Faut-il utiliser les C3G dans les infections à entérobactéries du 3ème groupe ?

Prof. Hatem KALLEL

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Research Team« Tropical Biome and Immunopathology CNRS UMR-9017, Inserm U 1019, French Guiana university»

ATR – 28ème Congrès National de Réanimation – Hammamet du 28 au 30 novembre 2024

Peut-on utiliser les C3G dans les infections à entérobactéries du 3ème groupe sauvages ?

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ATR – 28ème Congrès National de Réanimation – Hammamet du 28 au 30 novembre 2024

Pas de conflit d'intérêt

Infections caused by naturally AmpC-producing Enterobacteriaceae: Can we use third-generation cephalosporins? A narrative review

A. Mizrahi[a,b,1,*], T. Delerue[c,1], H. Morel[c], A. Le Monnier[a,b], E. Carbonnelle[c,d], B. Pilmis[e], J.R. Zahar[c,d], on behalf the Saint-Joseph/Avicenna Study Group

Based on **small clinical studies**, international guidelines and expert recommendations suggest that **3GCs should be avoided** as definitive therapy for infections caused by **ESCPM group organisms**.

Michéa-Hamzehpour et al. Drugs (1988)
EUCAST
Clinical and Laboratory Standards Institute (CLSI)
Acar J . Clin Infect Dis (1998)
Sanders et al. Clin Infect Dis (1996)

Mizhari et al. Int. J of Antimicrob. Agents (2020)

Résistances naturelles des Entérobactéries

Groupe	β-lactamase	Enterobactérie
Groupe 0	Absence de β-lactamase	*Salmonella spp, Proteus mirabilis*
Groupe 1	Céphalosporinase non exprimée	*E. coli, Shigella*
Groupe 2	Pénicillinase chromosomique (Bas niveau)	*Klebsiella* (sauf *K. aerogenes*), *C. koseri*
Groupe 3	**Céphalosporinase inductible (AmpC)**	***Enterobacter, Morganella, C. freundii, Hafnia alvei, Serratia, Providencia, K.aerogenes***
Groupe 4	Pénicillinase + Céphalosporinase	*Yersinia, Serratia Fonticola*
Groupe 5	Céfuroximase	*Proteus vulgaris, Proteus penneri*

REVIEW

Mechani
in Gram-

Étienne Ruppé[1], Pau

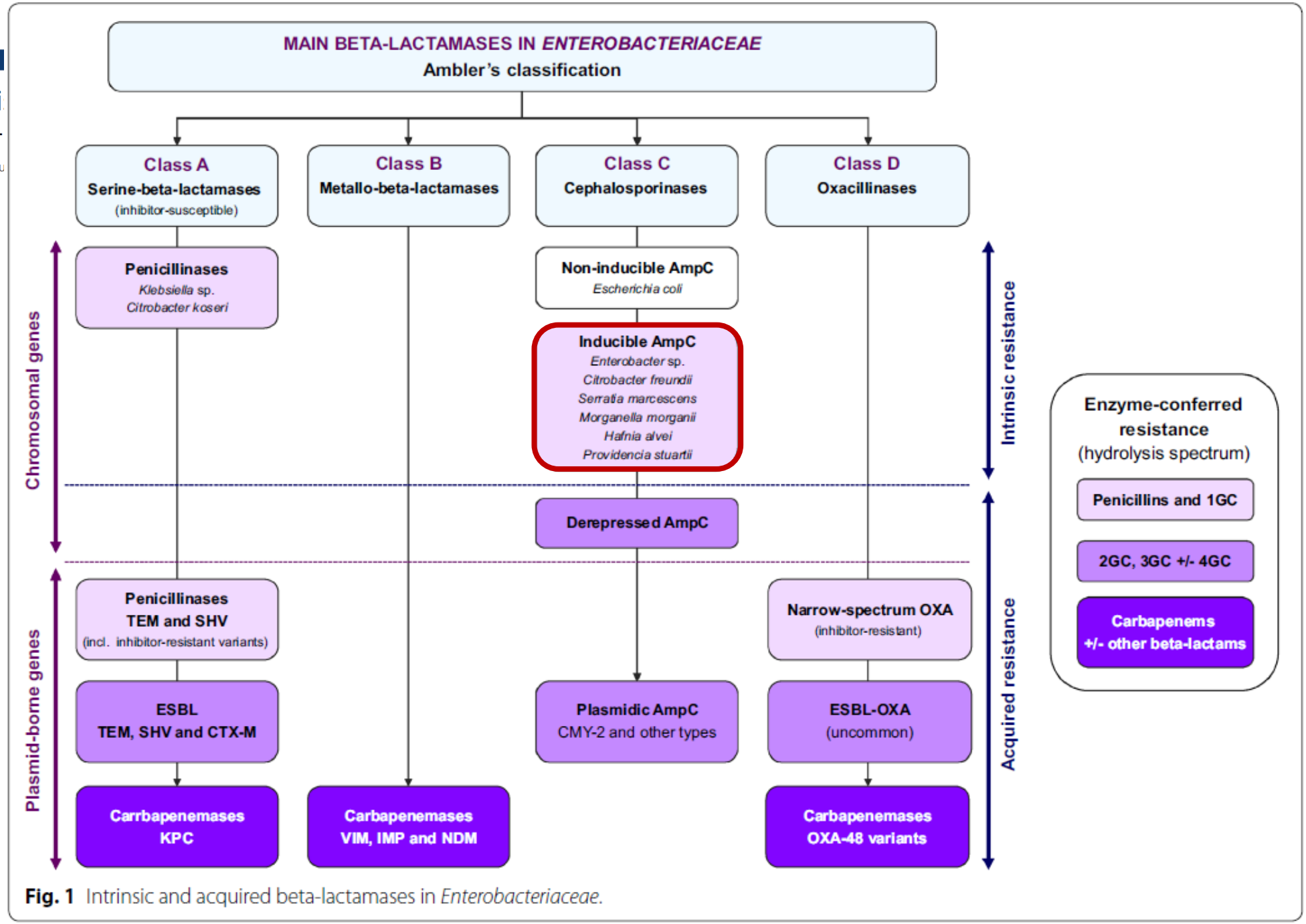
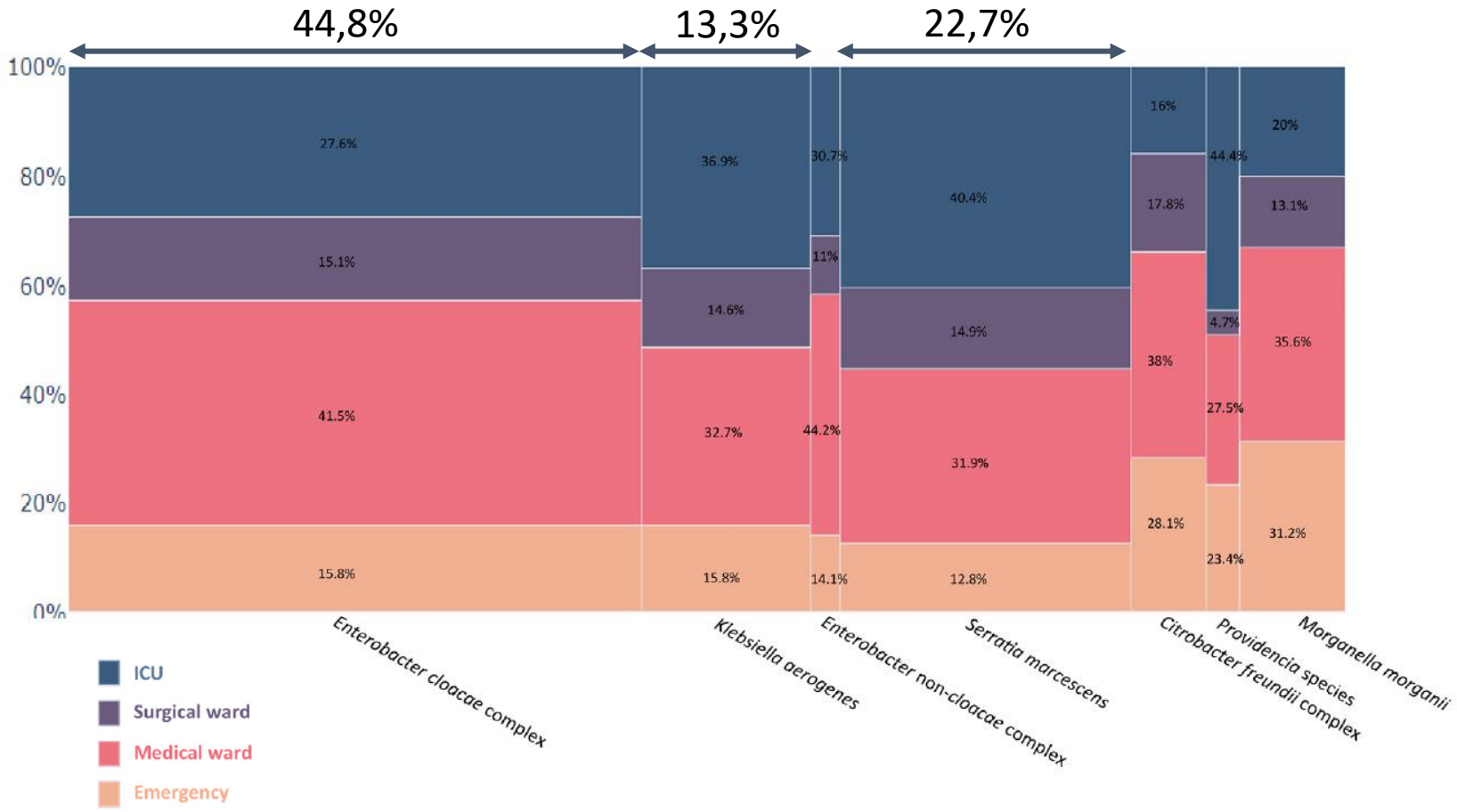


Fig. 1 Intrinsic and acquired beta-lactamases in *Enterobacteriaceae*.

(2015)

Enterobacterales carrying chromosomal AmpC β-lactamases in Europe (EuESCPM): Epidemiology and antimicrobial resistance burden from a cohort of 27 hospitals, 2020–2022



Boattini et al. Int. J Antimicr Agents (2024)

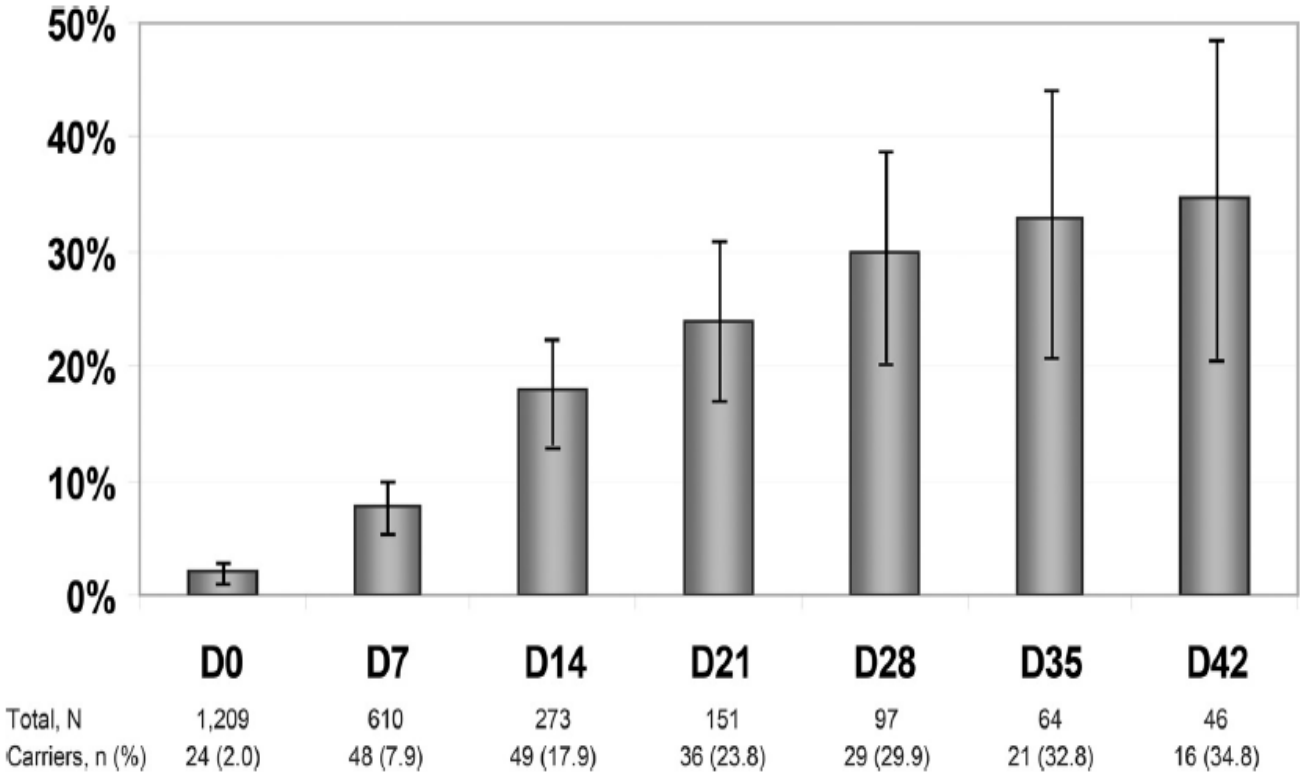
Risk Factors and Outcomes for Intestinal Carriage of AmpC-Hyperproducing *Enterobacteriaceae* in Intensive Care Unit Patients

2008 to 2010
1,209 ICU patients

<u>Multivariate analysis:</u>
LOS was the main predictor of carriage acquisition after adjustment on antimicrobial exposure.

<u>HLAC-PE infection</u> occurred in 15% of carriers.

<u>Carriage and infection</u> were associated with a marked increase in carbapenem consumption.



Poignant et al. Antimicrobial Agents and Chemotherapy (2016)

Species-specific mutation rates for *ampC* derepression in Enterobacterales with chromosomally encoded inducible AmpC β-lactamase

Rebekka Kohlmann*, Tobias Bähr and Sören G. Gatermann

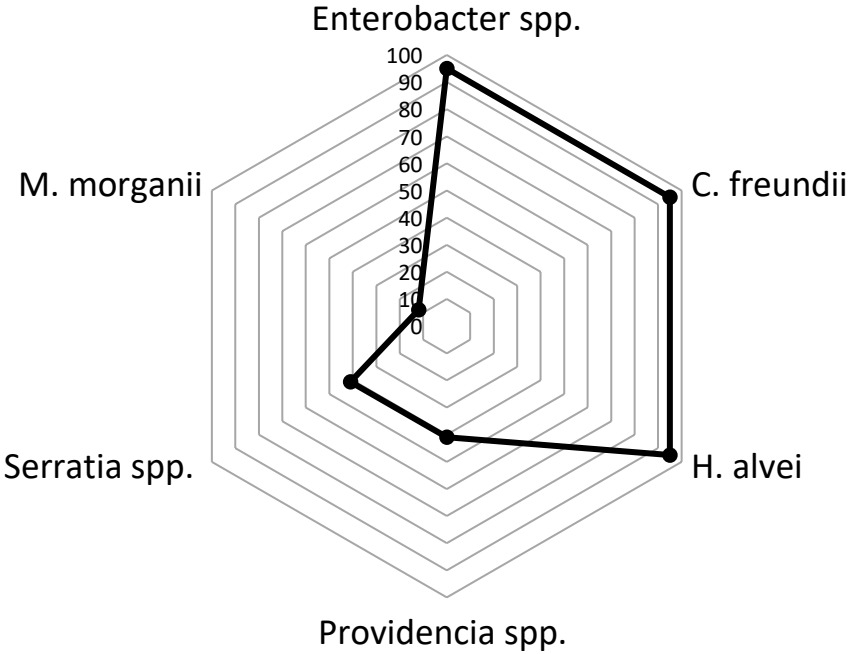
- ✓ Department of Medical Microbiology, Ruhr-Universitat Bochum, Germany

- ✓ 237 Souches de :
  E. cloacae, E. aerogenes, C. freundii, H. alvei, P. rettgeri, P. stuartii, S. marcescens, S. liquefaciens et M. morganii

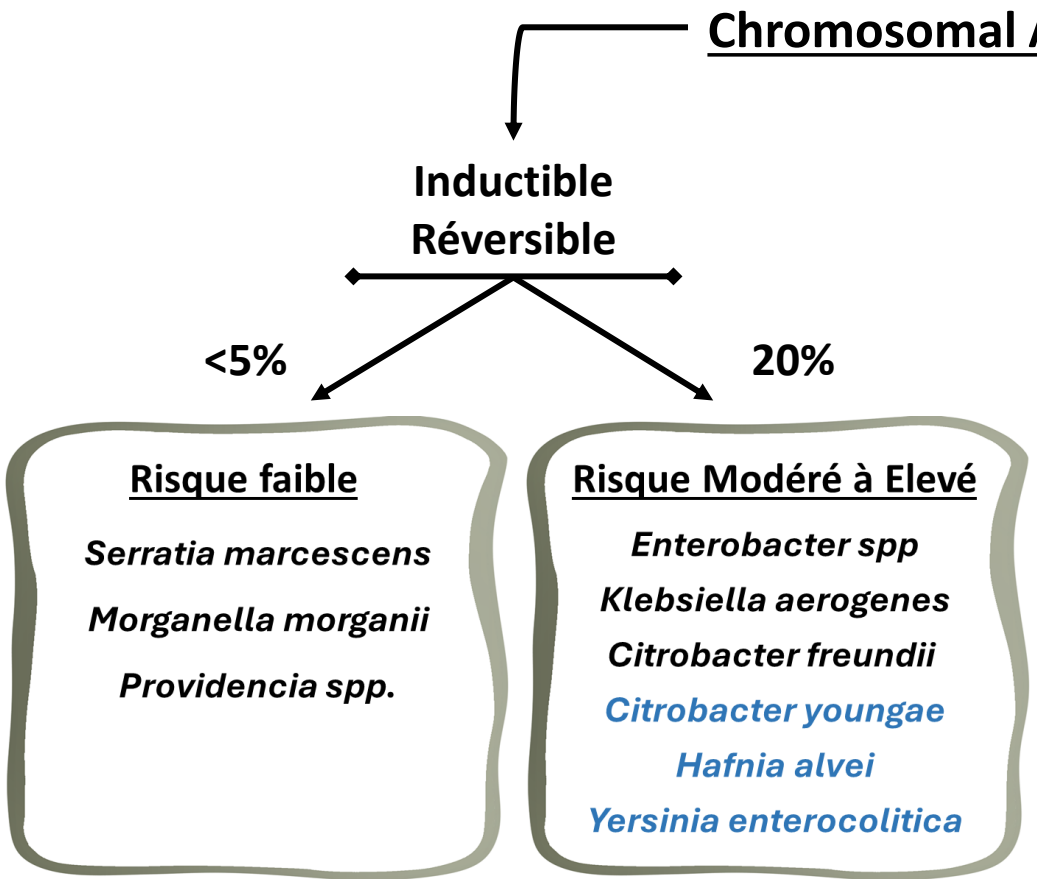
- ✓ CTX-S (CMI 1mg/L pour CTX et CAZ)

- ✓ Collectées entre Janvier 2016 et Juillet 2017
- ✓ Examens microbiologiques de routine
- ✓ Culture sur une gélose contenant la CTX (8mg/L)

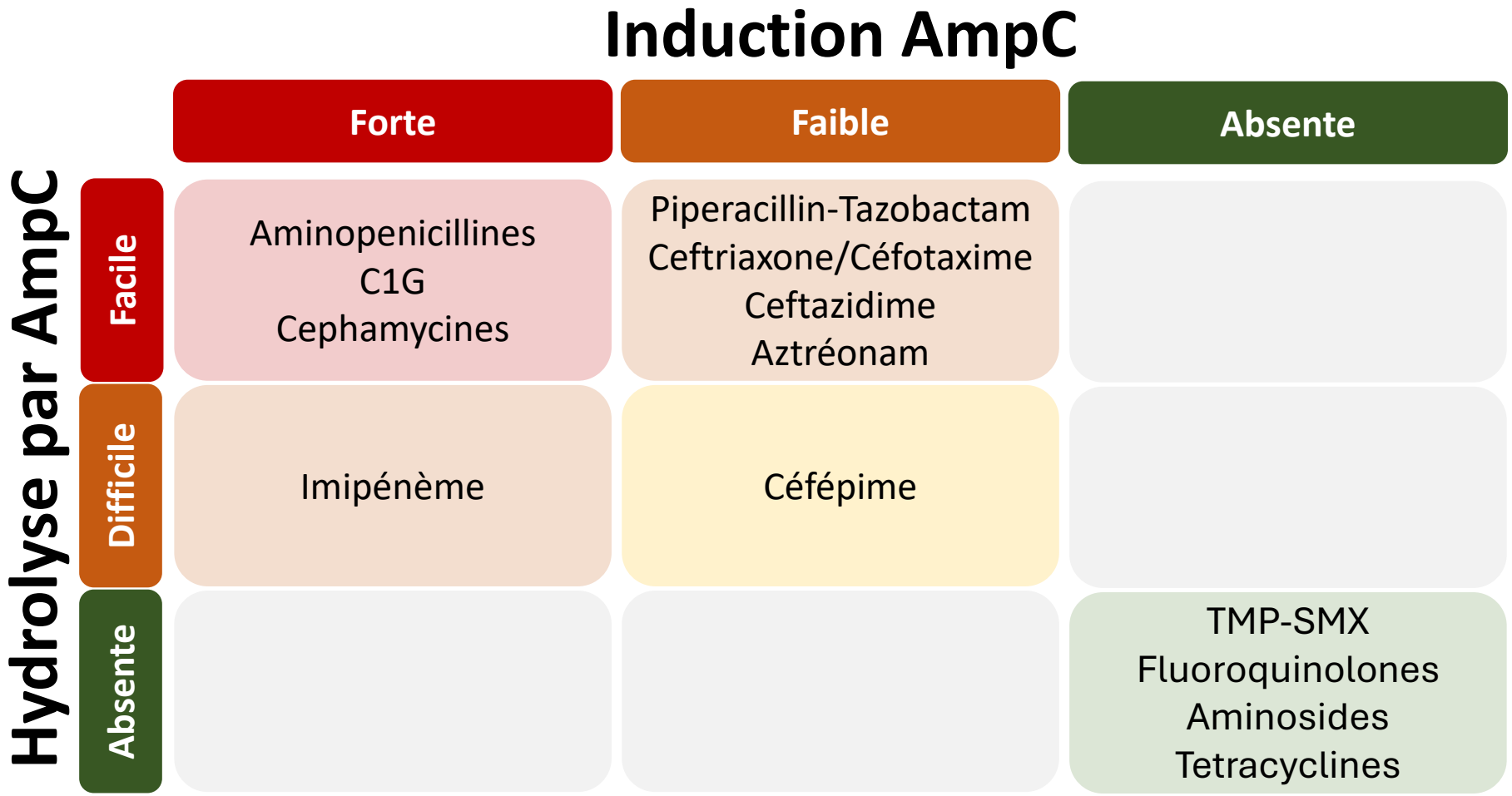
% de Résistance par hyperexpression de l'AmpC



Kohlmann et al. JAC (2018)



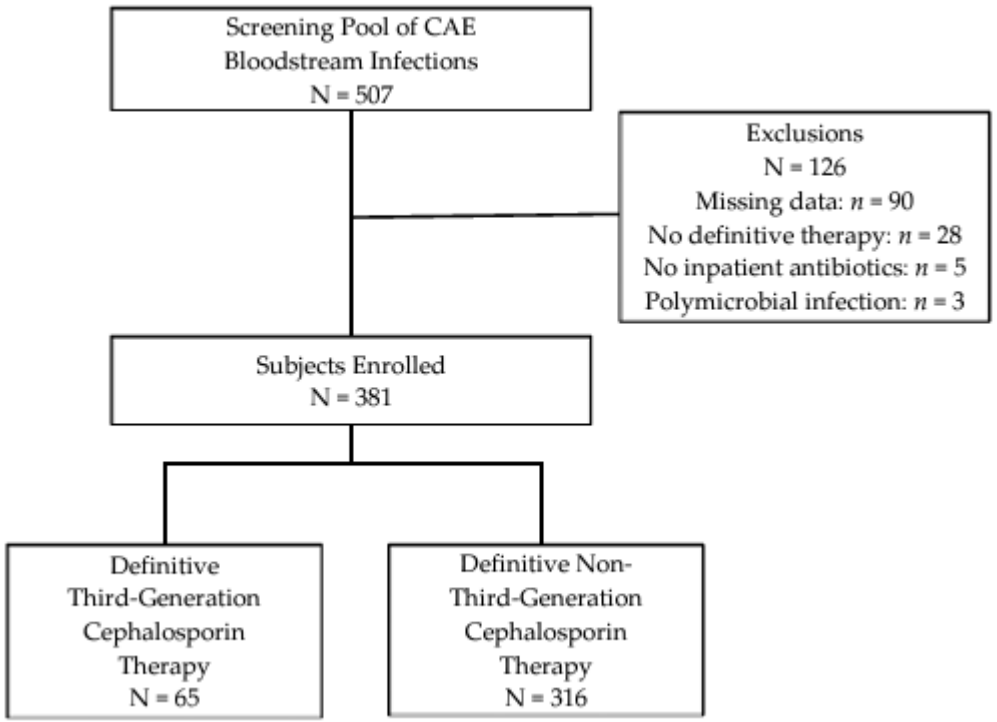
Tebano et al. Pharmacy (2024)
Tamma et al. CID (2023)

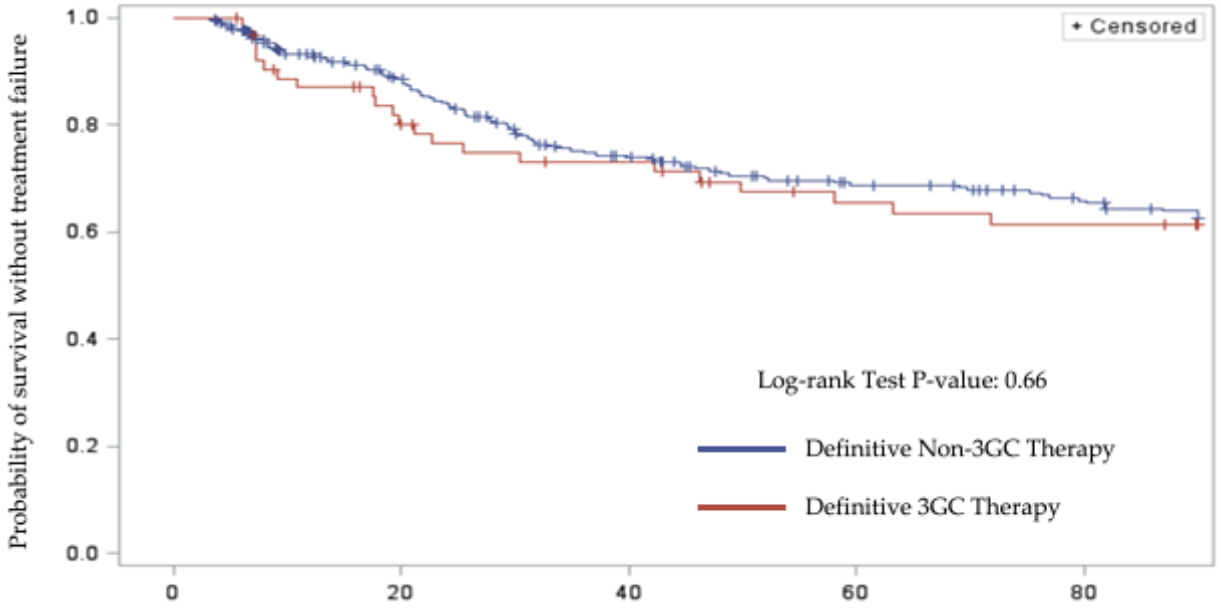


Tamma et al. CID (2023)

Article

Multicenter, Observational Cohort Study Evaluating Third-Generation Cephalosporin Therapy for Bloodstream Infections Secondary to *Enterobacter*, *Serratia*, and *Citrobacter* Species





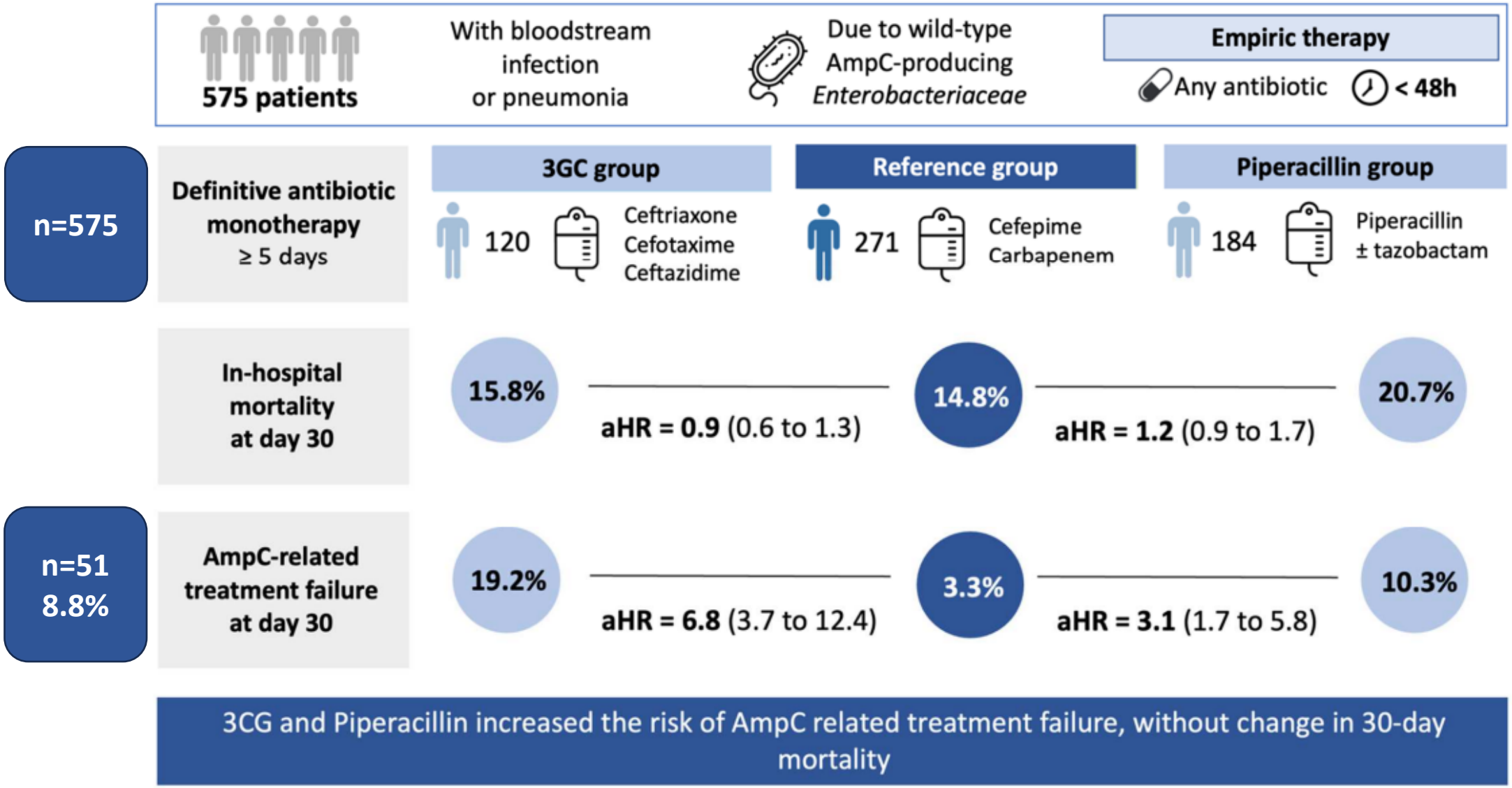
Derrick et al. Antibiotics (2020)

Article

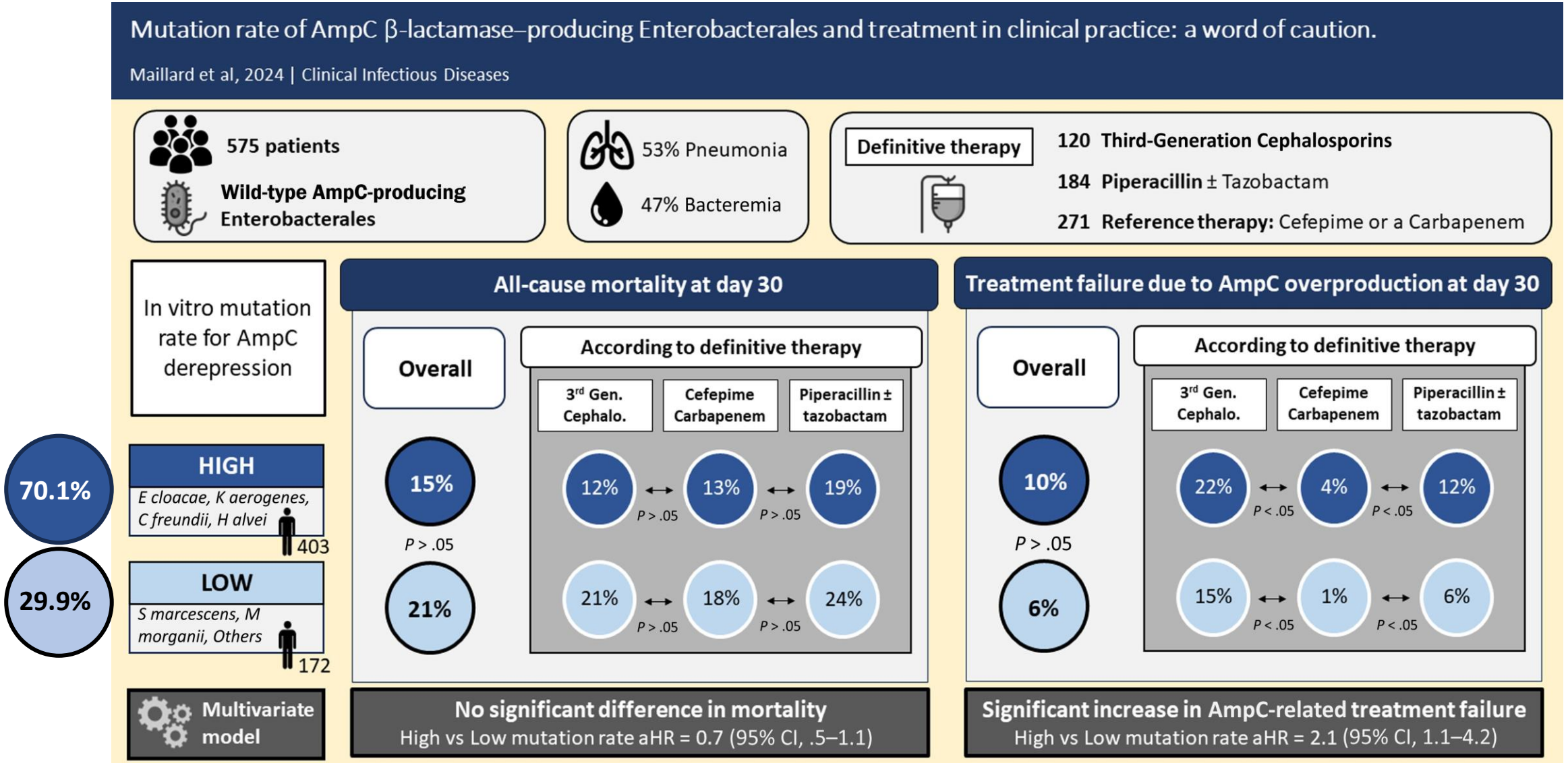
Multicenter, Observational Cohort Study Evaluating Third-Generation Cephalosporin Therapy for Bloodstream Infections Secondary to *Enterobacter*, *Serratia*, and *Citrobacter* Species

Characteristic	Definitive 3GC Therapy [a] N = 65	Definitive Non-3GC Therapy [a] N = 316	*p*-Value
Source of Infection			
Central Venous Catheter	17 (26.2)	61 (19.3)	0.213
Urinary Tract	15 (23.1)	63 (19.9)	0.568
Skin- or Skin Structure-Related	9 (13.9)	35 (11.1)	0.525
Intra-Abdominal	6 (9.2)	34 (10.8)	0.714
Respiratory	3 (4.6)	42 (13.3)	0.049
Other	6 (9.2)	16 (5.1)	0.237
Unknown Source	9 (13.9)	76 (24.1)	0.072

Derrick et al. Antibiotics (2020)



Maillard et al. IJAA (2023)



Maillard et al. CID (2024)

RESEARCH Open Access

Antibiotic definitive treatment in ventilator associated pneumonia caused by AmpC-producing Enterobacterales in critically ill patients: a prospective multicenter observational study

Prospective, Feb 20 – June 21
20 ICU (France)

Inclusion:

VAP due to wtAE
Adequate empirical AMT

PEP: TTT success at day 7

SEP: Recurrence of VAP, new AmpC-AE infection, C. difficile infection, MDRB, duration of MV, death at D28 and in hosp. mortality and LOS

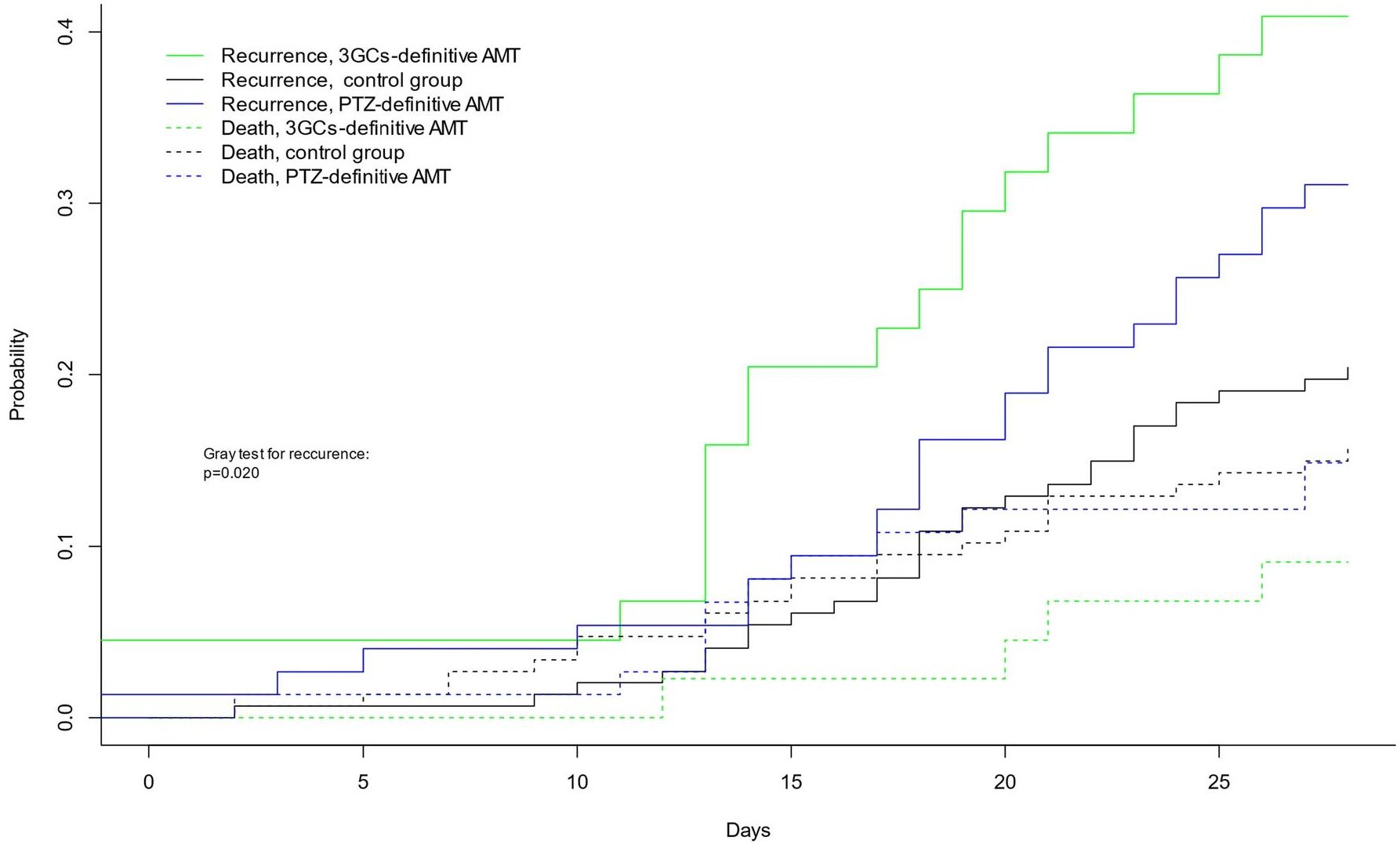
PEP:

Definitive AMT was not associated with the primary outcome for PTZ and 3GCs categories compared to the control group, respectively

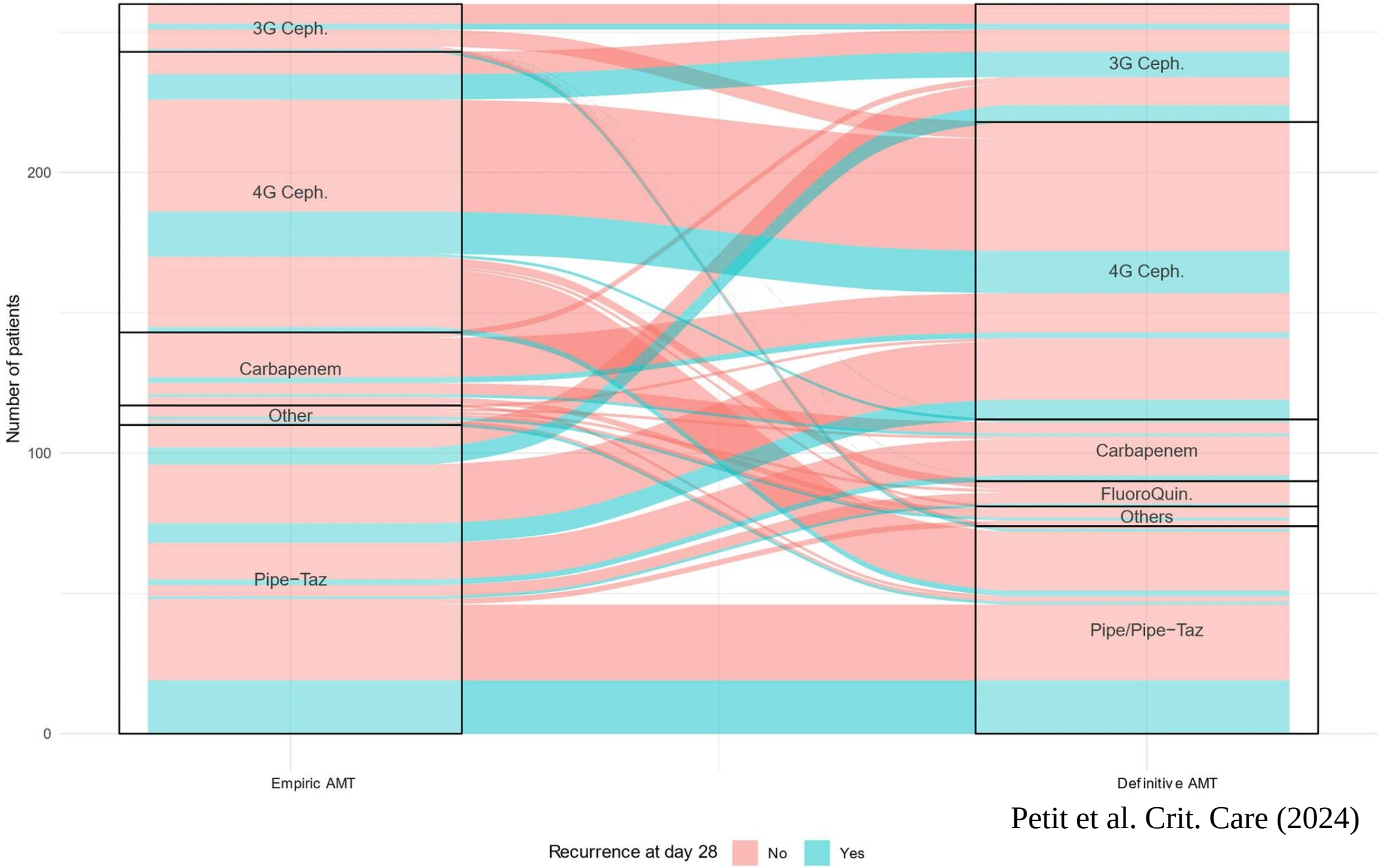
SEP:

- ✓ Vital status at day 28, ICU and hospital discharge were similar between the 3 groups
- ✓ **3GCs was associated with recurrence, as well as high risk of AmpC overexpression AE species.**

Petit et al. Crit Care (2024)



Petit et al. Crit. Care (2024)



Petit et al. Crit. Care (2024)

RESEARCH Open Access

Clinical outcome of wild-type AmpC-producing Enterobacterales infection in critically ill patients treated with β-lactams: a prospective multicenter study

Prospective, Sept 17 – Dec 20
4 ICU (APHP)
Inclusion: Documented wtAE infection (MIC≤1µg/ml), treated with β-lactams
Exclusion: Death within 48h
PEP: Prevalence of clinical failure
SEP: Risk factors for clinical failure & AmpC overproduction

PEP:
VAPs and *K. aerogenes* were independently associated with clinical failure.

SEP:

Patients who received CTX had a 20% risk reduction of clinical failure relative to those who did not receive CTX (p = 0.007).

Mounier et al. AIC (2024)

RESEARCH Open Access

Clinical outcome of wild-type AmpC-producing Enterobacterales infection in critically ill patients treated with β-lactams: a prospective multicenter study

Prospective, Sept 17 – Dec 20

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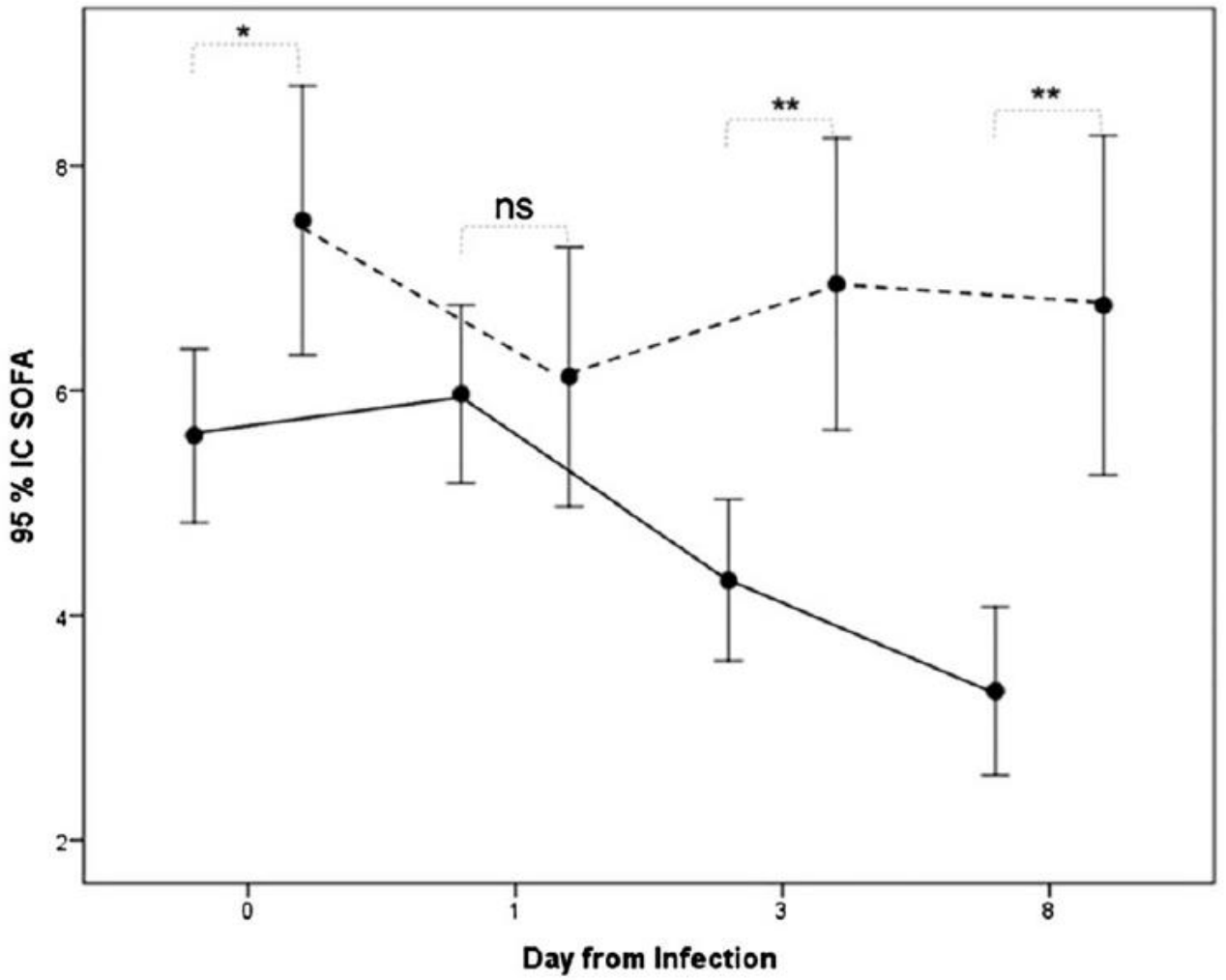


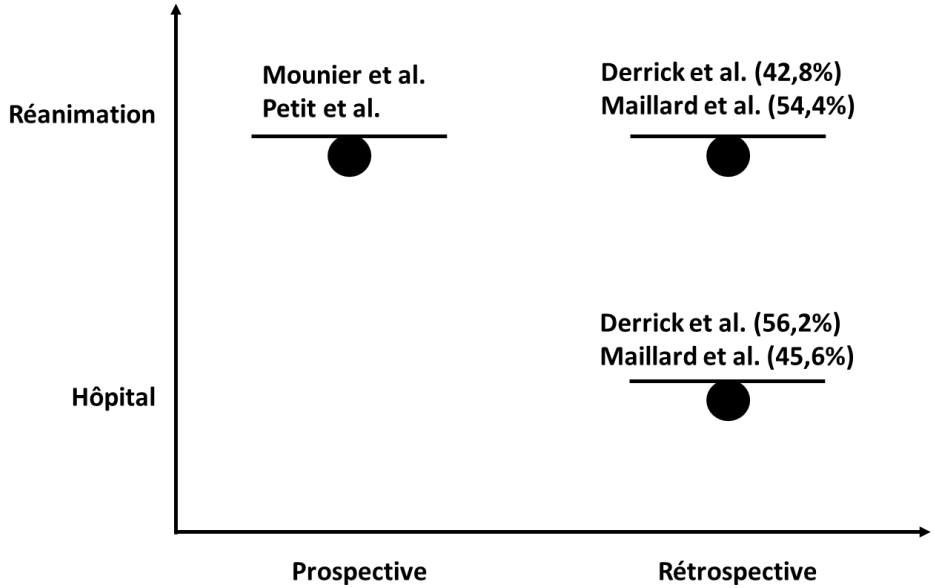
Mounier et al. AIC (2024)

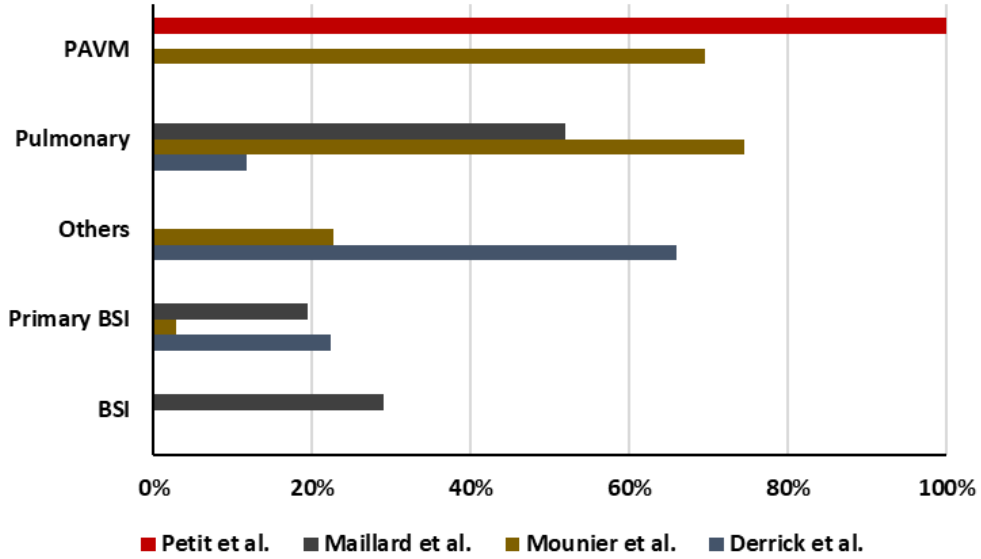
RESEARCH Open Access

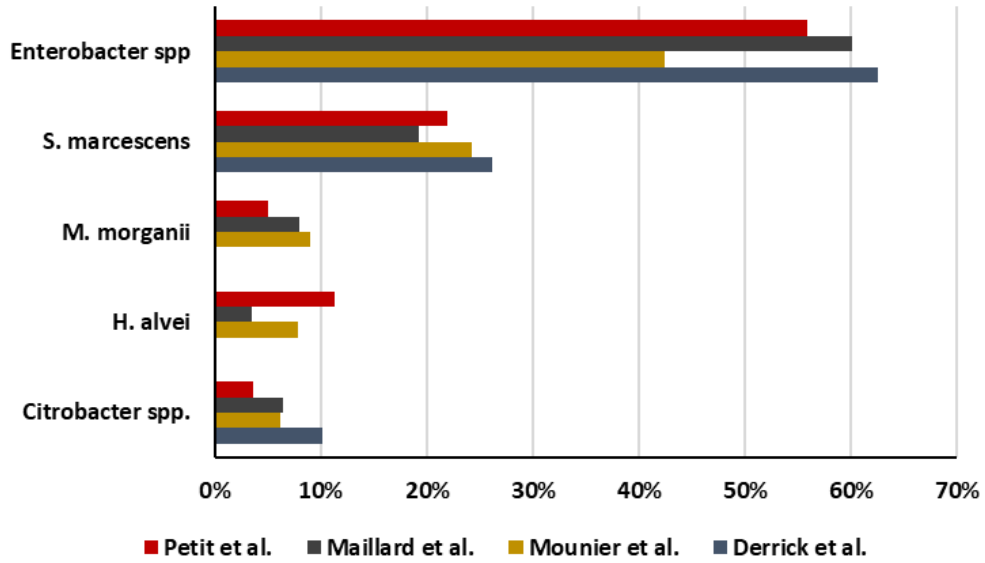
Clinical outcome of wild-type AmpC-producing Enterobacterales infection in critically ill patients treated with β-lactams: a prospective multicenter study

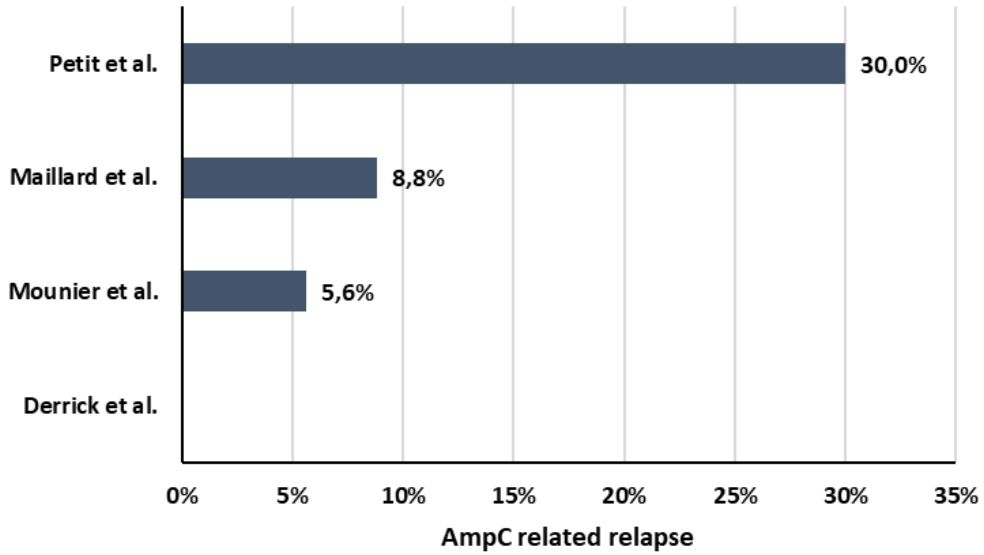
	All population ($n=177$)		clinical failure ($n=52$)		clinical cure ($n=125$)		p
	Nb	Results	Nb	Results	Nb	Results	
Site of wtAE infection							
Lung	177	132 (74.6%)	52	48 (92.3%)	125	84 (67.2%)	**0.000**
Ventilator-associated pneumonia	132	123 (93.2%)	52	47 (90.4%)	125	76 (60.8%)	**0.000**
Skin and Soft tissue	177	14 (7.9%)	52	2 (3.8%)	125	12 (9.6%)	0.196
Abdomen	177	11 (6.2%)	52	1 (1.9%)	125	10 (8%)	0.127
Primary bacteremia	177	5 (2.8%)	52	0 (0%)	125	5 (4%)	0.143
CSF	177	5 (2.8%)	52	0 (0%)	125	5 (4%)	0.323
Others	177	10 (5.6%)	52	1 (1.9%)	125	9 (7.2%)	0.285
				4 (7,7%)		**41 (32,8%)**	**0,000**

Mounier et al. AIC (2024)

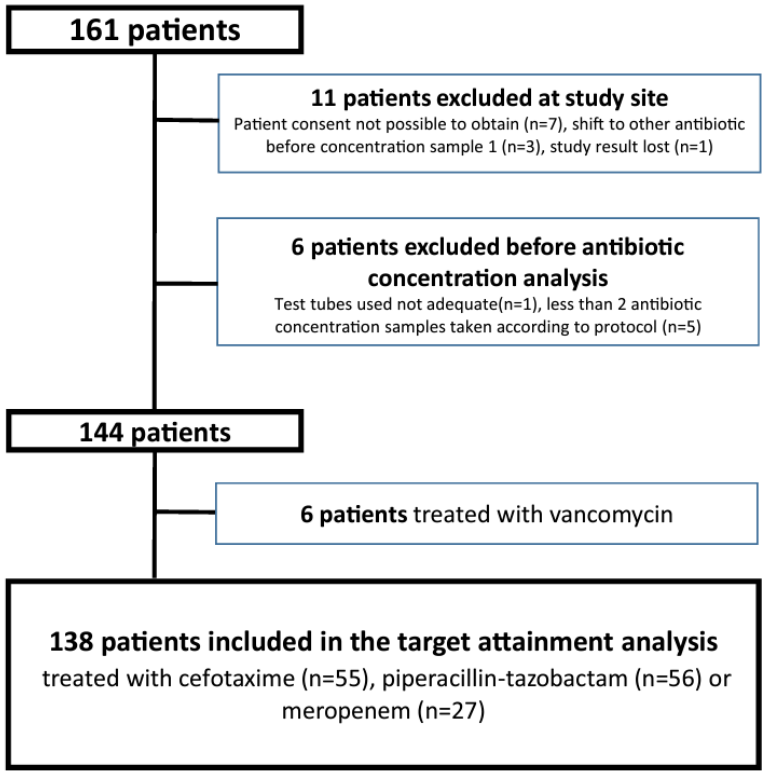

Réanimation
Hôpital
Mounier et al.
Petit et al.
Derrick et al. (42,8%)
Maillard et al. (54,4%)
Derrick et al. (56,2%)
Maillard et al. (45,6%)
Prospective
Rétrospective

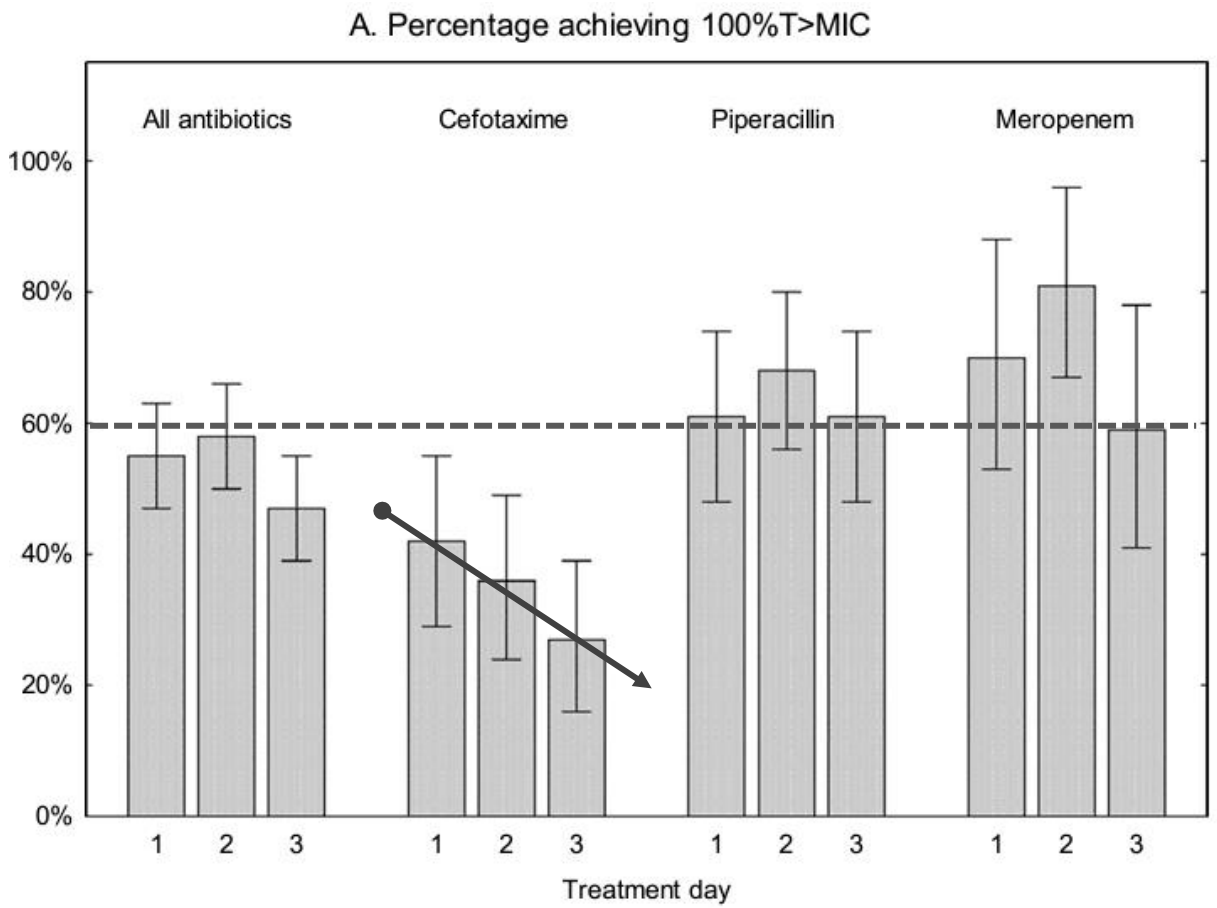

PAVM
Pulmonary
Others
Primary BSI
BSI
0%
20%
40%
60%
80%
100%
Petit et al.
Maillard et al.
Mounier et al.
Derrick et al.


Enterobacter spp
S. marcescens
M. morganii
H. alvei
Citrobacter spp.
0%
10%
20%
30%
40%
50%
60%
70%
Petit et al.
Maillard et al.
Mounier et al.
Derrick et al.


Petit et al.
30,0%
Maillard et al.
8,8%
Mounier et al.
5,6%
Derrick et al.
0%
5%
10%
15%
20%
25%
30%
35%
AmpC related relapse

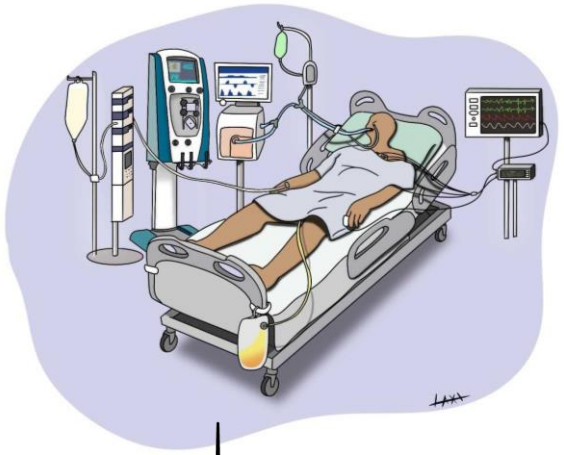
Low attainment to PK/PD-targets for β-lactams in a multi-center study on the first 72 h of treatment in ICU patients





Smekal et al. Nature (2022)

En pratique



Sepsis → **48 h** → **AmpC-EB**

Risque élevé
Enterobacter spp
K. aerogenes
C. freundii

Risque faible
S. marcescens
M. morganii
Providencia spp.

Evolution clinique favorable

CTX ?

PTZ	CTX	FEP	CARBA

CMI FEP

- **<4 µg/ml** → **FEP**
- **4-8 µg/ml*** → **CARBA**

* Co-ESBL production

CTX ? / FEP

Tamma et al. CID (2023)

Infectious Diseases Society of America 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections

When treating infections with a high bacterial burden and limited source control (eg, endocarditis, CNS infections) caused by:

- ✓*C. youngae, H. alvei, Y. enterocolitica*

or

- ✓*S. marcescens, M. morganii,* or *Providencia* spp.

it is alternatively **reasonable** to consider treatment with **cefepime** instead of ceftriaxone, even if the organism tests susceptible to CTR.

Tamma et al. CID (2023)

Perspectives

- ✓Le risque exact de dérépression chez différentes espèces et avec différents ATB
- ✓L'efficacité clinique des 3GC et du PTZ, en fonction du contexte clinique et du pathogène responsable
- ✓La pertinence d’une désescalade lorsque le germe responsable est disponible et que le patient présente une amélioration clinique sous 3GC
- ✓Le rôle de la désescalade vers les G3C (en particulier pour les traitements longs) lorsque le patient a déjà atteint la stabilité clinique et qu’il ne peut pas recevoir ses ATB par voie orale.

Tebano et al. Pharmacy (2024)

Merci