)
Dual therapy, including coverage for resistant organisms (e.g. MRSA/MDR pseudomonas) for all patients	616 (47.5%)
N/A	6 (0.4%)

47% of intensivists: dual therapy covering MDRB for all patients



Single-drug versus combination antimicrobial therapy in critically ill patients with hospital-acquired pneumonia and ventilator-associated pneumonia due to Gram-negative pathogens: a multicenter retrospective cohort study

Barbier *et al. Critical Care* (2024) 28:10



- Cohorte multicentrique / OutcomeRéa
- 391 patients avec pneumonie nosocomiale à BGN recevant une antibiothérapie active à J1J2 (monothérapie 39%, bithérapie 61%)
- Analyses ajustées sur IPTW
- **Bithérapie <u>non associée</u> à une réduction du risque :**
  - D'échec clinique à J14 (aOR 0,79; 0,53-1,20)
  - De décès à J28 (aOR 1,14; 0,73-1,77)

Single-drug versus combination antimicrobial therapy in critically ill patients with hospital-acquired pneumonia and ventilator-associated pneumonia due to Gram-negative pathogens: a multicenter retrospective cohort study

CRITICAL CARE

Barbier *et al. Critical Care* *(2024) 28:10*

Table 2 Impact of combination therapy on study endpoints: results of 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 Gram-negative bacteria	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 Gram-negative bacteria	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 no-fermenting Gram-negative bacteria	0.73 (0.30–1.73)	0.47	1.13 (0.49–2.56)	0.78	1.36 (0.54–3.46)	0.52
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Non-carbapenem-based regimen	[illegible]	0.77	[illegible]	0.98	0.81 (0.46–1.44)	0.48
Aminoglycoside-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-aminoglycoside-containing regimen	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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 score value < 7 at pneumonia onset	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 score value ≥ 7 at pneumonia onset	1.01 (0.54–1.91)	0.97	0.89 (0.43–1.84)	0.76	1.02 (0.50–2.09)	0.95
Septic shock at pneumonia onset	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 [a]	1.49 (0.29–7.74)	0.64	0.50 (0.10–2.43)	0.39	0.80 (0.17–3.77)	0.78

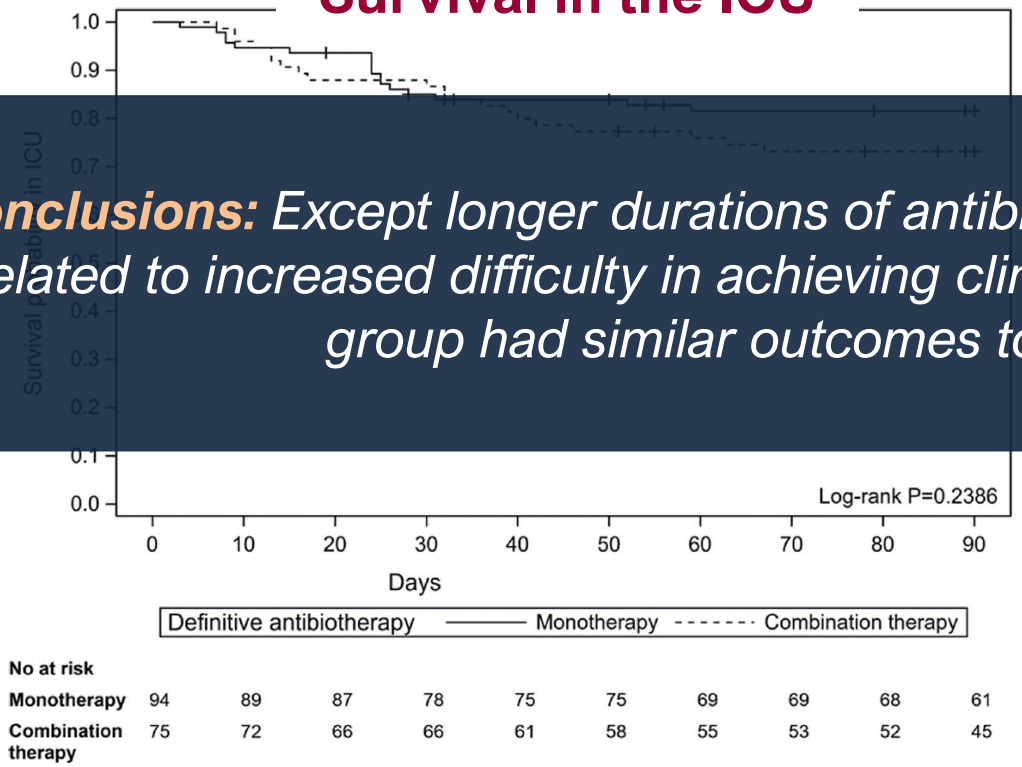
Subgroups analyses according to the causative pathogens (MDR or not), pivotal and companion drugs, duration of combination therapy, SOFA at pneumonia onset, and in patients with pneumonia due to non-fermenting GNB, pneumonia-related BSI or septic shock : **all NS**

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

CRITICAL CARE

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

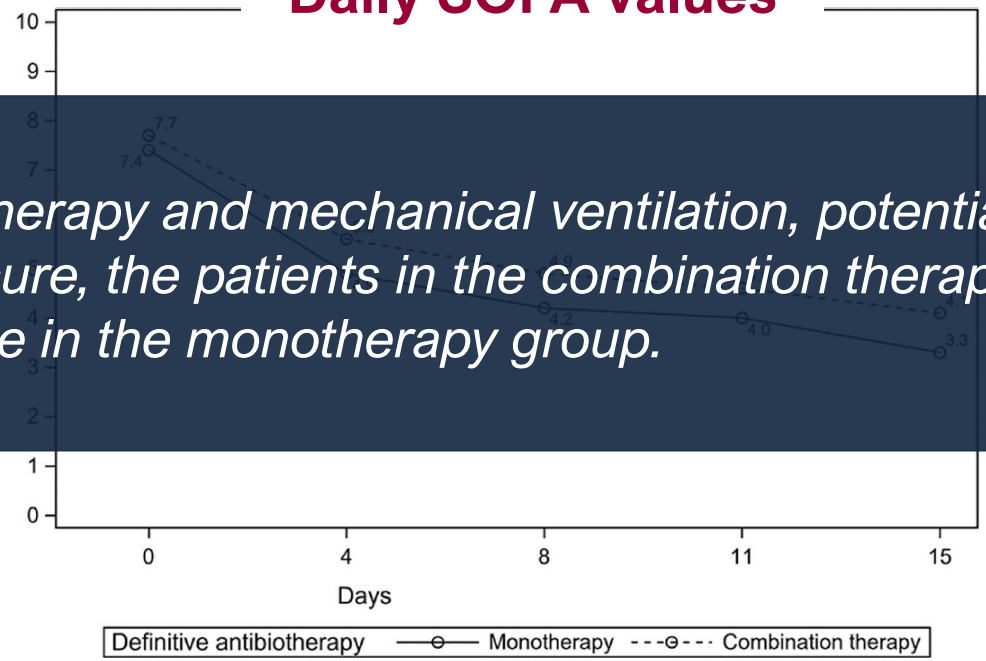
Survival in the ICU



No at risk										
Monotherapy	94	89	87	78	75	75	69	69	68	61
Combination therapy	75	72	66	66	61	58	55	53	52	45

Similar results after adjustment for randomization arm of iDIAPASON trial and SOFA score at ICU admission

Daily SOFA values



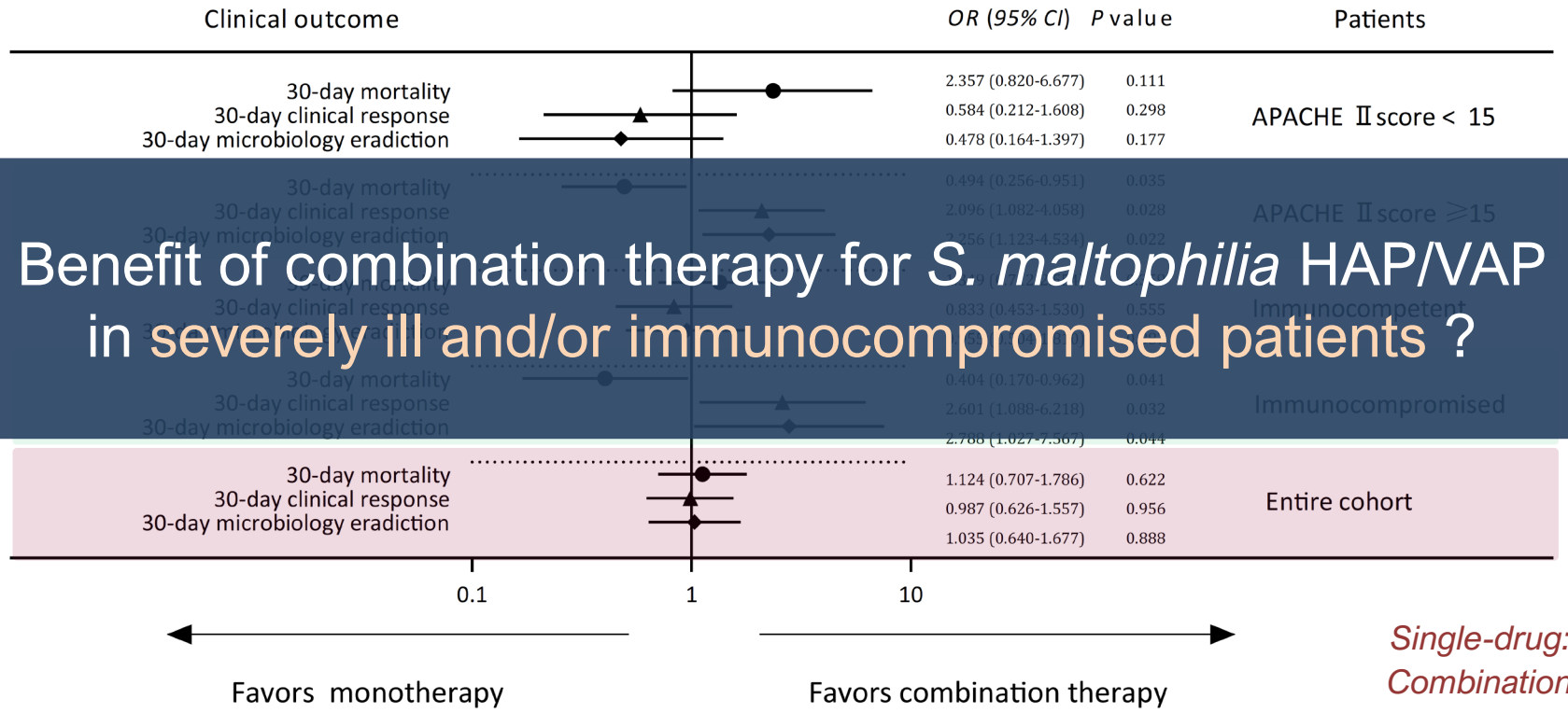
No. of patients					
Monotherapy	93	88	79	63	55
Combination therapy	75	73	68	61	54

Conclusions: *Except longer durations of antibiotic therapy and mechanical ventilation, potentially related to increased difficulty in achieving clinical cure, the patients in the combination therapy group had similar outcomes to those in the monotherapy group.*

Assessment of the relative benefits of monotherapy and combination therapy approaches to the treatment of hospital-acquired *Stenotrophomonas maltophilia* pneumonia: a multicenter, observational, real-world study

Chen *et al. Annals of Intensive Care* (2023) 13:47

Retrospective multicenter cohort (China, 2016-2022) – 307 patients with *S. maltophilia* HAP/VAP (definite combination therapy, 56%) / overall day-30 mortality 41% / IPTW-adjusted analyses



Benefit of combination therapy for *S. maltophilia* HAP/VAP in severely ill and/or immunocompromised patients ?

Single-drug: mostly TMP-SMX or FQ
Combination: mostly TMP-SMX + FQ

Antibiothérapie des PAVM

Quelle durée de traitement ?

Comparison of 8 versus 15 days of antibiotic therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia in adults: a randomized, controlled, open-label trial

Adrien Bouglé[1*], Sophie Tuffet[2], Laura Federici[3], Marc Leone[4], Antoine Monsel[5], Thomas Dessalle[1], Julien Amour[1], Claire Dahyot-Fizelier[6], François Barbier[7], Charles-Edouard Luyt[8], Olivier Langeron[5], Bernard Cholley[10], Julien Pottecher[11], Tarik Hissem[12], Jean-Yves Lefrant[13], Benoit Veber[14], Matthieu Legrand[15], Alexandre Demoule[9], Pierre Kalfon[16], Jean-Michel Constantin[17], Alexandra Rousseau[2], Tabassome Simon[2] and Arnaud Foucrier[18] on behalf of the iDIAPASON Trial Investigators

Intensive Care Med (2022) 48:841–849

Open-labeled non-inferiority RCT (margin, 10%): 8 versus 15 days of antimicrobial therapy for *P. aeruginosa* VAP

Primary end-point: death or *Pa*-VAP recurrence at Day 90 / N = 186 (planned enrollment, 600)

Table 2 Primary outcome and its components, according to study group

Outcome or event	15-day group (*N* = 98)	8-day group (*N* = 88)	Difference (90% CI)
Death or PA-VAP recurrence rate at day 90 during hospitalization in the ICU in ITT population—no. (%)	25/98 (25.5)	31/88 (35.2)	9.7% (— 1.9–21.2%)
Death or PA-VAP recurrence rate at day 90 during hospitalization in the ICU in PP population—no. (%)	22/80 (27.5)	29/72 (40.3)	12.8% (— 0.4–25.6%)
PA-VAP recurrence rate during hospitalization in the ICU in ITT population—no. (%)	9/98 (9.2)	15/88 (17)	7.9% (— 0.5–16.8%)

Similar results in the per-protocol analysis

Short-course versus prolonged-course antibiotic regimens for ventilator-associated pneumonia: A systematic review and meta-analysis of randomized controlled trials

Huzaifa Ahmad Cheema [a,*], Aayat Ellahi [b], Hassan Ul Hussain [c], Haider Kashif [c], Mariam Adil [c], Danisha Kumar [c], Abia Shahid [a], Muhammad Ehsan [a], Harpreet Singh [d], Natalie Duric [e], Tamas Szakmany [e,f,**]

J Crit Care 78 (2023) 154346

6 RCTs (1274 patients) – Short (≤8 days) vs longer durations of antimicrobial therapy

Day-28 mortality: no difference (overall, MRSA, non-NF-GNB, NF-GNB)

VAP due to NF-GNB: higher risk of recurrence with short durations (RR 1.73 95% CI 1.17-2.54)

Clinical resolution, MV duration, ICU LOS: no difference (low QoE)

	Short course		Prolonged course			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
1.1.1 NF-GNB							
Bougle et al, 2022	15	88	9	98	11.8%	1.86 [0.86, 4.03]	
Chastre et al, 2003	26	64	16	63	25.5%	1.60 [0.95, 2.68]	
Medina et al, 2007	12	27	5	22	9.2%	1.96 [0.81, 4.71]	
Subtotal (95% CI)		**179**		**183**	**46.5%**	**1.73 [1.17, 2.54]**	
Total events	53		30				

Heterogeneity: Tau² = 0.00; Chi² = 0.20, df = 2 (P = 0.91); I² = 0%

Test for overall effect: Z = 2.77 (P = 0.006)

NF-GNB / VAP recurrence

Individualised, short-course antibiotic treatment versus usual long-course treatment for ventilator-associated pneumonia (REGARD-VAP): a multicentre, individually randomised, open-label, non-inferiority trial

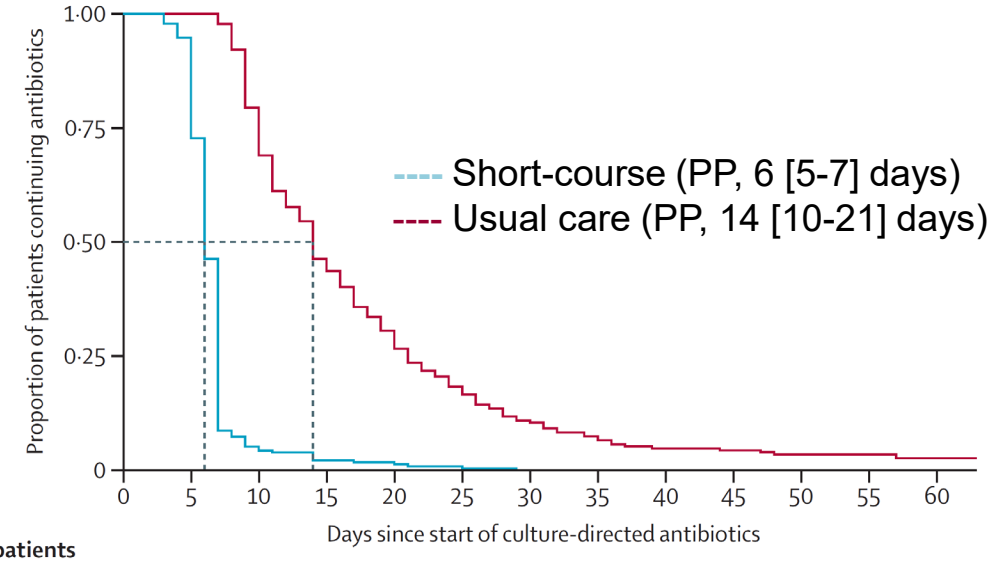
Yin Mo, Suchart Booraphun, Andrew Yunkai Li, Pornanan Domthong, Gyan Kayastha, Yie Hui Lau, Ploenchan Chetchotisakd, Direk Limmathurotsakul, Paul Anantharajah Tambyah, Ben S Cooper, on behalf of the REGARD-VAP investigators

***Lancet Respir Med* 2024; 12: 399–408**

Non-inferiority, open-label RCT (1:1) – 460 patients with VAP (NF-GNB 53%, culture-negative 30%)

Short-course treatment (3-7 days days) versus "usual" care (≥8 days)

Primary outcome: death or pneumonia recurrence at Day 60



Number of patients continuing antibiotics				
Usual care	229	70	11	6
Short-course therapy	231	4	0	0

	Mortality (%)	Recurrence of pneumonia (%)	Primary outcome (%)	Unadjusted absolute risk difference (one-sided 95% CI)	Adjusted absolute risk difference (one-sided 95% CI)
Intention-to-treat (n=460)	..	..	..	−3%(−∞ to 5%)	−2%(−∞ to 5%)
Short-course group (n=231)	81 (35%)	33 (14%)	95 (41%)	..	..
Usual care group (n=229)	88 (38%)	30 (13%)	100 (44%)	..	..
Per-protocol (n=435)	..	..	..	−3%(−∞ to 5%)	−2%(−∞ to 4%)
Short-course group (n=211)	76 (36%)	29 (14%)	87 (41%)	..	..
Usual care group (n=224)	87 (39%)	30 (13%)	99 (44%)	..	..

Acquisition of carbapenem-resistant GNB: no difference (18% vs 18%)

Less antibiotic-related AE in the intervention group (8% vs 38%, $p < 0.001$)

Antimicrobial Stewardship for Ventilator Associated Pneumonia in Intensive Care (the ASPIC trial): study protocol for a randomised controlled trial

BMJ open

Arnaud Foucrier ,[1] Antoine Roquilly,[2] Delphine Bachelet,[3] Ignacio Martin-Loeches,[4,5] Adrien Bougle,[6] Jean-François Timsit,[7] Philippe Montravers,[8] Jean-Ralph Zahar,[9] Philippine Eloy,[3] Emmanuel Weiss,[10] ASPIC study group

BMJ Open 2023;**13**:e065293.

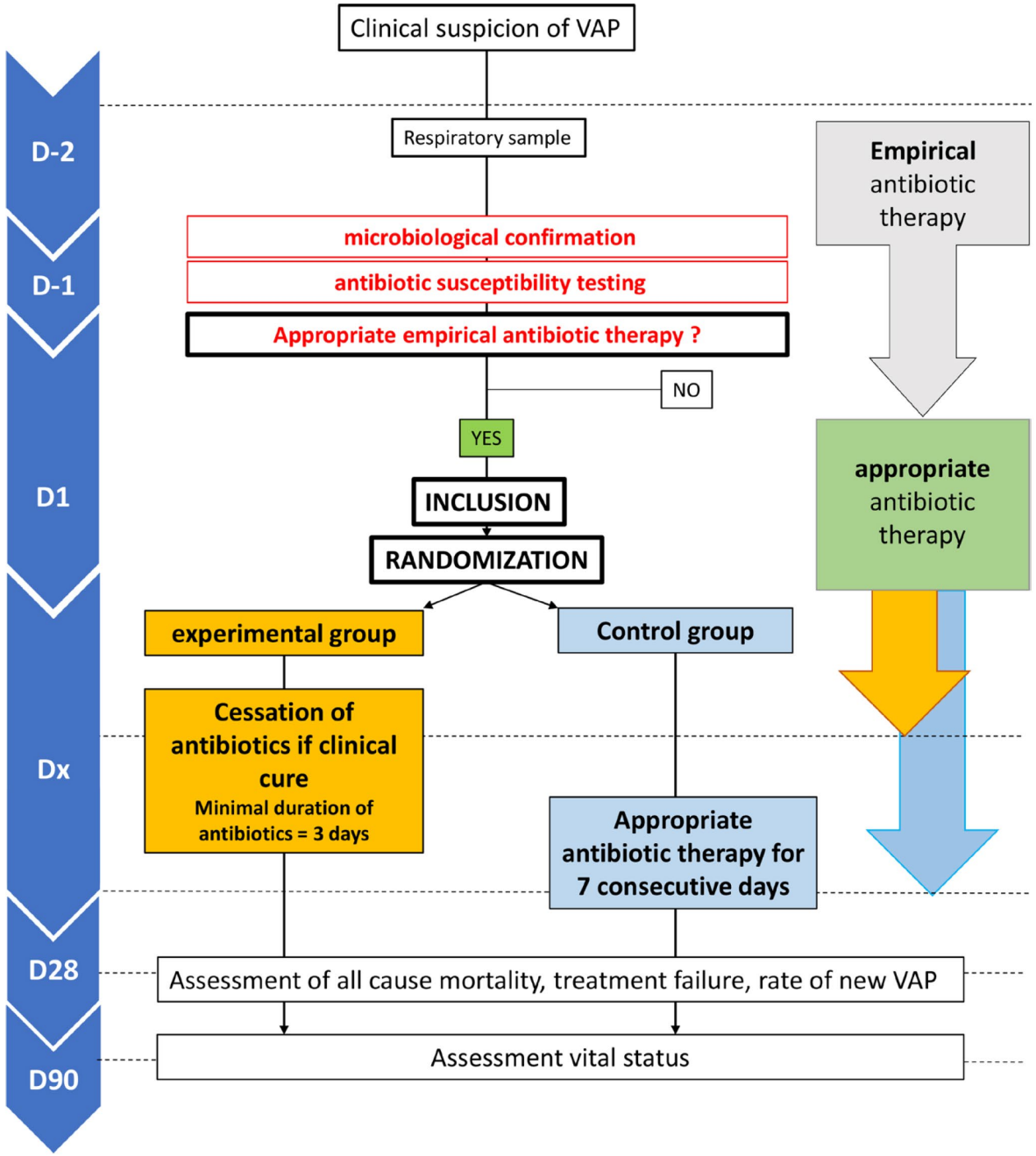
Experimental group

- Intensivists will perform clinical assessment daily in order to decide on the pursuit or discontinuation of antibiotic therapy.
- Antibiotic therepay is stopped if signs of **clinical cure** of pneumonia are met (after minimum 3 days of appropriate treatment)

CLINICAL CURE

STOP antibiotics if ≥ 3 criteria are met

1. Regression* of purulent trachael **S**ecretions
2. Normo**T**hermia 36°C < T < 38.3°C
3. **O**xygenation measured by an increase of PaO_2/FiO_2 ratio and PaO_2/FiO_2 >150
4. Absence of hy**P**otension



Prediction of ventilator-associated pneumonia outcomes according to the early microbiological response: a retrospective observational study

Adrian Ceccato, Cristina Dominedò, Miquel Ferrer, Ignacio Martin-Loeches, Enric Barbeta, Albert Gabarrús, Catia Cillóniz, Otavio Ranzani, Gennaro De Pascale, Stefano Nogas, Pierluigi Di Giannatale, Massimo Antonelli, Antoni Torres

Eur Respir J 2023; 59(4): 2100620

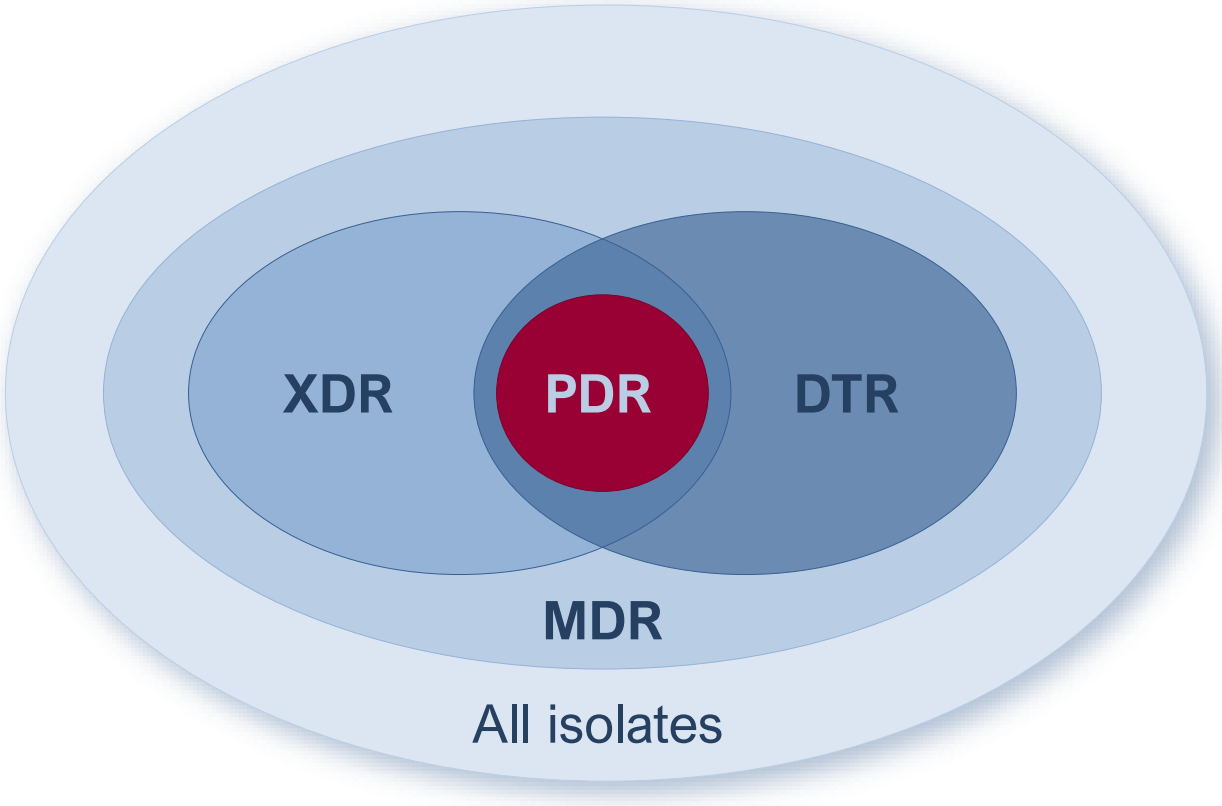
ERS EUROPEAN RESPIRATORY SOCIETY every breath counts

Retrospective study (Barcelona, 2004-2017), 157 patients with microbiologically documented VAP receiving adequate AMB therapy – Tracheal aspirate at Day 0 (diagnosis) and Day 3

Microbiology, n (%)	**Persistence** (n = 67)	**Superinfection** (n = 25)	**Eradication** (n = 65)	***P*-value**
Staphylococcus aureus	17 (44)	10 (26)	12 (30)	0.125
Streptococcus pneumoniae	1 (17)	1 (17)	4 (66)	0.346
Klebsiella spp.	10 (43)	2 (9)	11 (48)	0.519
Escherichia coli	1 (13)	2 (25)	5 (62)	0.189
Enterobacter spp.	2 (18)	3 (27)	6 (55)	0.194
Pseudomonas aeruginosa	**32 (58)**	**11 (20)**	**12 (22)**	**0.001**
MDR pathogens	**25 (50)**	**14 (28)**	**11 (22)**	**0.019**

Antibiothérapie des PAVM

Dans les pneumonie à BGN difficiles à traiter ?



Definitions

MDR (*multi-drug resistance*) [1]

Acquired resistance to ≥1 drug(s) in ≥3 distinct antimicrobial classes*

XDR (*extensive drug resistance*) [1]

Acquired resistance to ≥1 drug(s) in all classes* except 1 or 2

PDR (*pan-drug resistance*) [1]

Acquired resistance to all first-line drugs*

DTR (*difficult-to-treat resistance*) [2]

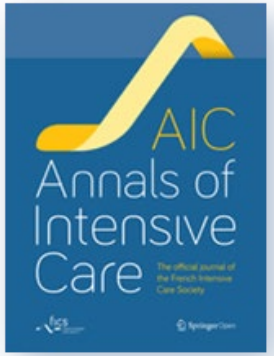
Acquired resistance to all fist-line β-lactams (including carbapenems) and fluoroquinolones

***First-line antimicrobial classes.** Enterobacterales: penicillins ± BLI, cephamycins, 1GC/2GC, 3GC/4GC, carbapenems (without BLI), monobactams (aztreonam), aminoglycosides, fluoroquinolones, cotrimoxazole, glycylcyclines (tigecycline), tetracycline, phenicols, fosfomycin, polymyxins (colistin) / *Pseudomonas aeruginosa*: anti-*Pseudomonas* penicillins with BLI, anti-*Pseudomonas* cephalosporins, anti-*Pseudomonas* carbapenems (without BLI), monobactams (aztreonam), aminoglycosides, anti-*Pseudomonas* fluoroquinolones, fosfomycin, polymyxins (colistin) / *Acinetobacter baumannii*: anti-*Pseudomonas* penicillins with BLI, ampicillin-sulbactam, 3GC/4GC, anti-*Pseudomonas* carbapenems (without BLI), aminoglycosides, anti-*Pseudomonas* fluoroquinolones, cotrimoxazole, tetracyclines, polymyxins (colistin)

[1] Magiorakos et al. *Clin Microbiol Infect* 2012;18(3):268-81
[2] Kadri et al. *Clin Infect Dis* 2018;67(12):1803-1814

Rationale and evidence for the use of new beta-lactam/beta-lactamase inhibitor combinations and cefiderocol in critically ill patients

François Barbier[1,2*], Sami Hraiech[3], Solen Kernéis[4], Nathanaël Veluppillai[4], Olivier Pajot[5], Julien Poissy[6], Damien Roux[2,7] and Jean-Ralph Zahar[2,8] On behalf of the French Intensive Care Society



Annals of Intensive Care (2023) 13:65

Main mechanisms of carbapenem resistance	**Enterobacterales**			***Pseudomonas aeruginosa***	***Acinetobacter baumannii***	***Stenotrophomonas maltophilia***
	Class A carbapenemase (KPC)	**Class D carbapenemase (OXA-48-like[a])**	**Class B carbapenemase (MBL[b])**	***OprD2* mutation Efflux[c] MBL[d]**	**OXA[e]**	**Chromosomal MBL**
Ceftolozane–tazobactam	–	–	–	+++ 75%-90% [f]	–[g]	–[g]
Ceftazidime–avibactam	+++ 96%-99%	+++ 96%-99%	–	++ 60%-70%	–[g]	–[g]
Ceftazidime–avibactam plus aztreonam	+++ 96–99%	+++ 96%-99%	+++ > 90%	± (MBL) 0–25%	–[g]	++[h] ~ 85%
Meropenem–vaborbactam	+++ 95–99%	–	–	–	–	–[g]
Imipenem–relebactam	+++ 88%-95%	±	–	++ 70%-90%	–	–[g]
Cefiderocol	+++ 84–91%	+++ 88–93%	++ VIM: 79%-81% NDM: 41%-51%	+++ > 90%	+++[i] MIC ≤ 2 mg/L for > 90% of isolates	+++[i] MIC ≤ 2 mg/L for > 90% of isolates

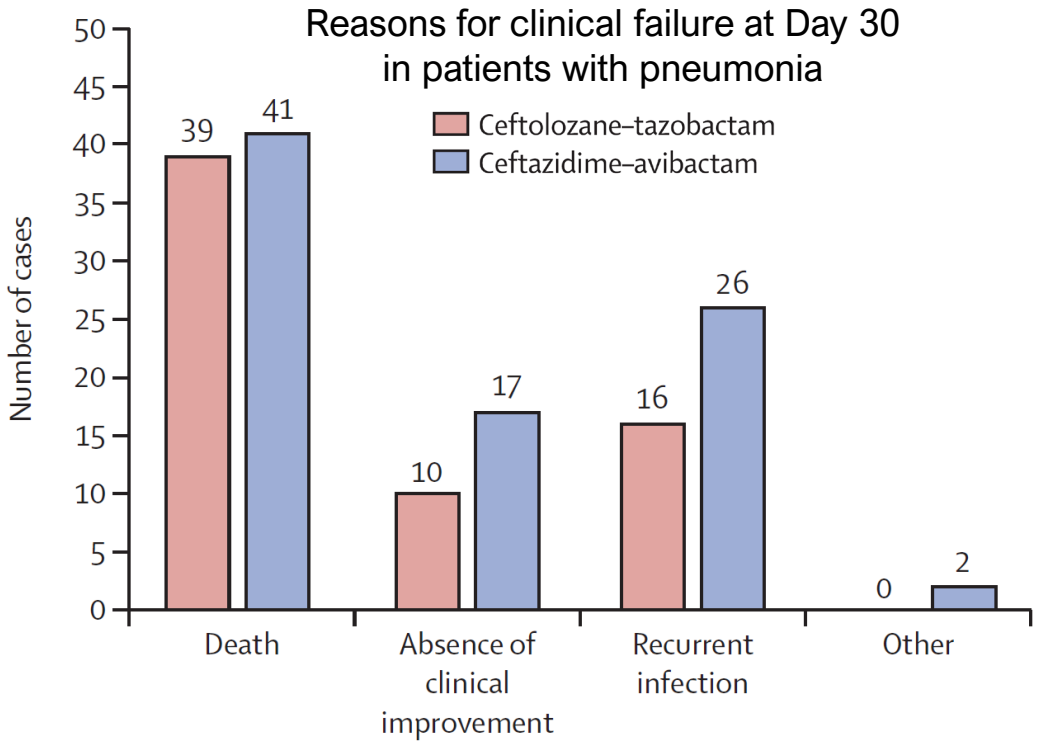
Effectiveness of ceftazidime–avibactam versus ceftolozane–tazobactam for multidrug-resistant *Pseudomonas aeruginosa* infections in the USA (CACTUS): a multicentre, retrospective, observational study

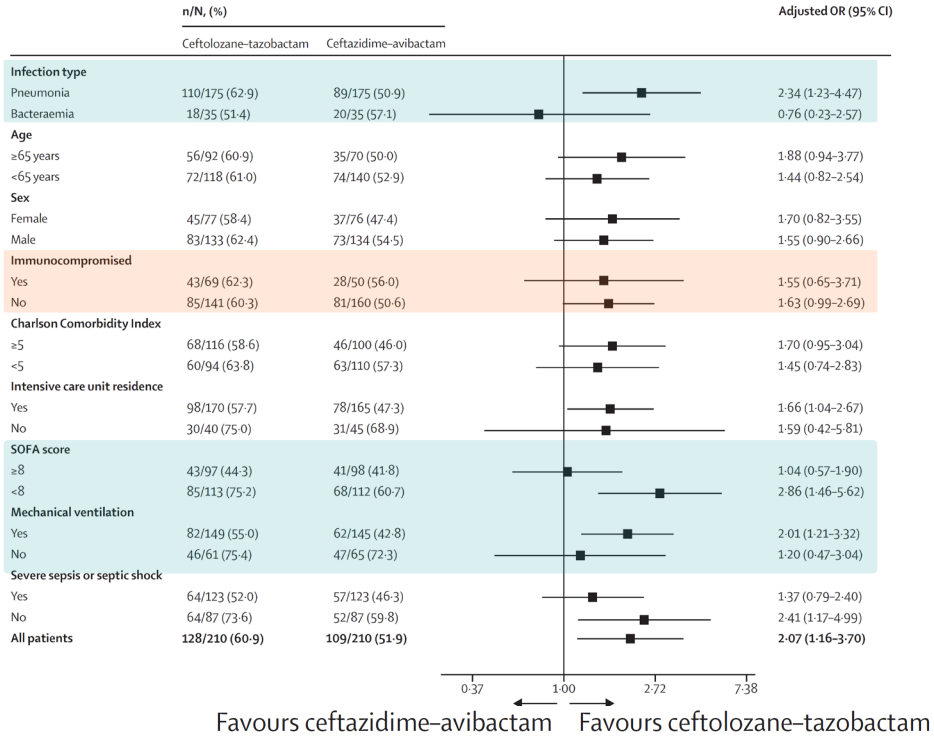
Lancet Infect Dis 2024

Published **Online**
December 16, 2024

*PRECEDENT Network**

C/TZ vs CAZ/AVI for MDR-*Pa* pneumonia or BSI – Primary outcome: clinical success at day 30
420 patients (matching 1:1), ICU 80%, MV 70%, HAP/VAP 83%





JAC Antimicrob Resist
https://doi.org/10.1093/jacamr/dlac104

Evaluation of ceftazidime/avibactam for treatment of carbapenemase-producing carbapenem-resistant Enterobacterales with OXA-48 and/or NDM genes with or without combination therapy

Hajar Alqahtani[1]*, Ahlam Alghamdi[2,3], Nouf Alobaidallah[4], Amal Alfayez[4], Rawan Almousa[4], Rawan Albagli[4], Nour Shamas[5], Fayssal Farahat[5,6], Ebrahim Mahmoud[7,8], Mohammad Bosaeed[7,8,9] and Reem Abanamy[7]

Clinical outcomes

	Monotherapy, *N* = 119 (OXA-48 = 119)	Combination therapy, *N* = 92 (OXA-48 = 52; NDM = 40)	Total, *N* = 211	*P* value
Clinical cure, *n* (%)	103 (87)	62 (67.4)	165 (78.2)	0.001
Isolates with OXA-48 gene	103 (87)	32 (61.5)	135 (79)	0.0001
Isolates with NDM ± OXA-48 genes	0	30 (75)		
30 day mortality, *n* (%)	19 (16)	25 (27)	44 (21)	0.05
Isolates with OXA-48 gene	19 (16)	18 (34.6)	37 (21.6)	0.006
Isolates with NDM ± OXA-48 genes	0	7 (17.5)		
60 day mortality, *n* (%)	24 (20.2)	33 (36)	57 (27)	0.011
Isolates with OXA-48 gene	24 (20.2)	23 (44)	47 (27.5)	0.001
Isolates with NDM ± OXA-48 gene	0	10 (25)		
Relapse within 30 days of completion of CAZ/AVI course, *n* (%)	9 (7.6)	12 (13)	21 (10)	0.19
Isolates with OXA-48 gene	9 (7.6)	6 (11.5)	15 (8.8)	0.42
Isolates with NDM ± OXA-48 genes	0	6 (15)		
Adverse drug reactions, *n* (%)				
AKI related to antimicrobial agent	8 (6.7)	8 (8.7)	16 (8)	0.652
C. difficile infection	5 (4.2)	4 (4.3)	9 (4)	0.982
Rash resulting in discontinuing CAZ/AVI	1 (0.8)	0	1(0.5)	
Liver function tests elevated (AST/ALT)	4 (3.4)	4 (4.3)	8 (3.8)	
Development of invasive fungal infection, *n* (%)	28 (23.5)	19 (21)	47 (22.8)	0.955

« Our findings suggested that combination therapy with ceftazidime/avibactam had no direct impact on clinical outcomes for CP-CRE with OXA-48. »

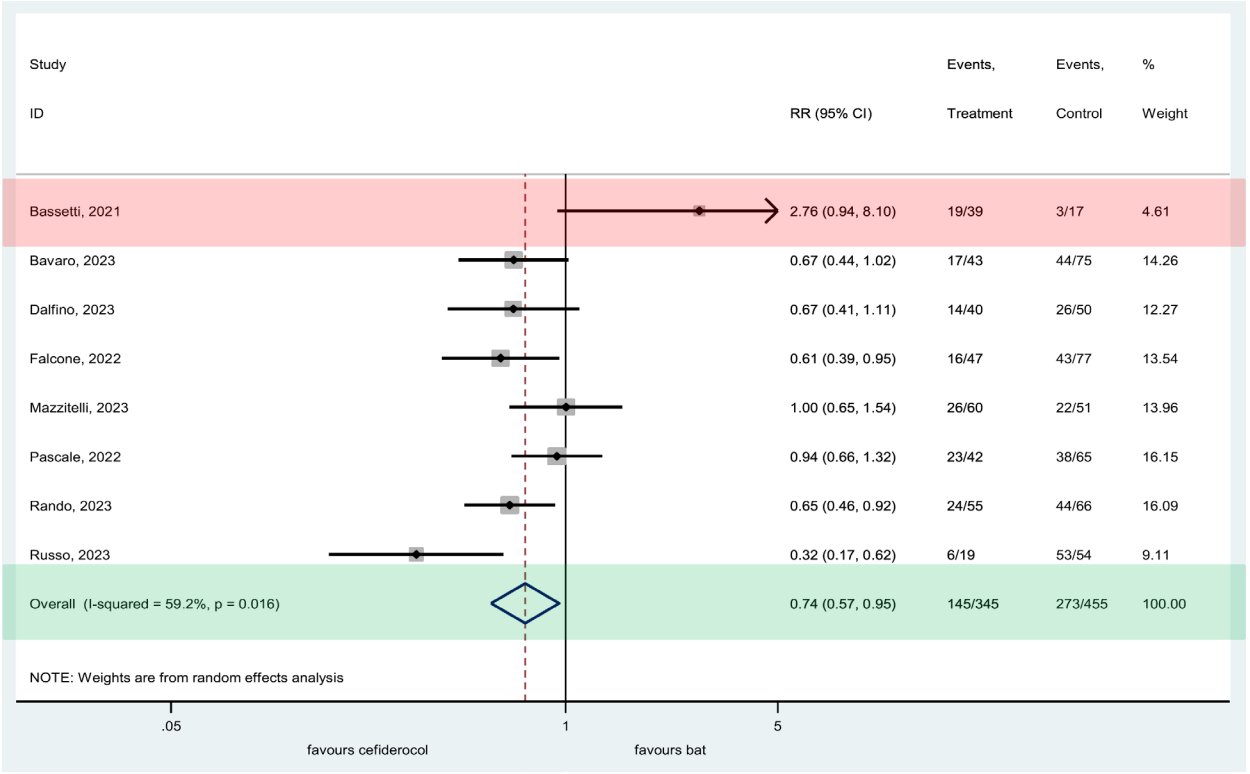
Cefiderocol either in monotherapy or combination versus best available therapy in the treatment of carbapenem-resistant *Acinetobacter baumannii* infections: A systematic review and meta-analysis

Lorenzo Onorato, Ilaria de Luca, Caterina Monari, Nicola Coppola *

Journal of Infection 88 (2024) 106113

- 18 studies (2 RCTs), 736 patients with a CFD-based regimen vs. 473 patients with BAT
- Mostly HAP/VAP and BSI
- Lower 30-day mortality rate (RR 0.74, 95% CI 0.57–0.95) and lower rate of adverse drug reactions (RR 0.28, 95% CI 0.09–0.91) with cefiderocol vs BAT
- No difference in microbiological and/or clinical failure rates

Cefiderocol vs BAT: 30-day mortality



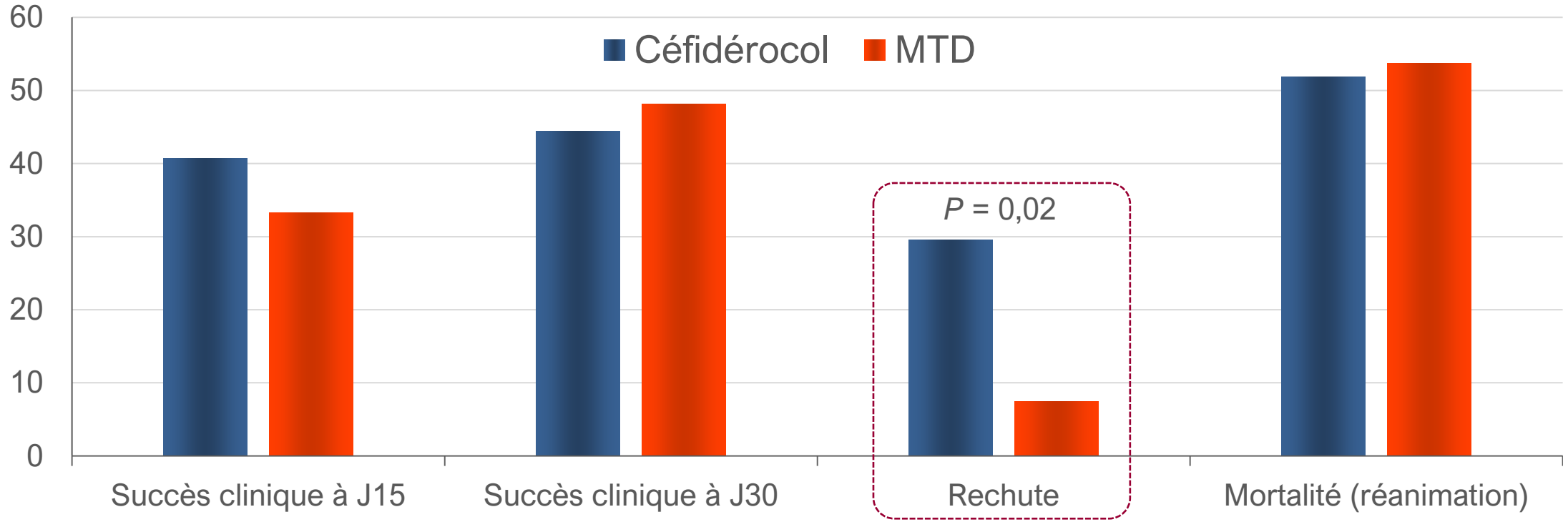
Cefiderocol in Difficult-to-Treat Nf-GNB in ICU Settings

Vacheron *et al. Annals of Intensive Care* (2024) 14:73

Cohorte rétrospective, 9 services de réanimation, France

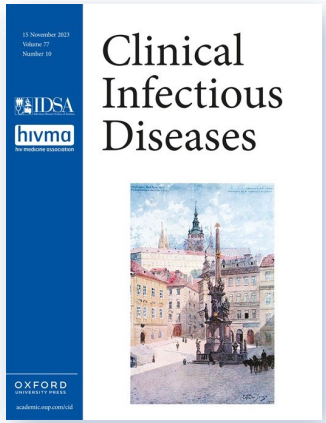
Céfidérocol (n = 27) vs meilleur traitement disponible (n = 54 / CAZ-AVI 52%, CTZ 15%, COL 26%)

P. aeruginosa : 79% (CFD) vs 94% (MTD) / Pneumonie : 78% (CFD) vs 94% (MTD)



Clinical Features and Outcomes of Infections Caused by Metallo-β-Lactamase–Producing Enterobacterales: A 3-Year Prospective Study From an Endemic Area

Marco Falcone,[1] Cesira Giordano,[2] Alessandro Leonildi,[2] Valentina Galfo,[1] Aurelio Lepore,[1] Lorenzo Roberto Suardi,[1] Niccolò Riccardi,[1] Simona Barnini,[2] and Giusy Tiseo[1]

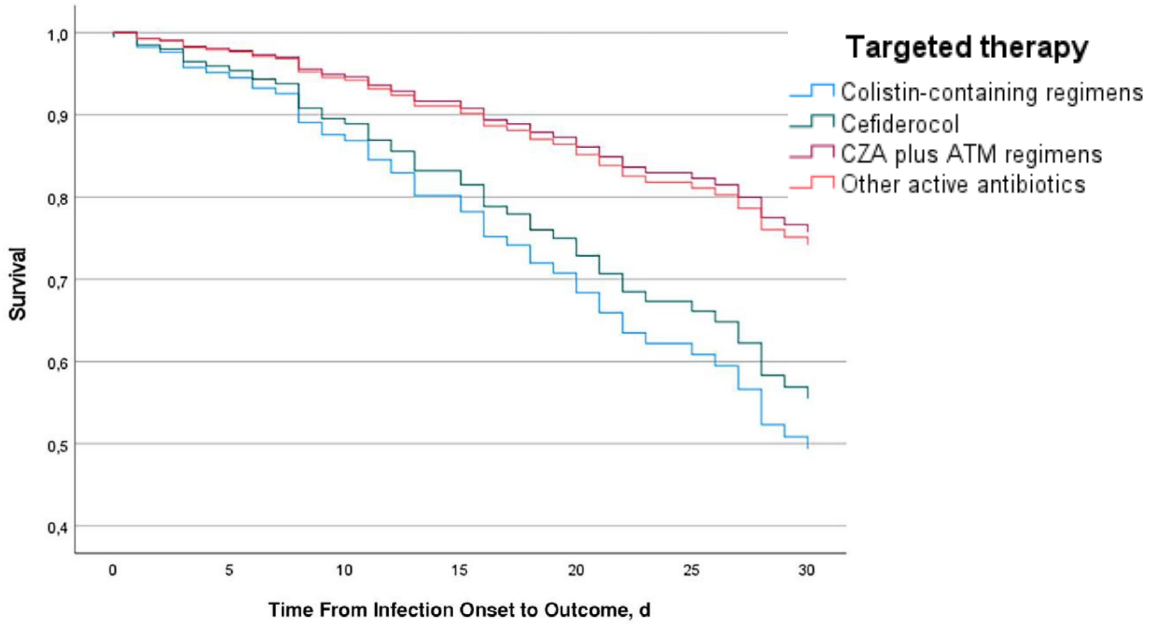


Clinical Infectious Diseases® 2024;78(5):1111–9

Prospective single-center study (Italy), 343 patients with CRE infection (MβL/NDM: 328/343)

Table 5. Sensitivity Analysis: Cox Regression of Factors Independently Associated With 30-Day Mortality Rate Among Patients Who Received Any Active Antibiotic Therapy[a]

Factor	aHR (95% CI)	*P* Value
Septic shock	2.38 (1.34–4.21)	.003
Charlson comorbidity index	1.08 (.98–1.19)	.10
Age	1.05 (1.02–1.08)	.002
Antibiotic regimen		
Colistin-containing regimens	Reference	…
FDC-containing regimens	0.83 (.31–2.24)	.72
CZA/ATM-containing regimens	0.39 (.18–0.86)	.02
Other active antibiotics	0.42 (.11–1.65)	.21



Sensitivity analysis showed that **CAZ/AVI + ATM (vs colistin) was independently associated with reduced 30-day mortality** (aHR 0.39, 95% CI 0.18-0.86, p = 0.019). Propensity score analyses confirmed these findings.

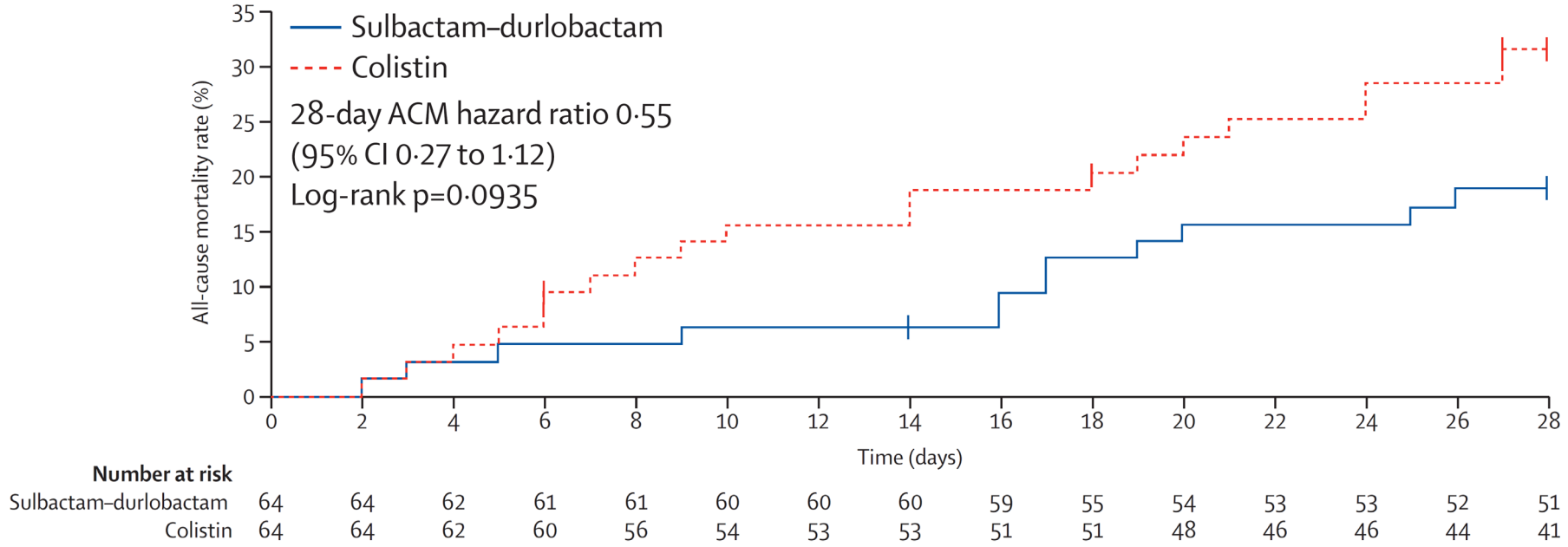
Efficacy and safety of sulbactam–durlobactam versus colistin for the treatment of patients with serious infections caused by *Acinetobacter baumannii–calcoaceticus* complex: a multicentre, randomised, active-controlled, phase 3, non-inferiority clinical trial (ATTACK)

Keith S Kaye, Andrew F Shorr, Richard G Wunderink, Bin Du, Gabrielle E Poirier, Khurram Rana, Alita Miller, Drew Lewis, John O'Donnell, Lan Chen, Harald Reinhart, Subasree Srinivasan, Robin Isaacs, David Altarac

Lancet Infect Dis 2023; 23: 1072–84

International non-inferiority RCT – 125 patients with HAP/VAP or BSI due to CR *A. baumannii*

Sulbactam–durlobactam (1g/1g/6h of over 3 h) versus colistin (2.5 mg/kg/12h) for 7-14 days plus imipenem 1 g/6h in both groups ("background therapy")

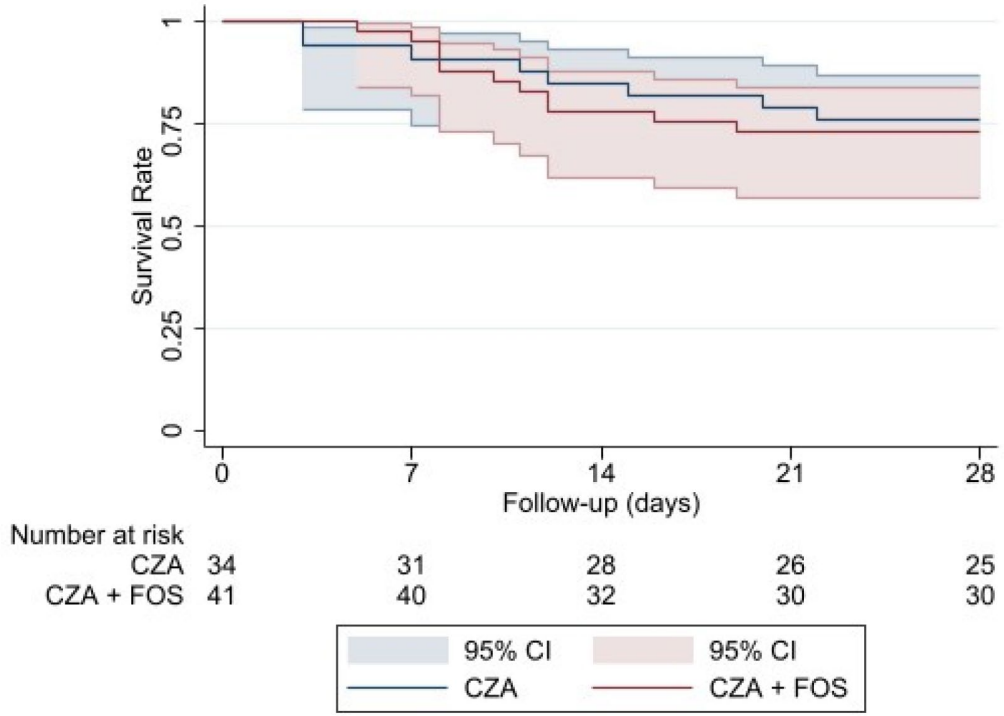


Efficacy and Safety of Ceftazidime–Avibactam Alone versus Ceftazidime–Avibactam Plus Fosfomycin for the Treatment of Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia: A Multicentric Retrospective Study from the SUSANA Cohort

Marco Fois [1], Andrea De Vito [1,*], Francesca Cherchi [1], Elena Ricci [2], Michela Pontolillo [3], Katia Falasca [3], Nicolò Corti [4,5], Agnese Comelli [6], Alessandra Bandera [6], Chiara Molteni [7], Stefania Piconi [7], Francesca Colucci [8], Paolo Maggi [8], Vincenzo Boscia [9], Aakash Fugooah [9], Sara Benedetti [10], Giuseppe Vittorio De Socio [10], Paolo Bonfanti [4,5] and Giordano Madeddu [1,*]

Antibiotics **2024**, *13*, 616.

- 75 patients with HAP/VAP due to *K. pneumoniae* or P*. aeruginosa* (carbapenem resistance, 57%)
- CZA (n = 34) versus CZ/A+FOS (n = 41)
- CZA+FOS: no independent association with survival at 28 days (aHR 0.32, 95% CI 0.07–1.39)
- *Clinical cure, microbiological eradication, relapses: not assessed*



IDSA Antimicrobial Resistant Treatment Guidance: Gram-Negative Bacterial Infections

Published on August 2020 / Updated on July 2024

BGN-MR/DTR	**Première intention** (si sensibilité confirmée)	Alternative(s)
EPC/KPC	Ceftazidime-avibactam, imipénème-relebactam, méropénème-vaborbactam	Céfidérocol
EPC/OXA-48	Ceftazidime-avibactam	Céfidérocol
EPC/MBL	(Ceftazidime)-avibactam + aztréonam, céfidérocol	Tigecycline, eravacycline (IAI)
***P. aeruginosa* DTR**	Ceftolozane-tazobactam, ceftazidime-avibactam, imipénème-relebactam	Céfidérocol
***A. baumannii* résistant aux carbapénèmes**	Sulbactam-durlobactam ou association (ampicilline-sulbactam, céfidérocol, colistine, aminoside, tigécycline)	-
S. maltophilia	Ceftazidime-avibactam + aztréonam ou association (cotrimoxazole, lévofloxacine, céfidérocol, tigécycline)	-

Penetration of Antibacterial Agents into Pulmonary Epithelial Lining Fluid: An Update

Emily N. Drwiega[1] · Keith A. Rodvold[1,2]

Clinical Pharmacokinetics (2022) 61:17–46

Antibiotiques	Ratio AUC_{ELF}/AUC_{plasma} (variable selon posologies & schémas d'administration)	
	Volontaires sains	Patients de réanimation
Pipéracilline / tazobactam	0,26 (PIP) / 0,54 (TAZ)	0,49 (PIP) / 1,21 (TAZ)
Ceftolozane / tazobactam	0, 48 (CTZ) / 0,44 (TAZ)	0,50 (CTZ) / 0,62 (TAZ)
Ceftazidime / avibactam	0,31-0,32 (CAZ) / 0,35-0,35 (AVI)	0,21-0,44 (CAZ) / ND (AVI)
Méropénème / vaborbactam	0,63-0,65 (MER) / 0,53-0,79 (VAB)	0,20-0,36 (MER) / ND (VAB)
Imipénème / relebactam	0,36-0,55 (IMI) / 0,43-0,54 (REL)	0,44
Amikacine	0,18 (pic)	0,10-0,25 (pic)
Tigécycline	1,71	2,41
Linézolide	2,3	1,06-1,50
Lévofloxacine	1,6-2,6	1,13-1,29

AUC, area under the curve; ELF, epithelial lining fluid

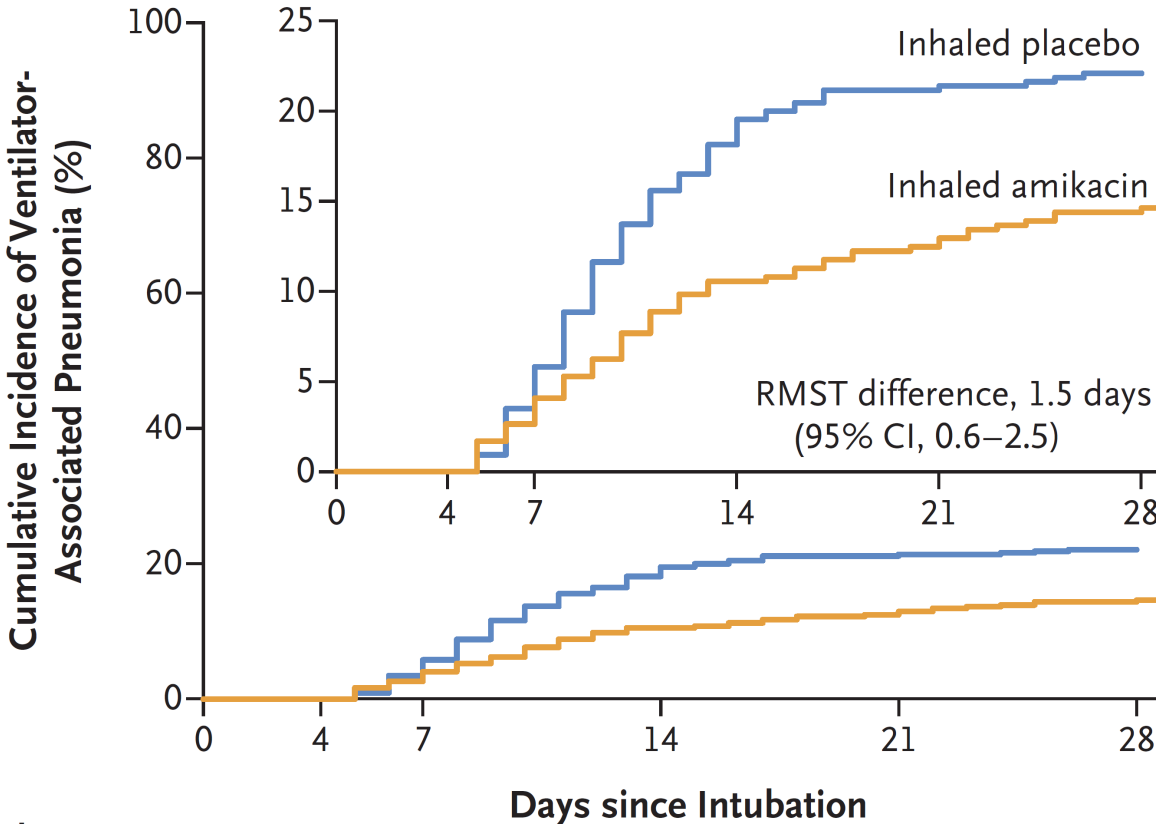
Antibiothérapie des PAVM

Quelle place pour l’antibioprophylaxie ?

Inhaled Amikacin to Prevent Ventilator-Associated Pneumonia

Stephan Ehrmann, MD, PhD, François Barbier, MD, PhD, Julien Demiselle, MD, et al,
for the Reva and CRICS-TRIGGERSEP F-CRIN Research Networks

N Engl J Med 2023;389:2052-62.



At 28 days, VAP had developed in 62 patients (15%) in the amikacin group and in 95 patients (22%) in the placebo group

(difference in restricted mean survival time to ventilator-associated pneumonia, 1.5 days; 95% CI 0.6-2.5; P = 0.004)

Prophylactic Antibiotics Delivered Via the Respiratory Tract to Reduce Ventilator-Associated Pneumonia: A Systematic Review, Network Meta-Analysis, and Trial Sequential Analysis of Randomized Controlled Trials

Jie Lie, (…), Stephan Ehrmann. *Crit Care Med* 2024 • Volume 52 • Number 10

- 7 RCTs, 1445 patients
- **Reduced risk of VAP with aminoglycosides (RR, 0.67 [0.47–0.97]) and/or nebulization (RR, 0.64 [0.49–0.83])**, but not with ceftazidime/colistin or intratracheal instillation
- No significant differences in mortality, MV duration, ICU and hospital LOS, or *exposure to systemic antimicrobials*

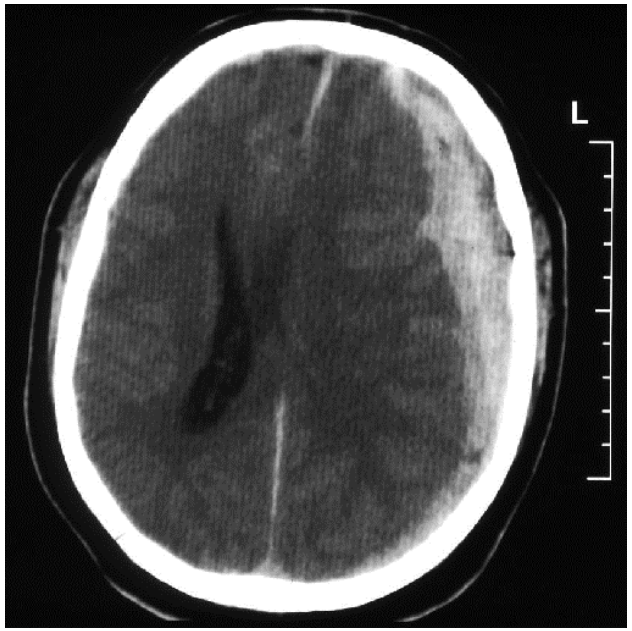
Risk factors and outcomes of ventilator-associated pneumonia in patients with traumatic brain injury: A systematic review and meta-analysis

Diego Enrique Prieto-Alvarado [a,g,h], Henry Mauricio Parada-Gereda [b,*], Daniel Molano [c], Yamil Liscano Martinez [d], Giovanna Patricia Rivas Tafurt [a,g], Joan-Ramon Masclans [e,f]

J Crit Care 85 (2025) 154922

Prophylactic antibiotic use reduces the risk of VAP in TBI patients

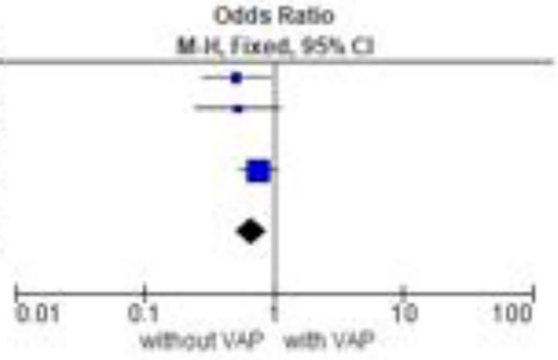
(OR 0.67, 95% CI 0.51-0.88), I^2 0%)



Use of prophylactic antibiotics subgroup analysis

Study or Subgroup	With VAP Events	Total	without VAP Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Esnault P et al. 2017	41	105	38	69	23.2%	0.51 [0.28, 0.95]
Lepelletier D et al. 2010	17	34	83	127	14.4%	0.53 [0.25, 1.14]
Plurad DS et al 2013	24	33	35	61	0.0%	1.98 [0.79, 4.97]
Robba C et al. 2020	130	196	552	766	62.3%	0.76 [0.55, 1.07]
Total (95% CI)		336		962	100.0%	0.67 [0.51, 0.88]
Total events	188		673			

Heterogeneity: Chi² = 1.65, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.85 (P = 0.004)



Ceftriaxone to prevent early ventilator-associated pneumonia in patients with acute brain injury: a multicentre, randomised, double-blind, placebo-controlled, assessor-masked superiority trial

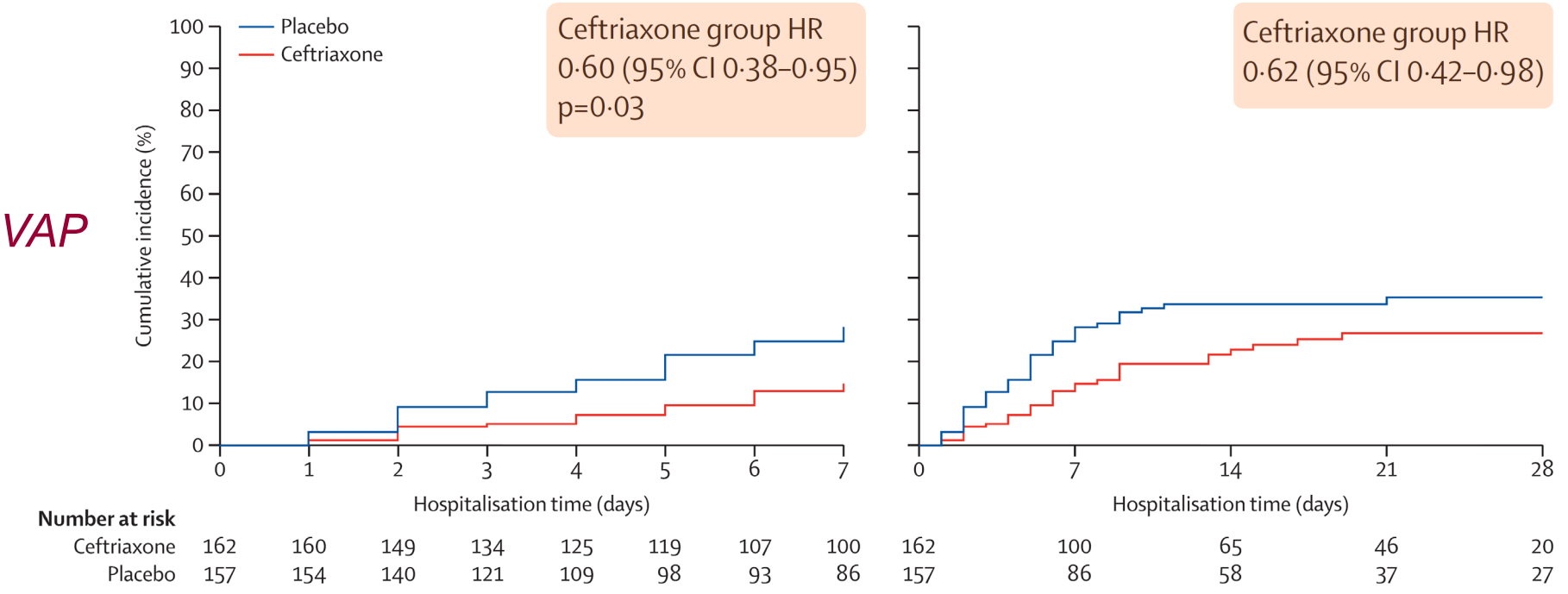
*Claire Dahyot-Fizelier, Sigismond Lasocki, Thomas Kerforne, Pierre-Francois Perrigault, Thomas Geeraerts, Karim Asehnoune, Raphaël Cinotti, Yoann Launey, Vincent Cottenceau, Marc Laffon, Thomas Gaillard, Matthieu Boisson, Camille Aleyrat, Denis Frasca, Olivier Mimoz, on behalf of the PROPHY-VAP Study Group and the ATLANREA Study Group**

Lancet Respir Med 2024; 12: 375–85

Multicenter double-blind RCT, comatose patients with expected MV duration >48h (n = 317 / stroke, SAH or TBI)

Ceftriaxone (2 g IV) or placebo, once within 12h following intubation

Early-onset VAP



All VAP

ANTHARTIC Study Group*

Prevention of Early Ventilator-Associated Pneumonia after Cardiac Arrest

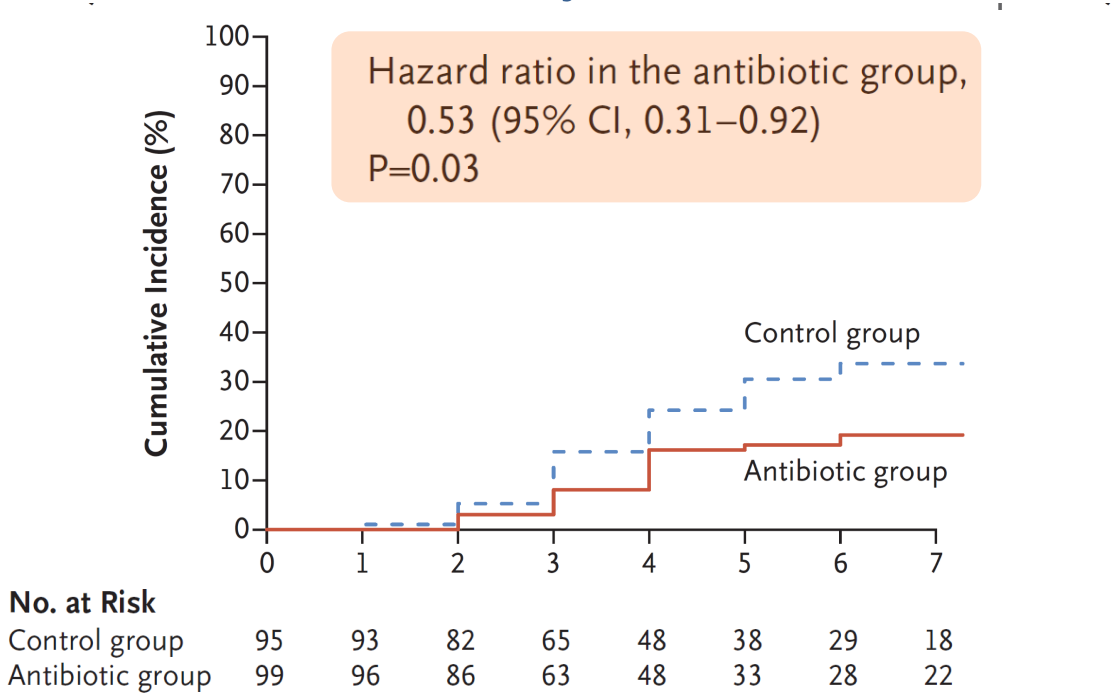
NEJM

N Engl J Med 2019;381:1831-42.

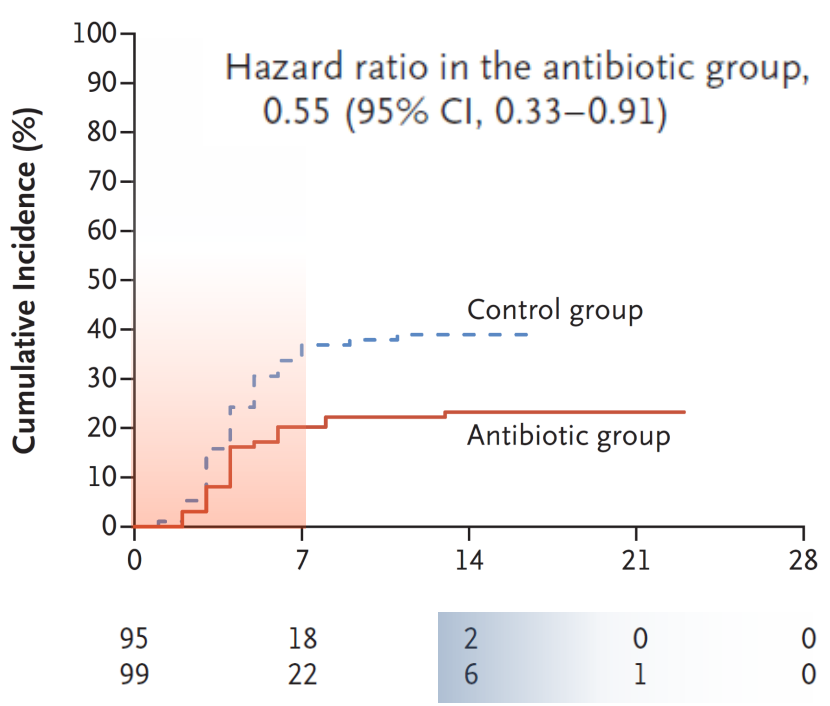
Multicenter double-blind RCT, patients admitted for OHCA (n = 198, shockable rhythm, TTC 32-34°C)

Amoxicillin-clavulanate (1 g/200 mg x 3/24h, IV) versus placebo for 2 days

Early-onset VAP



All VAP



Antibiothérapie des PAVM

Take-hospital messages

1. Prélever et attendre les cultures avant d'initier l'antibiothérapie hors signes de gravité immédiat? RCT nécessaire (PHRC à venir)
2. mPCR : rentabilité thérapeutique dépendante de la question pré-test?
3. Bithérapie active : bénéfice non démontré en 1ère intention si β-lactamine active (et aspects PK/PD optimisés), y compris sur *Pseudomonas aeruginosa*
4. Durée de traitement : prolonger >8 jours dans certains cas si *P. aeruginosa* ? Intérêt des prélèvements de contrôle??
5. Antibioprophylaxie initiale : chez les patients cérébrolésés?

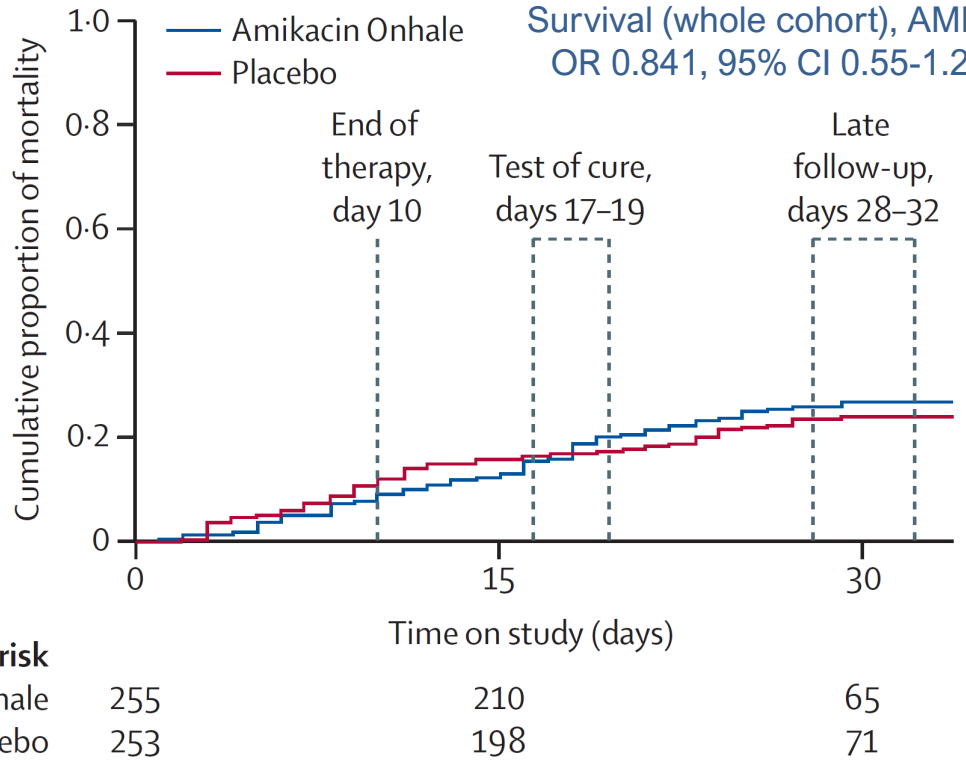
Antibiothérapie des PAVM

Place de l’antibiothérapie inhalée ?

Inhaled amikacin adjunctive to intravenous standard-of-care antibiotics in mechanically ventilated patients with Gram-negative pneumonia (INHALE): a double-blind, randomised, placebo-controlled, phase 3, superiority trial

Michael S Niederman, Jeff Alder, Matteo Bassetti, Francis Boateng, Bin Cao, Kevin Corkery, Rajiv Dhand, Keith S Kaye, Robert Lawatscheck, Patrick McLeroth, David P Nicolau, Chen Wang, G Christopher Wood, Richard G Wunderink, Jean Chastre

Lancet Infect Dis 2020; 20: 330–40



	Amikacin Inhale group	Placebo group
Microbiological response		
Pseudomonas aeruginosa		
Eradication	55/75 (73%)	44/88 (50%)
Persistence	20/75 (27%)	44/88 (50%)

A Randomized Trial of the Amikacin Fosfomycin Inhalation System for the Adjunctive Therapy of Gram-Negative Ventilator-Associated Pneumonia

IASIS Trial

CHEST

Kollef *et al*. CHEST 2017; 151(6): 1239-1246

Multicenter RCT – IV antimicrobials plus inhaled AMK/FOS versus placebo for GNB-VAP

Organism	AFIS Group (n = 71)	Placebo Group (n = 71)	Carbapenem Resistant	Colistin Resistant
Acinetobacter baumannii	16	13	27 (93)	27 (93)
Pseudomonas aeruginosa	18	13	16 (52)	5[a] (16)
Enterobacteriaceae	36	26	4 (6)	20 (32)
Enterobacter aerogenes	2	2	…	…
Enterobacter cloacae	6	5	…	2 (18)
Escherichia coli	7	6	…	…
Klebsiella oxytoca	1	2	…	…
Klebsiella pneumonia	10	5	4 (27)	2 (13)
Proteus mirabilis	3	3	…	6 (100)
Serratia marcescens	7	3	…	10 (100)
Stenotrophomonas maltophilia	3	1	4 (100)	1 (25)

A Randomized Trial of the Amikacin Fosfomycin Inhalation System for the Adjunctive Therapy of Gram-Negative Ventilator-Associated Pneumonia

IASIS Trial

CHEST

Kollef *et al*. CHEST 2017; 151(6): 1239-1246

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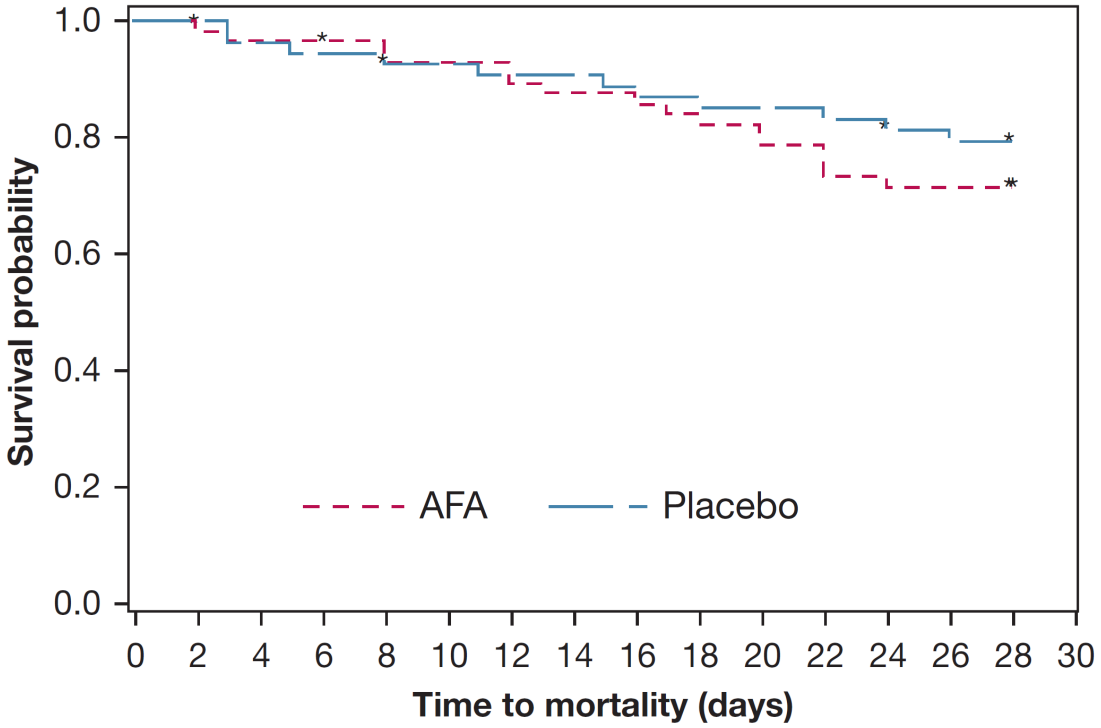


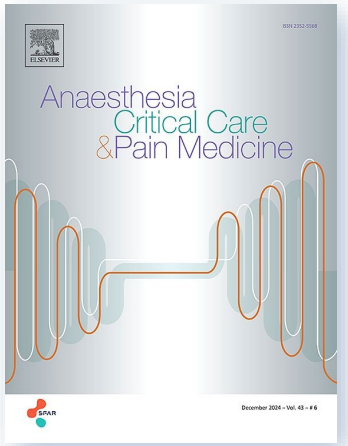
TABLE 3] Secondary Efficacy and Microbiologic End Points

Secondary Efficacy End Point	AFIS Group (n = 71)	Placebo Group (n = 71)	Difference Between Groups (95% CI)	*P* Value
Hierarchical composite end point of mortality and time to clinical cure[a,b]				
Mortality first	10	10	…	…
Clinical cure	15	18	…	…
Hierarchical composite end point of mortality and ventilator-free days[b]				
Mortality first	10	10	…	…
Ventilator free days	13	27	…	…
Days free of mechanical ventilation (days 1-28)	9.8 ± 9.7	12.5 ± 9.72	−2.7 (5.9 to 0.5)	.02
Days of IV antibiotics	18.6 ± 8.6	17.0 ± 8.8	1.6 (−1.3 to 4.5)	.13
No. of ICU days (days 1-28)	28.9 ± 12.4	26.2 ± 15.6	2.7 (−2.0 to 7.4)	.09
Mortality (days 1-28)	17 (24)	12 (17)	7 (−6 to 20)	.32
Clinical relapse rates[c]	10 (14)	14 (20)	−6 (−18 to 7)	.37
Tracheal culture at day 3 postive for gram-negative bacteria[d]	19 (27)	40 (56)[d]	−29 (−44 to −13)	< .001
Tracheal culture at day 7 postive for gram-negative bacteria[e]	12 (17)	29 (41)[e]	−24 (−37 to −9)	.002

A prospective phase IIA multicenter double-blinded randomized placebo-controlled clinical trial evaluating the efficacy and safety of inhaled Tobramycin in patients with ventilator-associated pneumonia (iToVAP)

Stefan Angermair [a,*], Maria Deja [b], Anja Thronicke [c], Claudia Grehn [d], Nilufar Akbari [e], Alexander Uhrig [f], Golschan Asgarpur [a], Claudia Spies [g], Sascha Treskatsch [a], Carsten Schwarz [h]

Anaesth Crit Care Pain Med 42 (2023) 101249



Primary and secondary endpoints	Tobra Inhal group (n = 14)	Placebo group (n = 12)	*p*-Value
Primary endpoint			
Eradication at visit 6	14 (100%)	3 (25%)	<0.001
Secondary endpoints			
Length of stay in ICU			
Median (IQR)	12 (7.5; 19)	14 (10; 27)	0.465
Duration of systemic antibiotic treatment			
Median (IQR)	8 (7; 9.5)	6 (6; 9)	0.324
Systemic antibiotic free days (after the inclusion)			
Median (IQR)	5 (3; 7)	4 (2.8; 6.5)	0.712
Duration of mechanical ventilation for pneumonia (days)			
Median (IQR)	7 (5; 10.8)	7 (6.8; 8)	0.812
Ventilator-free days			
Median (IQR)	3 (2; 10)	7 (3; 10)	0.624
Reinfection of pneumonia caused by the same pathogen			
No	5 (36%)	8 (67%)	NA

VAP mostly due to (not MDR) Gram-negative bacteria

Nebulized colistin as the adjunctive treatment for ventilator-associated pneumonia: A systematic review and meta-analysis

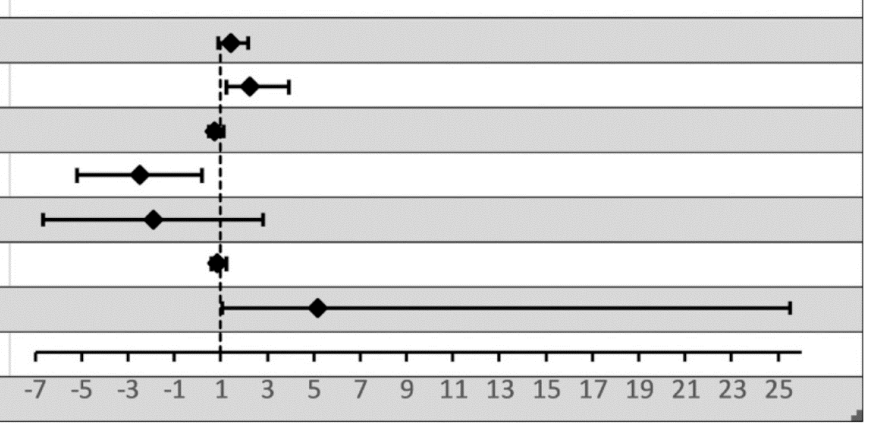
Xiaoyu Zhang, MM [a,b,c], Xuanxuan Cui, MM [a,b,c], Mengke Jiang, MM [a,b,c], Shanshan Huang, MM [a,b,c], Min Yang, MD [a,b,c,*]

J Crit Care 77 (2023) 154315

7 observational studies and 3 RCTs – Active IV antimicrobials with/without inhaled colistin for VAP

Adjunctive inhaled colistin: higher microbiological eradication rate but no difference in clinical response, MV duration, ICU LOS or overall mortality – *higher risk of bronchospasm*

Outcomes	No. of studies	No. of patients	Heterogeneity (I^2)	OR [95% CI]
Clinical response	8	850	56%	1.39 [0.87, 2.20]
Microbiological eradication	8	760	64%	2.21 [1.25, 3.92]
Overall mortality	10	950	50%	0.74 [0.50, 1.12]
MV length	7	658	0%	-2.50 [-5.20, 0.19]
Length of ICU stay	2	180	38%	-1.91 [-6.66, 2.84]
Nephrotoxicity	4	264	41%	0.86 [0.60, 1.23]
Bronchospasm	3	280	0%	5.19 [1.05, 25.52]

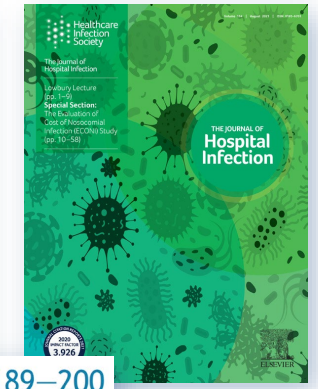


Antibiothérapie des pneumonies nosocomiales

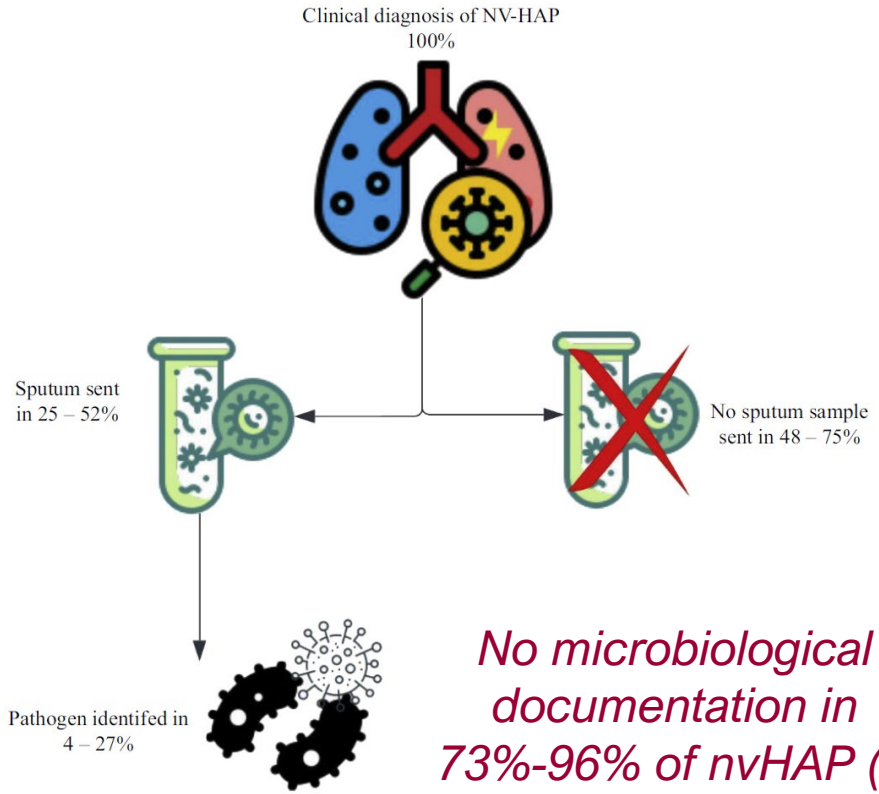
Dans les PN non acquises sous ventilation ?

Clinical challenge of diagnosing non-ventilator hospital-acquired pneumonia and identifying causative pathogens: a narrative review

S. Quarton [a,*], A. Livesey [b], H. Pittaway [c], A. Adiga [d], F. Grudzinska [e], A. McNally [f], D. Dosanjh [e], E. Sapey [a,g,h], D. Parekh [e]



Journal of Hospital Infection 149 (2024) 189–200



No microbiological documentation in 73%-96% of nvHAP (!)

Organism	Prevalence
Staphylococcus aureus	17.0–41.4%
Pseudomonas aeruginosa	9.2–30%
Other Gram-negative bacilli *Escherichia coli* *Klebsiella* spp. *Enterobacter* spp. *Acinetobacter baumanii* *Stenotrophomonas maltophillia* *Citrobacter* spp. *Serratia* marcescens *Proteus* spp.	20.8–59.0%
Common ‘community-acquired’organisms *Streptococcus pneumoniae* *Haemophilus influenzae* *Moraxella catarrhalis*	0–14%
Fungi	2.9–8%
Viruses	1.85–22.5%

Empiric antibiotic regimens in adults with non-ventilator-associated hospital-acquired pneumonia: a systematic review and network meta-analysis of randomized controlled trials

Maryam Ghadimi [1,*], Reed A.C. Siemieniuk [1,2], Gordon Guyatt [1,2,3], Mark Loeb [1,4], Afeez Abiola Hazzan [5], Danial Aminaei [1], Huda Gomaa [6], Ying Wang [1], Liang Yao [1,7], Arnav Agarwal [1,2], John Basmaji [1,8], Alexandre Grant [9], William S.H. Kim [10], Giancarlo Alvarado-Gamarra [11,12], Valery Likhvantsev [13,14], João Pedro Lima [1], Shahrzad Motaghi [1], Rachel Couban [7], Behnam Sadeghirad [1,7], Romina Brignardello-Petersen [1]

Clinical Microbiology and Infection 30 (2024) 1351–1363

	Treatment failure					All-cause mortality				
Baseline risk [a]	145 per 1000					150 per 1000				
Small important difference [b]	25 per 1000					10 per 1000				
Intervention vs. cephalosporins	RR (95% CI)	RD (95% CI)	Certainty of evidence	Classification	Narrative summary	RR (95% CI)	RD (95% CI)	Certainty of evidence	Classification	Narrative summary
Penicillin + Aminoglycoside	2.78 (1.28, 5.62)	258 (55, 667)	Low	Among the least effective	May be inferior to cephalosporins and some alternatives	1.5 (0.47, 4.78)	75 (−80, 587)	Very low	NA [c]	NA
Piperacillin-tazobactam	0.65 (0.42, 1.01)	−51 (−87, 2)	Low	Among the most effective	May be superior to cephalosporins and some alternatives	0.43 (0.19, 0.97)	−84 (−121, −3)	Very low	NA [c]	NA
Imipenem + Netilmicin	0.71 (0.29, 1.75)	−42 (−103, 107)	Very low	NA [c]	NA	—	—	—	—	—
Carbapenems	0.77 (0.53, 1.11)	−33 (−68, 16)	Low	Among the most effective	May be superior to cephalosporins and some alternatives	0.65 (0.26, 1.68)	−53 (−111, 102)	Very low	NA [c]	NA
Cephalosporin + Aminoglycoside	0.97 (0.62, 1.53)	−4 (−55, 77)	Very low	NA [c]	NA	—	—	—	—	—
Ceftazidime + Pefloxacin	1.89 (0.76, 4.66)	129 (−35, 531)	Very low	NA [c]	NA	—	—	—	—	—
Ceftriaxone + Clindamycin	0.18 (0.02, 1.55)	−119 (−142, 80)	Very low	NA [c]	NA	—	—	—	—	—
Ceftazidime + Linezolid	1.02 (0.5, 1.74)	3 (−58, 107)	Very low	NA [c]	NA	1.07 (0.75, 1.54)	11 (−38, 81)	Low	Intermediate effectiveness	May not be convincingly different than cephalosporins
Fluoroquinolones	0.85 (0.56, 1.28)	−22 (−64, 41)	Very low	NA [c]	NA	0.77 (0.33, 1.82)	−35 (−101, 123)	Very low	NA [c]	NA
Aztreonam + Clindamycin	0.53 (0.12, 2.33)	−68 (−128, 193)	Very low	NA [c]	NA	0.32 (0.03, 3.54)	−102 (−146, 381)	Very low	NA [c]	NA
Cephalosporin + Aztreonam	0.64 (0.2, 2.1)	−52 (−116, 160)	Very low	NA [c]	NA	1.6 (0.62, 4.1)	90 (−57, 465)	Very low	NA [c]	NA
Tigecycline	0.81 (0.42, 1.55)	−28 (−84, 80)	Very low	NA [c]	NA	0.64 (0.23, 1.79)	−54 (−116, 119)	Very low	NA [c]	NA

Compared to all cephalosporins: **reduction in the risk of treatment failure with piperacillin-tazobactam** (RR 0.65, 95% CI 0.42-1.01) **and carbapenems** (RR 0.77, 95% CI 0.53-1.11) (30 RCTs, 4807 patients, low certainty)

Compared to cephalosporins alone: no reduction in all-cause mortality with ceftazidime + linezolid (11 RCTs, 2531 patients, low certainty)

Evidence on other antibiotic regimens: highly uncertain