26es JNI 2025 TOURS
et la région Centre - Val de Loire VINCI
Journées Nationales d'infectiologie
du mercredi 11 juin 2025 au vendredi 13 juin 2025
Journée Nationale de Formation
des Paramédicaux en Infectiologie
Jeudi 12 juin 2025

Infections bactériennes chez l'Immunodéprimé

Faut-il une bi-antibiothérapie ? (Pour qui)

Pr Benjamin Gaborit, CHU de Nantes

Le 12 juin 2025

26es JNI 2025 TOURS
et la région Centre - Val de Loire VINCI

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Déclaration de liens d'intérêt avec les industriels de santé en rapport avec le thème de la présentation (loi du 04/03/2002) :

L'orateur ne souhaite pas répondre ☐

- **Intervenant** : GABORIT Benjamin
- **Titre** : **Infections bactériennes chez l'immunodéprimé : quelle place pour les associations antibiotiques en première ligne ?**

- Consultant ou membre d'un conseil scientifique — ☐ OUI ☑ NON
- Conférencier ou auteur/rédacteur rémunéré d'articles ou documents — ☐ OUI ☑ NON
- Prise en charge de frais de voyage, d'hébergement ou d'inscription à des congrès ou autres manifestations — ☐ OUI ☑ NON
- Investigateur principal d'une recherche ou d'une étude clinique — ☐ OUI ☑ NON

Plan

CONTEXTE

- Epidémiologie
- Pourquoi envisager la Bithérapie?

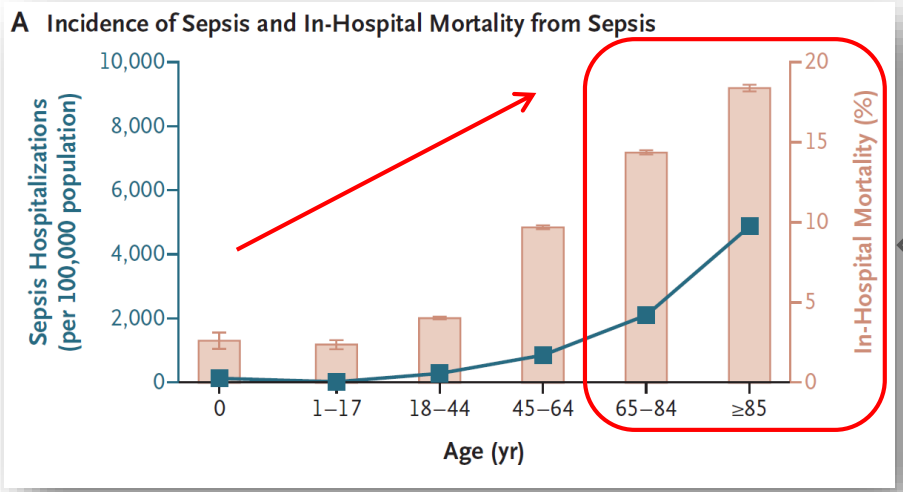
POUR QUI ENVISAGER LA BITHÉRAPIE CHEZ L'ID ?

- Sepsis et choc septique
- En fonction du pathogène et du contexte d'ID
- Les risques

MAIS, UTILISONS – NOUS BIEN LA MONOTHÉRAPIE ?

Etat des lieux : Pourquoi s'intéresser au sepsis chez ID?

Concernant les patients **ID**?



2021 *(Nationwide Inpatient Sample, HCUP net)*

2013 : 2.7% of US adults

2021 : 6.6% of US adults **X 3**

December 20, 2016

Prevalence of Immunosuppression Among US Adults, 2013

Rafael Harpaz, MD, MPH[1]; Rebecca M. Dahl, MPH[1]; Kathleen L. Dooling, MD, MPH[1]

Author Affiliations | Article Information

JAMA. 2016;316(23):2547-2548. doi:10.1001/jama.2016.16477

February 15, 2024

Prevalence of Immunosuppression Among US Adults

Melissa L. Martinson, PhD[1]; Jessica Lapham, PhD[1]

Author Affiliations

JAMA. Published online February 15, 2024. doi:10.1001/jama.2023.28019

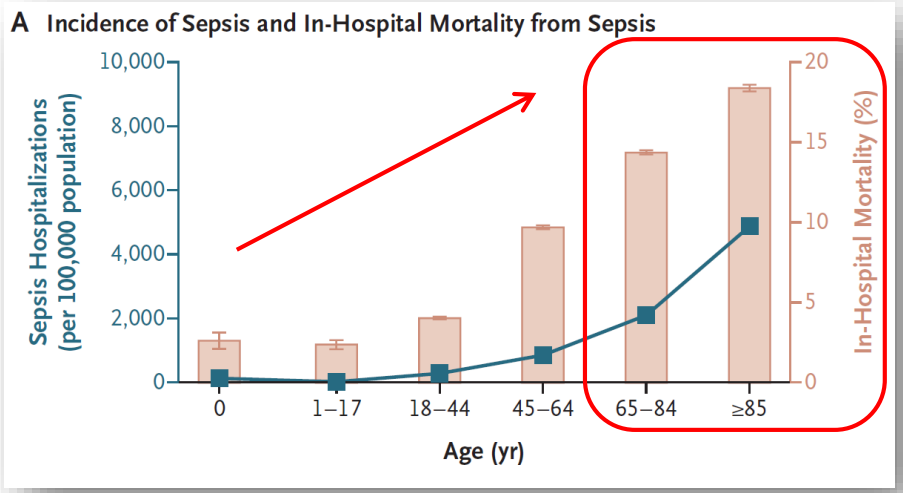
Vieillissement de la population **et augmentation du nombre global de patients immunodéprimés** !

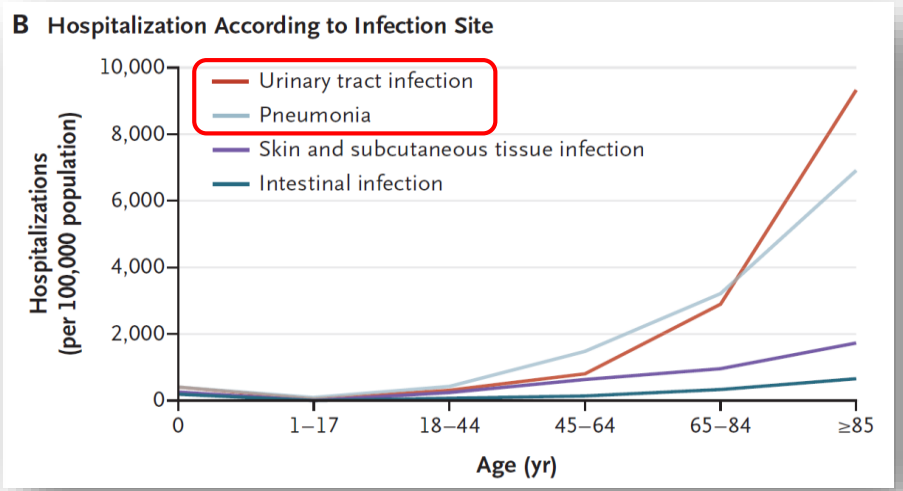
The NEW ENGLAND JOURNAL of MEDICINE

Nuala J. Meyer, M.D., and Hallie C. Prescott, M.D. Sepsis **NEJM Dec, 2024**

JAMA® The Journal of the American Medical Association

Etat des lieux : Fardeau de l'immunodepression ?





2021 *(Nationwide Inpatient Sample, HCUP net)*

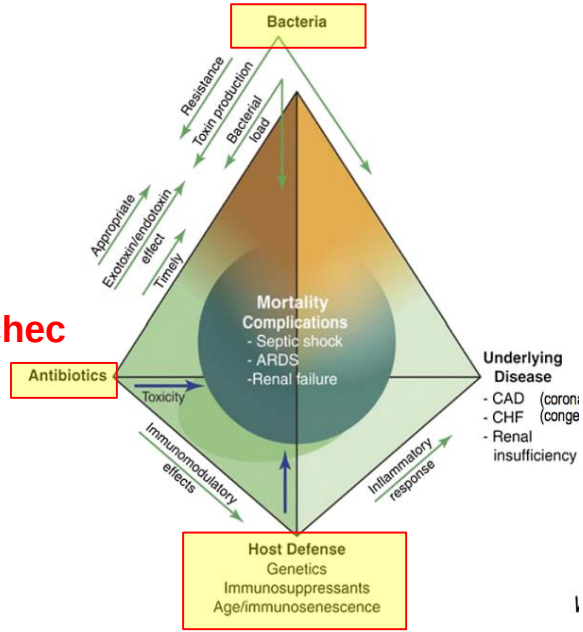
- Infections **bactériennes**
- Pneumonies > IU et infections intra abdominales

The NEW ENGLAND JOURNAL of MEDICINE

Nuala J. Meyer, M.D., and Hallie C. Prescott, M.D. Sepsis **NEJM Dec, 2024**

Comment faire mieux ?

↗ **Résistance au ATB**



↗ **échec**

Immunodépression

Le traitement **probabiliste, un pari difficile**

En suivant les recommandations, traitement optimal d'emblée dans ~ 60 % des cas

Sur-traitement

~ 20% de large spectre évitable

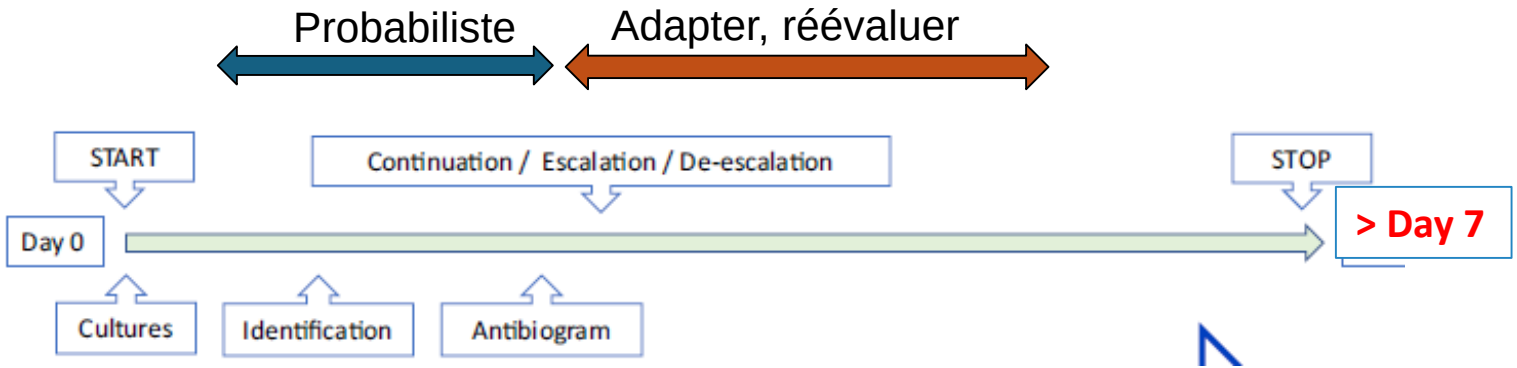
impacts sur le microbiote dès J3

Sous-traitement

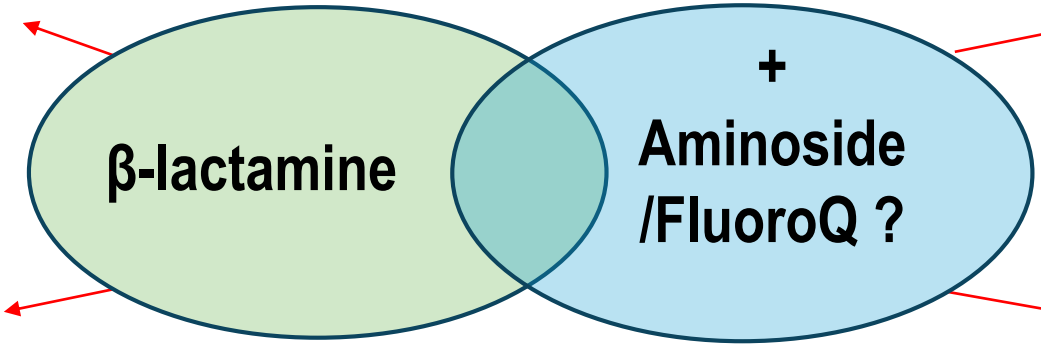
~ 10-15 % nécessitant une adaptation

Nikolay P Braykov lancet infect dis 2014
Armand-Lefèvre AAC 2013
Tamma PD, Clin Microbiol Rev. 2012

Les hypothèses pour améliorer le pronostic des **patients immunodéprimés**?



Le **spectre** ?



Effet **synergique** ?

La **toxicité** ?

En fonction du **germe** ou **contexte ID** ?

Jan J. De Waele ICM 2020

Plan

Faut-il élargir le spectre antibiotique chez l'ID ?

Oui, mais quelle cible chez l'Immunodéprimé

Taux de traitement probabiliste inapproprié ?

Neutropénie fébrile **à haut risque**

- **Barcelone bicentrique**
- **NF + Bactériémie -> Taux IEAT**
  - **N = 1 615** épisodes: **E.coli > SCN > *P.A***
  - **87 % suivi reco IDSA**

Taux **IEAT :**

24 % des patients

39% des MDR-BGN (Vs 7%, P<.001)

Taux **Mortalité IETA :**

BGN 36% (Vs 24%, *P.004*)

***P.A* 48%** (Vs 31%, *P.02*)

CGP pas d'impact

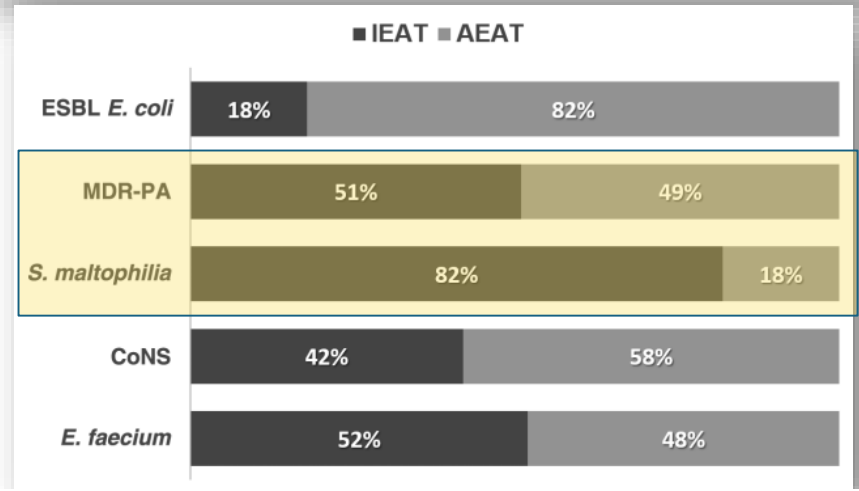
Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Inappropriate Empirical Antibiotic Treatment in High-risk Neutropenic Patients With Bacteremia in the Era of Multidrug Resistance

Gemma Martinez-Nadal,[1,a] Pedro Puerta-Alcalde,[2,a] Carlota Gudiol,[3,4] Celia Cardozo,[2] Adaia Albasanz-Puig,[3] Francesc Marco,[5,6] Júlia Laporte-Amargós,[3] Estela Moreno-García,[2] Eva Domingo-Doménech,[7] Mariana Chumbita,[2] José Antonio Martínez,[2,8] Alex Soriano,[2,8] Jordi Carratalà,[3,4] and Carolina Garcia-Vidal[2,8]



IEAT fréquent (malgré le suivi des reco) ++

Impact clinique = BGN et *P.A* (11% R AMIKLIN)

Choc septique et Pneumonie

Oui, mais quelle cible chez l'Immunodéprimé

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Table 5. Independent Risk Factors for Mortality in Bloodstream Infection Caused by *Pseudomonas aeruginosa*

Risk Factor	Adjusted OR[a] (95% CI)	*P* Value
IEAT	3.02 (1.29–7.07)	.011
Septic shock at onset	4.05 (1.81–9.09)	.001
Pneumonia	2.62 (1.22–5.64)	.014

Abbreviations: CI, confidence interval; IEAT, inappropriate empirical antibiotic treatment; OR, odds ratio.

[a]Adjusted for endogenous source of infection and multidrug-resistant *Pseudomonas aeruginosa*.

IEAT fréquent (malgré le suivi des reco) ++

Impact clinique = BGN et *P.A* (11% R AMIKLIN)

Choc septique et Pneumonie

Elargir le spectre : Le spectre efficace précoce au cours du **choc septique** ?

RESEARCH Open Access

Adequate antibiotic therapy prior to ICU admission in patients with severe sepsis and septic shock reduces hospital mortality

José Garnacho-Montero[1,2,3*], Antonio Gutiérrez-Pizarraya[2,3,4], Ana Escoresca-Ortega[1], Esperanza Fernández-Delgado[1] and José María López-Sánchez[1]

CRITICAL CARE

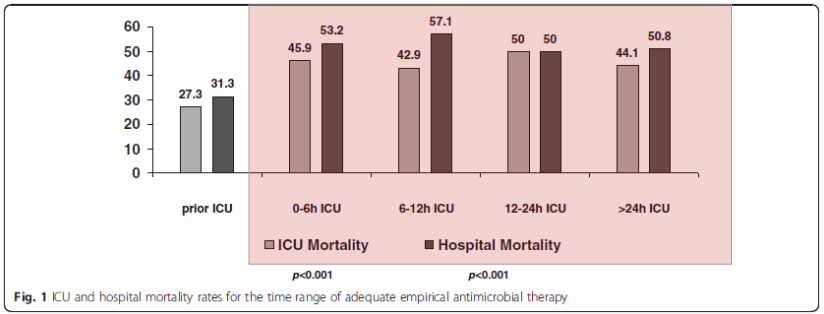


Fig. 1 ICU and hospital mortality rates for the time range of adequate empirical antimicrobial therapy

Table 4 Multivariate analysis of risk factors for hospital mortality in patients with severe sepsis and septic shock

	Severe sepsis		Septic shock	
	Adjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)	*p* value
Age	1.02 (1.00–1.05)	0.033		
APACHE II score	1.07 (1.01–1.14)	0.020	1.11 (1.07–1.15)	<0.001
Cirrhosis			4.49 (1.55–13.04)	0.006
Immunosuppression	4.39 (1.64–11.72)	0.003		
Urinary sepsis source			0.11 (0.05–0.27)	<0.001
Nosocomial infection	6.53 (2.74–15.55)	<0.001		
Prior ICU adequate antimicrobial therapy	0.29 (0.13–0.63)	0.002	0.40 (0.24–0.65)	<0.001

APACHE Acute Physiology and Chronic Health Evaluation, *CI* confidence interval, *OR* odds ratio

- **Cohorte prospective monocentrique 2008-2013**
- **Sepsis sévère et choc septique (n=638)**
- Mortalité hospitalière Vs du délai adéquation ATB

- **98% ATB** au SAU
- **30% inadéquation**
- 15% ID et 20% cancer

- **Effet protecteur d'un traitement adapté précoce (>6h)**

Garnacho et al. 2015 Crit Care

Elargir le spectre : Qui bénéficie de la bithérapie au cours du choc septique ?

Influence of empirical double-active combination antimicrobial therapy compared with active monotherapy on mortality in patients with septic shock: a propensity score-adjusted and matched analysis

Marco Ripa[1,2]†, Olga Rodríguez-Núñez[2]†, Celia Cardozo[2], Antonio Naharro-Abellán[3], Manel Almela[4], Francesc Marco[4], Laura Morata[2], Cristina De La Calle[2], Ana Del Rio[2], Carolina Garcia-Vidal[2], María Del Mar Ortega[2], María De Los Angeles Guerrero-León[2], Csaba Feher[2], Berta Torres[2], Pedro Puerta-Alcalde[2], Josep Mensa[2], Alex Soriano[2] and José Antonio Martínez[2]*

Etude rétrospective 2010-2015,
Mortalité **J7->J30** au cours **choc septique**
*Score **propension***
Neutropénie (13%), cancer (20%)

Bi (n=340) versus Monothérapie (n=236)

Table 5. PS-adjusted OR (95% CI) of the association of DACT with 7, 15 and 30 day mortality in specific subgroups

	7 day mortality		15 day mortality		30 day mortality	
Subgroup	adjusted OR (95% CI)	*P* value	adjusted OR (95% CI)	*P* value	adjusted OR (95% CI)	*P* value
Neutropenia ($N = 69$)[a]						
DACT	0.36 (0.11–1.23)	0.103	0.29 (0.09–0.92)	**0.036**	0.25 (0.08–0.79)	**0.019**
PS	1.27 (0.09–18.16)	0.862	1.13 (0.09–13.92)	0.923	4.22 (0.34–52.16)	0.262
Haematological malignancy ($N = 89$)						
DACT	0.74 (0.23–2.35)	0.609	0.45 (0.15–1.32)	0.144	0.45 (0.16–1.29)	0.138
PS	0.43 (0.03–5.44)	0.514	0.34 (0.03–3.76)	0.380	0.47 (0.05–4.74)	0.521
Unknown focus of infections ($N = 94$)						
DACT	0.47 (0.17–1.28)	0.139	0.39 (0.15–1.03)	0.056	0.44 (0.17–1.14)	0.090
PS	0.09 (0.01–0.99)	**0.049**	0.05 (0.01–0.52)	**0.013**	0.03 (0.01–0.33)	**0.004**
Pulmonary focus of infections ($N = 98$)						
DACT	0.89 (0.34–2.31)	0.804	0.88 (0.36–2.18)	0.782	0.68 (0.28–1.65)	0.396
PS	0.32 (0.03–3.56)	0.354	0.31 (0.03–3.11)	0.321	0.57 (0.06–5.38)	0.625
Time to blood culture positivity <7.5 h ($N = 139$)						
DACT	0.60 (.25–1.44)	0.251	0.75 (0.32–1.76)	0.501	0.86 (0.38–1.95)	0.717
PS	0.14 (0.02–0.95)	**0.044**	0.06 (0.01–0.44)	**0.005**	0.09 (0.02–0.56)	**0.010**
Pseudomonas aeruginosa ($N = 61$)[b]						
DACT	0.12 (0.02–0.70)	**0.018**	0.34 (0.09–1.27)	0.107	0.26 (0.08–0.92)	**0.036**
PS	82.18 (1.71–3952.63)	**0.026**	6.79 (0.38–122.12)	0.194	8.79 (0.56–136.83)	0.121
Empirical active β-lactam ($N = 482$)						
DACT	0.84 (0.49–1.44)	0.528	0.85 (0.52–1.39)	0.516	1.06 (0.67–1.67)	0.820
PS	0.63 (0.20–1.95)	0.422	0.63 (0.22–1.81)	0.396	0.56 (0.21–1.49)	0.246

Conclusions: All-cause mortality at 7, 15 and 30 days was similar in patients with monomicrobial septic shock receiving empirical double-active combination therapy and active monotherapy. However, a beneficial influence of empirical double-active combination on mortality in patients with neutropenia and those with *P. aeruginosa* infection is worthy of further study.

Journal of Antimicrobial Chemotherapy

- **Pas de bénéfice pour l'ensemble des patients**

Ripa et al. JAC **2017**

Plan

Un effet synergique de la bithérapie ?

Une synergie : un bénéficie de la bithérapie « universelle

Large spectre +/- Moxifloxacin ?

Sepsis et choc septique

- **RCT, 44 USI, 2007-2010**
- **Sepsis/choc septique (< 24h)**
- **Mero (1g/8h sur 15 min) +/- Moxiflo 400mg/J**
- **Score SOFA et mortalité**
  - **N = 551, SOFA = 9.5**

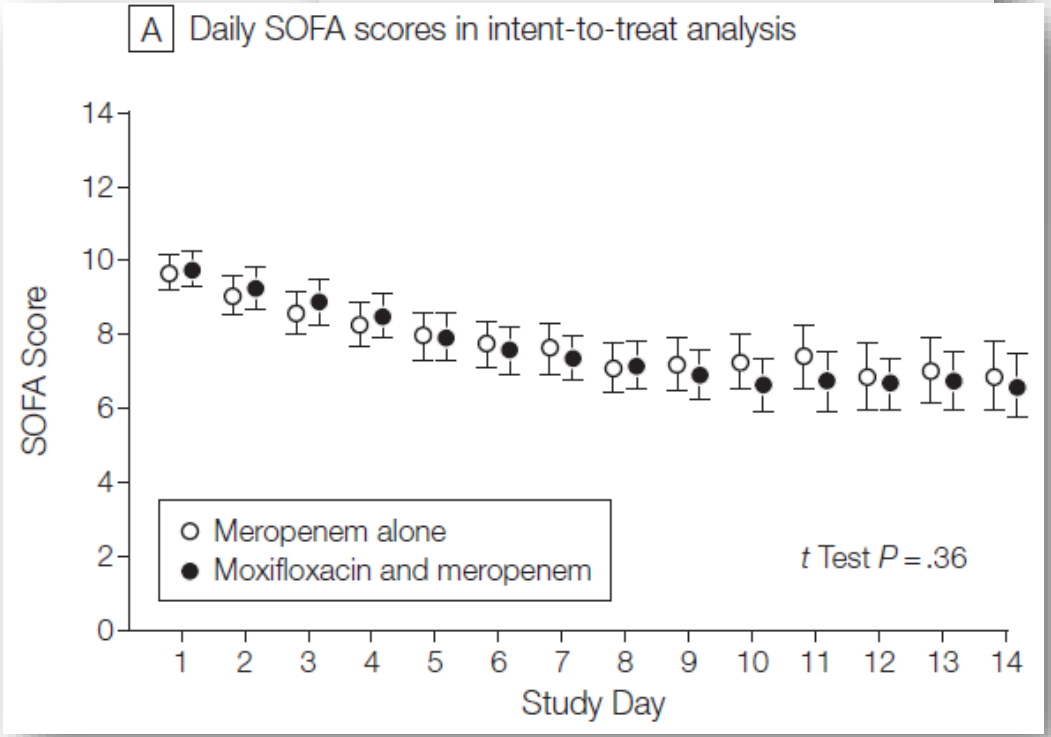
Pas d'impact: SOFA, mortalité, durée d'hospitalisation, infection secondaires ..

Mortality D28: **23.9% Vs 21.9%** (*P*=.58).

En cas de germes sensibles

= PAS d'intérêt de la bithérapie

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



F. Brunkhorst et al. **JAMA 2012**

Plan

Intérêt de la bithérapie sur Pseudomonas, EPC ?

La synergie: la bithérapie et *Pseudomonas aeru*

Impact d'une bithérapie précoce sur P.A ?

BSI **avec choc septique**

- **14 hopitaux, 2021-> 2022**
- ***Choc septique Bactériémie à P.a* (< 24h)**
- **Traitement adapté => mono Vs bi-thérapie**
  - **N = 98, 24 (combiné) Vs 74 monothérapie**
  - **Aminoside ++**

Mortalité D30

Combiné (25%, 6/24) Vs Mono (56.8%, 42/74) ***P = 0.007***

Pas d'impact pour le **traitement définitif**

aHR 0.73; 95% CI 0.25–2.14; ***P = 0.568***

J Antimicrob Chemother 2024; **79**: 2846–2853
https://doi.org/10.1093/jac/dkae296 Advance Access publication 3 September 2024

Journal of Antimicrobial Chemotherapy

Impact of adequate empirical combination therapy on mortality in septic shock due to *Pseudomonas aeruginosa* bloodstream infections: a multicentre retrospective cohort study

Antonio Vena[1,2]*†, Michela Schenone[1]†, Silvia Corcione[3,4]†, Maddalena Giannella[5,6], Renato Pascale[5,6], Daniele Roberto Giacobbe[1,2], Marco Muccio[1], Simone Mornese Pinna[3], Bianca Pari[3], Francesca Giovannenze[7], Nicholas Geremia[8], Malgorzata Mikulska[1,2], Eleonora Taddei[7], Flavio Sangiorgi[9], Davide Fiore Bavaro[10,11,12], Vincenzo Scaglione[13], Veronica Vassia[14,15], Marco Merli[16], Michele Bartoletti[10,11], Pierluigi Viale[5,6], Francesco Giuseppe De Rosa[3] and Matteo Bassetti[1,2]; on behalf of SITA GIOVANI (Young Investigators Group of the Società Italiana Terapia Antinfettiva)‡

Variable	Total (*n* = 98)
Age (years), median (Q1–Q3)	68.0 (58.0–76.0)
Male sex, *n* (%)	63 (64.3)
Underlying diseases, *n* (%)	
Cardiovascular disease	33 (33.7)
Solid malignancy	24 (24.5)
Neurological disease	23 (23.5)
Diabetes mellitus	17 (17.3)
Chronic obstructive pulmonary disease	14 (14.3)
Gastrointestinal disease	13 (13.3)
Chronic renal failure	13 (13.3)
Haematological malignancy	13 (13.3)
Charlson comorbidity index (median, Q1–Q3)	4.0 (2.0–6.0)
Immunosuppression, *n* (%)	44 (44.9)
Neutropenia, *n* (%)	10 (10.2)

Possible bénéfice précoce (aminoside)

Pas d'impact en traitement définitif … effectif faible

Vena et al. **JAC 2024**

La synergie: la bithérapie et *Pseudomonas aeru*

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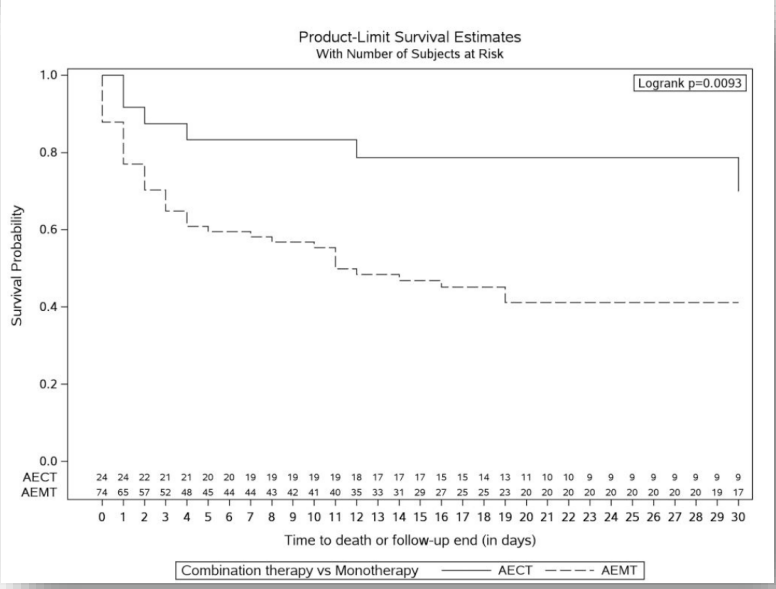


Possible bénéfice précoce (aminoside)

Pas d'impact en traitement définitif … effectif faible

Vena et al. **JAC 2024**

La synergie: la bithérapie et EPC ?

Lancet Infect Dis 2017; 17: 726–34

Impact d'une bithérapie sur EPC?

BSI avec EPC

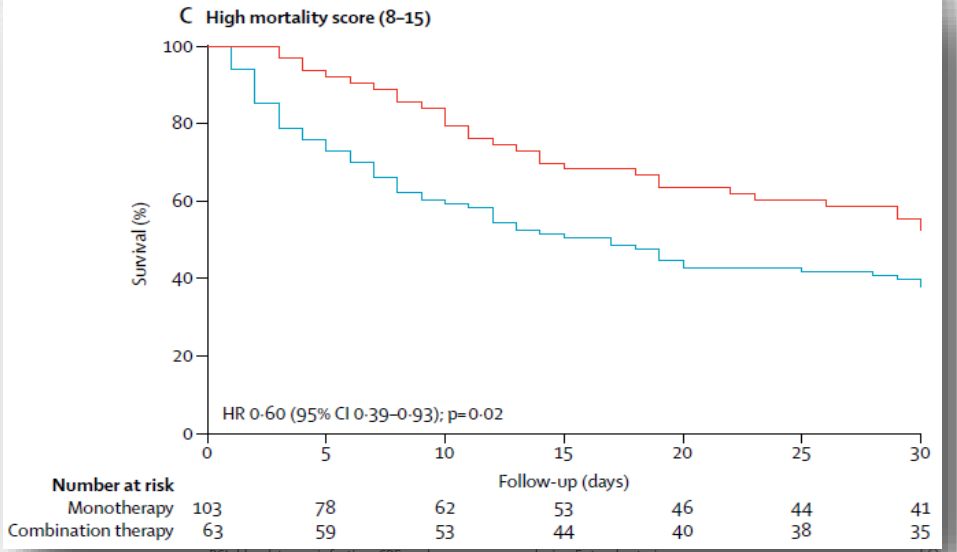
- Rétrospectif, 26 centres, 10 pays,
- Bactériémie à EPC (< 24h)
- Score propension (2004-2013), N = 437
  - 22% inappropriée Vs 78 % Approprié
  - 39% combo Vs 61% mono

Traitement approprié : mortalité **38% Vs 57% (p>.001)**
Mortalité globale COMBO = MONO
Benéfice si risque de mortalité élevée (>25%)

Bithérapie pour les + graves ?
Monothérapie pour les autres ..

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

Belén Gutiérrez-Gutiérrez*, Elena Salamanca*, Marina de Cueto, Po-Ren Hsueh, Pierluigi Viale, José Ramón Paño-Pardo, Mario Venditti, Mario Tumbarello, George Daikos, Rafael Cantón, Yohei Doi, Felipe Francisco Tuon, Ilias Karaiskos, Elena Pérez-Nadales, Mitchell J Schwaber, Özlem Kurt Azap, Maria Souli, Emmanuel Roilides, Spyros Pournaras, Murat Akova, Federico Pérez, Joaquín Bermejo, Antonio Oliver, Manel Almela, Warren Lowman, Benito Almirante, Robert A Bonomo, Yehuda Carmeli, David L Paterson, Alvaro Pascual, Jesús Rodríguez-Baño, and the REIPI/ESGBIS/INCREMENT Investigators†



BSI=bloodstream infection. CPE=carbapenemase-producing Enterobacteriaceae.

La synergie: la bithérapie et EPC ?

Lancet Infect Dis 2017; 17: 726–34

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Mortalité globale COMBO = MONO
Benéfice si risque de mortalité élevée (>25%)

Bithérapie pour les + graves ?
Monothérapie pour les autres ..

	All patients (n=343)	Low-mortality score (0–7; n=177)	High-mortality score (8–15; n=166)
Monotherapy			
Any	85/208 (41%)	21/105 (20%)	64/103 (62%)
Colistin	40/74 (54%)	12/32 (38%)	28/42 (67%)
Meropenem or imipenem	16/43 (37%)	5/25 (20%)	11/18 (61%)
Other active β-lactams	3/19 (16%)	2/17 (12%)	1/2 (50%)
Cefepime	1/13 (8%)	0/11	1/2 (50%)
Aztreonam	1/4 (25%)	1/4 (25%)	0/0
Ceftazadime	1/2	1/2	0/0
Tigecycline	14/37 (38%)	0/15	14/22 (64%)
Aminoglycosides	11/27 (41%)	1/9 (11%)	10/18 (56%)
Others	1/8 (13%)	1/7 (14%)	0/1
Cloramphenicol	1/1 (100%)	1/1 (100%)	0/0
Ciprofloxacin	0/4	0/3	0/1
Fosfomycin	0/1	0/1	0/0
Levofloxacin	0/2	0/2	0/0
Combination therapy*†			
Any	47/135 (35%)	17/72 (24%)	30/63 (48%)
Tigecycline included	29/82 (35%)	10/45 (22%)	19/37 (51%)
Colistin included	28/74 (38%)	11/36 (31%)	17/38 (45%)
Aminoglycosides included	19/56 (34%)	4/27 (15%)	15/29 (52%)
Carbapenem included	14/37 (38%)	4/19 (21%)	10/18 (56%)
Fosfomycin included	3/9 (33%)	1/4 (25%)	2/5 (40%)
Others	6/17 (35%)	3/11 (27%)	3/6 (50%)

Plan

Au cours de la neutropénie fébrile ?

En pratique : au cours de la Neutropénie Fébrile ?

monotherapy vs. combination therapy

Key questions	Answers
1) Does empirical combination therapy with a beta-lactam plus an aminoglycoside (BL+A) decrease mortality in febrile neutropenic patients?	**No evidence** that BL+A combination therapy improves outcomes, but recent literature is limited: - *6 meta-analyses, some – not the same beta-lactam in mono and in combination* - *3 RCT (1 pip-tazo +/- tigecycline-no diff in mortality, 1 small pediatric study-no diff in IRM, 1 different BL-no diff in mortality)* - *9 observational studies* - *different endpoints and timepoints used*
2) In which patients does empirical combination therapy (primarily BL+A) decreases mortality?	1) In patients who eventually develop **GN bacteremia** or **pneumonia** *(4 non-RCT, 2 of them – PsA BSI or pneumonia)* 2) In patients with **BSI and septic shock** *(1 non-RCT significant decrease with combi, 1 non-RCT – no significant decrease (trend, p=0.07, PsA BSI+shock; 1 non-RCT – no difference in patients with acute hypoxemic respiratory failure and sepsis/septic shock, mixed population (HM majority); 1 non-RCT appropriate empirical combination decreases mortality PsA BSI+shock, mixed population)* **Caveats:** 1) In studies performed mainly in countries from **high resistance setting** *(2 studies: 34 centers: 21 HR, 4 LR, 9 others; 1 study: 5/6 hospitals HR, GN BSI; 1 study: Spain)* 2) In studies including **"old" BLs** (carbapenems and non-carbapenem BLs) 3) Appropriate combination therapy vs. monotherapy addressed in 2 studies
3) Does empirical combination therapy targeting resistant Gram-positive bacteria decrease mortality in febrile neutropenic patients?	**No** *(2 metaanalysis, 1 retro, 1 RCT, similar mortality)*

En pratique : au cours de la NF ?

10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

Situations for which combination with an aminoglycoside is indicated as the empirical regimen (in red changes vs ECIL4)

ECIL-4	ECIL-10
1. In seriously-ill patients e.g. septic shock, pneumonia **BIII**	1. In critically-ill patients e.g. sepsis/septic shock, pneumonia **AIIu** *(3 non-RCT; in all: appropriate combination vs appropriate mono)*
2. If resistant non-fermenters (*P. aeruginosa* or *Acinetobacter* spp.) are likely, based upon **BIII:** a. Local epidemiology b. Previous colonization or infection with these pathogens, c. Previous use – during the last month – of carbapenems	2 If Gram-negative bacteria **resistant to the available beta-lactams** are likely **AIIu** *(lower mortality with combination therapy shown in retro studies)*, based upon: a. Local epidemiology b. Known colonization or previous infection with these pathogens c. Previous use of carbapenems within 30 d

Plan

En fonction du germe (neutropénie fébrile) ?

En pratique : au cours de la NF avec germe DRT ?

10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

DTR *Pseudomonas aeruginosa:* combination therapy

B Moderate evidence to support a recommendation for use

➢ **Recommendation:**

Combination of active non-beta lactam antibiotic (amikacin, tobramycin, fosfomycin, FQ – particularly for pneumonia) might be considered in patients who are **critically-ill** (sepsis, septic shock, pneumonia), infections due to PsA with **MIC-value close to resistance breakpoint** OR **uncontrolled infection**, in combination with **ceftolozane-tazobactam BII r, ceftazidime-avibactam (BIII), imipenem-cilastatin–relebactam (BIII), cefiderocol (BIII)**

Treatment of carbapenemase-producing *Enterobacteriaceae*: Combination therapy

➢ **Recommendations:** In carbapenem-resistant infection combination therapy with another non-BL active agent is generally discouraged but might be considered until clinical improvement in:

C Poor evidence to support a recommendation

- **Critically-ill** (sepsis) patients **(C III)**
- In **difficult to treat infections** (such as source control not performed, pneumonia), **OR** due to CRE with **MIC-value close to resistance breakpoint (C III)**

Plan

Concernant la tolérance de la bithérapie (aminoside) ?

La toxicité induite par la bithérapie ?

Tolérance des aminosides ?

Sepsis

- **Prospective, 2011-2015, Pays bas (MARS consortium)**
- **2 Centres : GENTA+ Vs GENTA-**
- **Mortalité, IRA à D14**
  - **N = 648 : 245 (GENTA+) Vs 403 (GENTA-); 5mg/Kg <3j**
  - **Taux de résistance ATB faible**

GENTA **3 jours**

-> Pas d'impact pronostique (mortalité et CHOC)

-> Mais augmentation du risque **d'insf. rénale**

Pas d'aminoside « universel »

Dosage et traitement court ++

Clinical Infectious Diseases

MAJOR ARTICLE

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]

Table 3. Crude Clinical Outcomes by Gentamicin Exposure

Clinical Outcome	Gentamicin Exposed (n = 245)	Non-Gentamicin Exposed (n = 403)
Number of days alive and free of renal failure on day 14		
0	74 (30)	102 (25)
1–13	61 (25)	89 (22)
14	110 (45)	214 (53)
Number of days alive and free of shock on day 14		
0	75 (31)	95 (24)
1–13	123 (50)	222 (55)
14	47 (19)	86 (21)
Day 14 mortality	72 (29)	92 (23)

Data are presented in absolute number (percentage).

Ong et al. **CID 2025**

Paul M et al. **Cochrane 2014 (Sepsis)**

Paul M et al. **Cochrane 2013 (neutropénie)**

Plan

Encore faudrait-il bien utiliser la monothérapie ….

Encore faudrait-il bien utiliser la monothérapie ….

Impact de l'adiministration prolongée (+bolus) ?

NF post allogreffe ou LA

- **RCT, ouverte, 4 hopitaux**
- **NF à haut risque (allogreffés ou LA)**
- **Bolus puis**
  - Extend EI = ½ du temps entre le temps de 2 doses
  - Intermittent II = 30 min
- **Succès clinique**
- **Dosage pour PkPD**

77 extend Vs 73 intermittent

Pas d'impact sur le taux de succès thérapeutique 50 Vs 63 %

Clinical Microbiology and Infection
Volume 31, Issue 2, February 2025, Pages 211-219

Original article

Efficacy of extended infusion of β-lactam antibiotics for the treatment of febrile neutropenia in haematologic patients (BEATLE): a randomized, multicentre, open-label, superiority clinical trial

Julia Laporte-Amargos [1], Francisco Carmona-Torre [2], Maria Huguet [3], Pedro Puerta-Alcalde [4], Raul Rigo-Bonnin [5], Marta Ulldemolins [1], Montserrat Arnan [6 7], Jose Luis del Pozo [2 8], Anna Torrent [3], Carolina Garcia-Vidal [4], Natàlia Pallarès [7 9], Cristian Tebé [9], Carme Muñoz [10], Fe Tubau [11 12], Ariadna Padullés [13 14 15], Ana-Maria Sureda [6], Jordi Carratalà [1 7 14 15], Carlota Gudiol [1 7 14 15 16]

Laprte-Amargos et al. **CMI 2025**

Encore faudrait-il bien utiliser la monothérapie ….

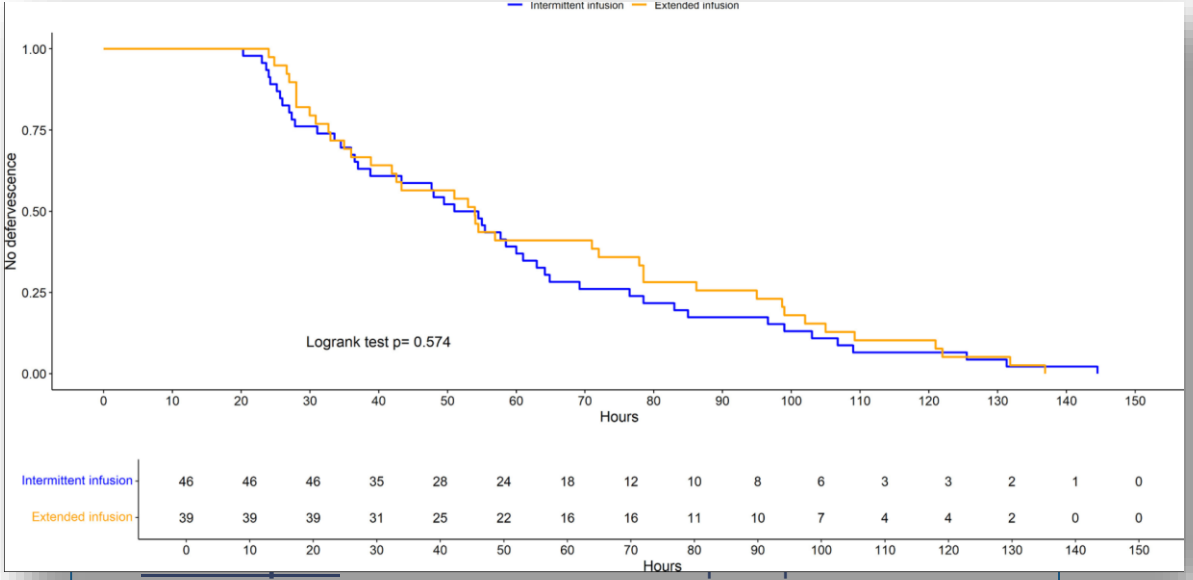
Clinical Microbiology and Infection
Volume 31, Issue 2, February 2025, Pages 211-219

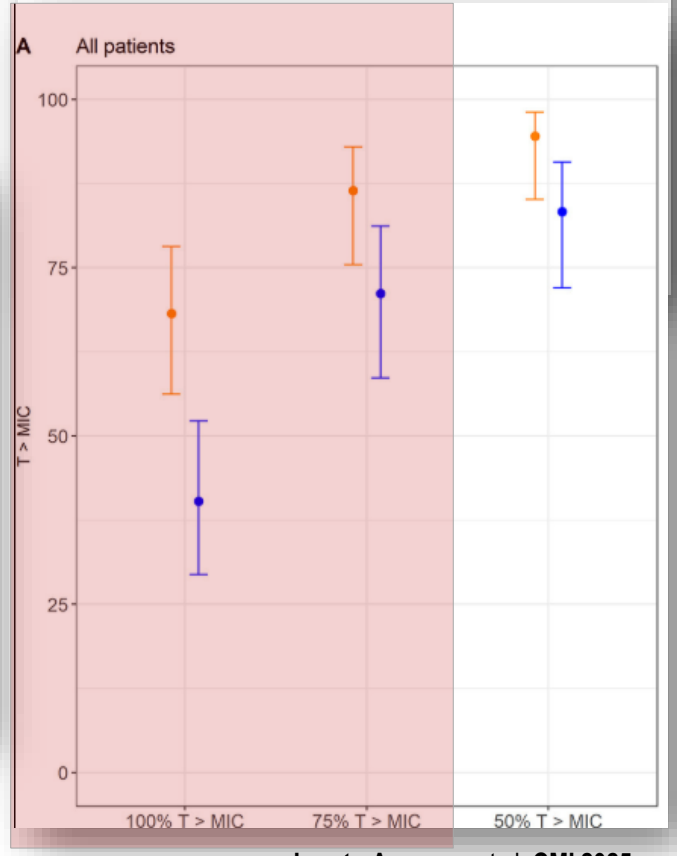
Original article

Efficacy of extended infusion of β-lactam

Impact de l'adiministration prolongée (+bolus) ?

NF post allogreffe ou LA





Laprte-Amargos et al. **CMI 2025**

Chez qui optimiser la monothérapie ?

Clinical Infectious Diseases

MAJOR ARTICLE

Extended vs Bolus Infusion of Broad-Spectrum β-Lactams for Febrile Neutropenia: An Unblinded, Randomized Trial

Ron Ram,[1,2] Yael Halavy,[2] Odelia Amit,[1,2] Yael Paran,[2,3] Eugene Katchman,[2,3] Bruria Yachini,[1] Svetlana Kor,[1] Irit Avivi,[1,2] and Ronen Ben-Ami[2,3]

[1]Bone Marrow Transplantation Unit, Tel Aviv Medical Center, [2]Sackler Faculty of Medicine, Tel Aviv University, and [3]Infectious Diseases Unit, Tel Aviv Medical Center, Israel

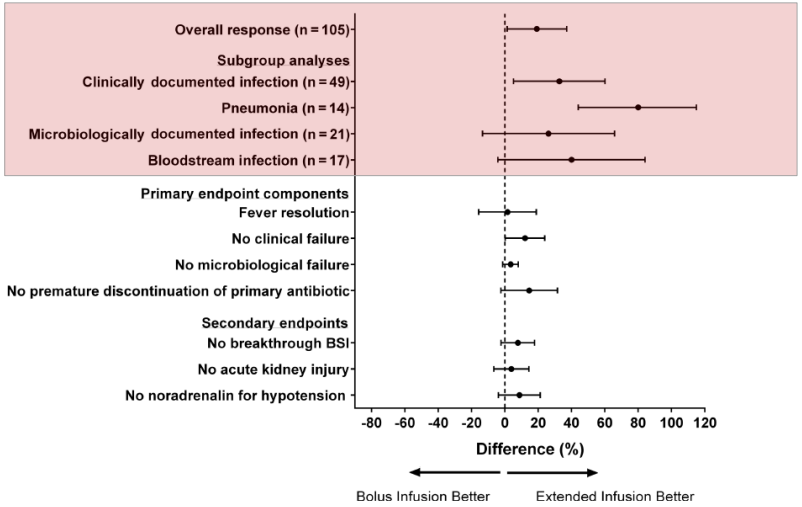
Etude **randomisée**, Israël 2015-2017

Neutropénie à haut risque *(greffe CSH, LA induction/conso)*

Randomisation de la durée de perfusion

30min versus 4 heures
90% TAZO

Critère principale composite J4 *(résolution hyperthermie*, hc, absence de changement ATB)



Ram R et al. **CID 2018**

Take Home Message

- **Epidémiologique** : taux élevé de traitement **empirique inefficace (20-30%) malgré le suivi des recommandations**
- **Diagnostic :** Besoin de nouvelles **stratégies, d'outils** de **stratification du risque**
- **Thérapeutique : faible niveau de preuve chez la patient ID, mais intérêt de la bithérapie pour**
  - **Intérêt d'ELARGIR le spectre** pour **les patients « critiques » (>25% décès)**
  - **Pour la neutropénie avec Bactériémie à BGN (et BMR)**
- **En pratique :**
  - **Aminosides** pour le choc septique et bactériémie
  - **Peu de preuves pour la synergie**
- **Les limites** : Toxicité, microbiote, émergence de résistance, les complications secondaires (flore anaérobie et NF) ?
- **Optimiser l'administration de la monothérapie** :explication à l'avantage à la bithérapie des patients critiques ?

Merci pour votre attention

CHU NANTES
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Nantes Université

En pratique : au cours de la NF ?

10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

Revision of recommendations for empirical antibiotic therapy: de-escalation approach (in red changes vs ECIL4)

	De-escalation approach ECIL 4	De-escalation approach ECIL 10
Indication	1) Complicated presentations BII 2) Known colonization with resistant bacteria BII 3) Previous infection with resistant bacteria BII 4) In centers where resistant pathogens are regularly seen at the onset of febrile neutropenia BII	1) Sepsis/Septic shock 2) Known colonization with resistant bacteria; 3) Previous infection with resistant bacteria; 4) In centers where resistant pathogens are regularly seen at the onset of febrile neutropenia.
Options for initial antibiotic therapy	1) Carbapenem monotherapy BII 2) Combination of anti-pseudomonal beta-lactam + aminoglycoside or qu[illegible]one (with carbapenem as the beta- lactam in seriously ill-patients) BIII 3) C[illegible]in + beta-lactam +/- rifa[illegible]cin (for PsA, AB, SM) BIII 4) Early coverage of resistant-Gram-positives with a glycopeptide or newer agent (If risk factors for Gram-positives present) CIII	1) Carbapenem monotherapy 2) Combination of anti-pseudomonal beta-lactam + aminoglycoside 3) Beta lactam targeting the suspected colonizing pathogen based on susceptibility testing 4) Early coverage of resistant-Gram-positives with a glycopeptide or newer agent if risk factors for Gram-positives present

En pratique : au cours de la NF avec germe DRT ?

10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

Stenotrophomonas maltophilia: ECIL-10 treatment recommendations

AB	Recommendation	Grading
If TMP/SMX feasible	TMP/SMX in combination with other agent: levofloxacin, or tetracycline derivate (HD minocycline or HD tigecycline) or cefiderocol	B II tu
If TMP/SMX resistant or intolerant	Two-drug combination of levofloxacin (if susceptible), tetracycline derivate (HD minocycline or HD tigecycline) or cefiderocol	B II u
	Combination of ceftazidime/avibactam+aztreonam and levofloxacin (if susceptible) or tetracycline (HD minocycline or HD tigecycline)	C III
Step down to monotherapy can be considered after clinical (and microbiological, if applicable) response is obtained and susceptibility to the single agent confirmed		

B Moderate evidence to support a recommendation for use

C Poor evidence to support a recommendation

En pratique : au cours de la NF avec germe DRT ?

10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

Carbapenem-resistant *Acinetobacter baumanii* (CRAB)

ECIL-10 treatment recommendations

We recommend combination therapy for CRAB **A II t**

AB	RCTs	Observational data in HM/HSCT/IC	Proposed grading
Sulbactam-durlobactam* + high-dose imipenem	Not inferior to comparator		
High-dose sulbactam (≥ 9gr/day) + other drug[1, 2] Colistin, Tigé, fosfo, mino	Good efficacy in general populations	No data in HM/HSCT Data in general population	**B II t**
Other combinations[3]	Data on cefiderocol[4], tigecycline [5]	Some data on cefiderocol[4] in HM; Some data on fosfomycin, tigecycline[5] minocycline[6] in general population	**B II t**

A Strongly supports a recommendation for use

B Moderate evidence to support a recommendation for use

En pratique : au cours de la NF ?

10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

Revision of recommendations for empirical antibiotic therapy: Addition of anti-Gram-positive agents

Routine addition of glycopeptides or other antibiotics active against resistant GP bacteria is not recommended (**DIIru**)
(metaanalysis 2014 + update 2017, 1 uncontrolled study, 1 RCT)

Situations for which antibiotics active against resistant Gram-positive bacteria should be used as a part of empirical antibiotic regimen (in red changes vs ECIL4)

ECIL-4	ECIL-10
1. Haemodynamic instability, or other evidence of severe sepsis, septic shock or pneumonia CIII	1. Haemodynamic instability, or other evidence of sepsis, septic shock or pneumonia in patients: a. with known colonization with MRSA (AIIt) *[delay in appropriate therapy in patients with SA BSI and septic shock increases mortality in general population: 1 non-RCT]* b. known colonization with VRE and severe mucositis (CIII) c. without known colonization with MRSA (CIII)
2. Colonisation with MRSA, VRE or penicillin-resistant S. pneumoniae CIII	2. Colonisation with MRSA **BII r t** *[delay in appropriate therapy was associated with increased mortality in meta-analysis of 20 studies, 17 of them included patients with malignancy; 5/9 uncontrolled studies in general population]*
3. Suspicion of serious catheter-related infection: e.g. chills or rigours with infusion through catheter and cellulitis around the catheter exit site CIII	3. Suspicion of serious catheter-related infection: e.g. chills or rigors with infusion through catheter and cellulitis around the catheter exit site **BIII**
4. Skin or soft-tissue infection at any site CIII	4. Skin or soft-tissue infection at any site **BIII**

En pratique : au cours de la NF ?

Situations for which novel anti-Gram-negative beta-lactams are indicated as the empirical regimen (not covered by ECIL-4)

In patients colonized or previously infected with carbapenem-resistant Gram-negative bacteria:

KPC-producers	ceftazidime-avibactam **(AIIu),** meropenem-vaborbactam **(BIItu),** imipenem-cilastatin-relebactam **(CIIt),** cefiderocol **(CIII)**
OXA-48 -producers	ceftazidime avibactam **(AIItu),** cefiderocol **(CIII)**
MBL- producers	ceftazidime-avibactam plus aztreonam **AIItu ,** cefiderocol **(CIII);**

In patients colonized or previously infected with DTR *Pseudomonas aeruginosa*:

High dose ceftolozane tazobactam (**AIItu),** ceftazidime-avibactam **(AIItu),** imipenem/cilastatin/relebactam **(BIIt),** cefiderocol (**CIII**);

*Coverage against invasive streptococcal infections should be considered if antibiotics with limited activity against Gram-positive organisms are used (e.g., ceftazidime with or without avibactam or cefiderocol), especially in patients with severe mucositis (**CIII**).

** screening for resistant bacteria should be performed in high-risk setting

The strength of recommendations is based on: 1) on the experience with specific compounds (such as ceftazidime, carbapenems, cefiderocol) in FN in general; 2) Experience in the targeted treatment of patients known to have bacteremia with these resistant bacteria; 3) Experience as empirical therapy in patients colonized with resistant bacteria

Optimisation de la monothérapie ?

Original Investigation | Caring for the Critically Ill Patient

June 12, 2024

Prolonged vs Intermittent Infusions of β-Lactam Antibiotics in Adults With Sepsis or Septic Shock

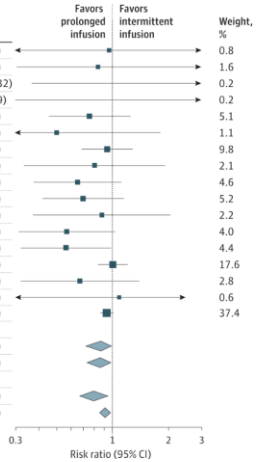
A Systematic Review and Meta-Analysis

Mohd H. Abdul-Aziz, BPharm, PhD[1]; Naomi E. Hammond, RN, PhD[2,3]; Stephen J. Brett, MD[4]; et al

Author Affiliations | Article Information

JAMA. 2024;332(8):638-648. doi:10.1001/jama.2024.9803

Study	Dead (prolonged)	Alive (prolonged)	Dead (intermittent)	Alive (intermittent)	Absolute difference (95% CI)	Risk ratio (95% CI)	Weight, %
Georges et al,[33] 2005	3	21	3	20	-0.01 (-0.20 to 0.19)	0.96 (0.21 to 4.27)	0.8
Rafati et al,[34] 2006	5	15	6	14	-0.05 (-0.33 to 0.23)	0.83 (0.30 to 2.29)	1.6
Roberts et al,[35] 2007	3	26	0	28	0.10 (-0.02 to 0.22)	6.77 (0.37 to 125.32)	0.2
Roberts et al,[36] 2009	2	3	0	5	0.33 (-0.12 to 0.79)	5.00 (0.30 to 83.69)	0.2
Chytra et al,[38] 2012	21	99	28	92	-0.06 (-0.16 to 0.04)	0.75 (0.45 to 1.24)	5.1
Dulhunty et al,[39] 2013	3	27	6	24	-0.10 (-0.28 to 0.08)	0.50 (0.14 to 1.82)	1.1
Dulhunty et al,[40] 2015	54	156	60	158	-0.02 (-0.10 to 0.07)	0.93 (0.68 to 1.28)	9.8
Jamal et al,[41] 2015	4	4	5	3	-0.12 (-0.61 to 0.36)	0.80 (0.33 to 1.92)	2.1
Jamal et al,[42] 2015	5	3	8	0	-0.33 (-0.69 to 0.02)	0.65 (0.38 to 1.12)	4.6
Abdul-Aziz et al,[43] 2016	18	52	26	44	-0.11 (-0.27 to 0.04)	0.69 (0.42 to 1.14)	5.2
Zhao et al,[44] 2017	7	18	8	17	-0.04 (-0.29 to 0.21)	0.88 (0.37 to 2.05)	2.2
Khan and Omar,[22] 2023	12	40	20	29	-0.18 (-0.36 to 0.00)	0.57 (0.31 to 1.03)	4.0
Mirjalili et al,[45] 2023	14	54	25	43	-0.16 (-0.31 to -0.01)	0.56 (0.32 to 0.98)	4.4
Monti et al,[14] 2023	127	176	127	177	0.00 (-0.08 to 0.08)	1.00 (0.83 to 1.21)	17.6
Saad et al,[46] 2024	8	22	12	18	-0.13 (-0.37 to 0.10)	0.67 (0.32 to 1.39)	2.8
Álvarez-Moreno et al,[47] 2024	2	10	2	11	0.01 (-0.28 to 0.30)	1.08 (0.18 to 6.53)	0.6
Dulhunty et al,[15] 2024	864	2610	939	2568	-0.02 (-0.04 to 0.00)	0.93 (0.86 to 1.01)	37.4
Bayesian							
Vague priors[a]					-0.03 (-0.08 to 0.00)	0.86 (0.72 to 0.98)	
Semi-informative priors[a]					-0.04 (-0.10 to 0.01)	0.86 (0.73 to 0.98)	
Frequentist							
Hartung-Knapp-Sidik-Jonkman					-0.05 (-0.10 to 0.00)	0.80 (0.67 to 0.94)	
DerSimonian-Laird					-0.03 (-0.07 to 0.00)	0.91 (0.85 to 0.97)	



Comment optimisée l'administration des Aminosides ? (1)

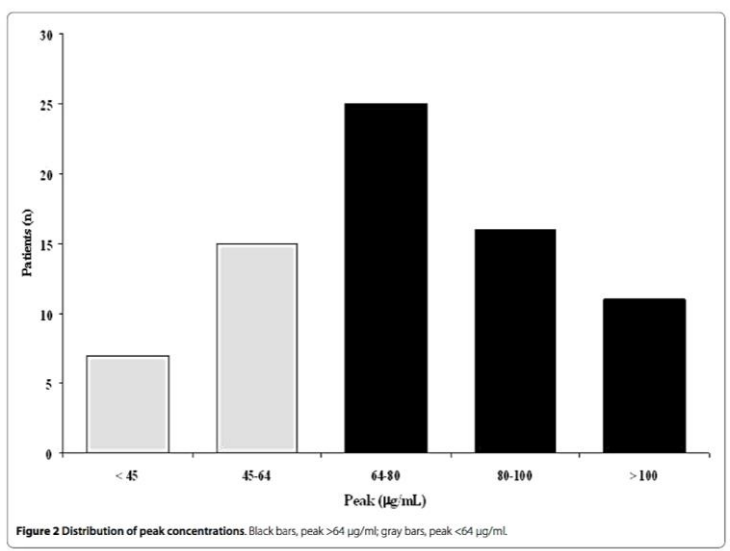
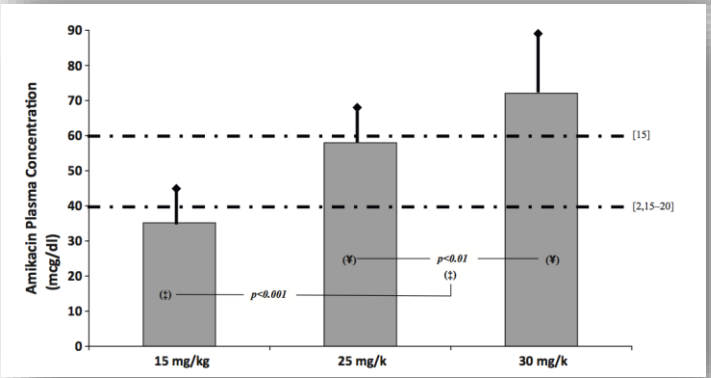


Figure 2 Distribution of peak concentrations. Black bars, peak >64 µg/ml; gray bars, peak <64 µg/mL



En réanimation sepsis ou choc septique :

25 mg/Kg
70% des patients PIC > 8X CMI

Sur simulation :

15 mg/Kg = 9%
30 mg/Kg = 80% sous 64 µg/ml

Taccone *et al. Critical Care* 2010, **14**:R53

Toxicité non augmentée (galvez 2011)

120 patients sepsis à 15/25/30 mg/kg
30mg/kg = 76% dans objectif

= Clearance identique J 28

Higher than recommended amikacin loading doses achieve pharmacokinetic targets without associated toxicity

Ricardo Gálvez[a,*], Cecilia Luengo[a], Rodrigo Cornejo[a], Johann Kosche[b], Carlos Romero[a], Eduardo Tobar[a], Victor Illanes[a], Osvaldo Llanos[a], José Castro[a]

[a] Critical Care Unit, Internal Medicine Department, Hospital Clínico Universidad de Chile, 999 Avenida Santos Dumont, 8380456 Independencia, Santiago de Chile, Chile
[b] School of Pharmacy, Faculty of Medicine, Universidad de Chile, Chile

Comment optimisée l'administration des ATB

Antibacterials	Activity against MDR pathogens	Class, PD index of choice Suggested dosage in critically–ill patients	Status
Amikacin	Possibly active against MDR-GNB, although increased resistance to classical aminoglycosides has been reported [79, 143]	Aminoglycosides, AUC/MIC 25-30 mg/kg q24h (modified according to TDM)	Approved
Aztreonam	Active against MBL producers not expressing mechanisms of aztreonam resistance (e.g., other beta-lactamases, AmpC hyperexpression, efflux pumps)	Monobactams, T > MIC 1–2 g q8h	Approved
Aztreonam/ Avibactam	ESLBL-PE CPE (all classes of carbapenemases, including MBL)	Monobactams plus BLI, T > MIC 6500 mg aztreonam/2167 mg avibactam q24h on day 1 followed by 6000 mg aztreonam/2000 mg avibactam q24h	In clinical development; potential indications according to phase-3 RCT are cIAI, HAP/VAP (NCT03329092) and serious infections due to MBL-producing bacteria (NCT03580044)
Cefepime	Active against AmpC hyperproducer enterobacterales	Cephalosporins, T > MIC 2 g q8h or continuous infusion	Approved
Cefiderocol	ESBL-PE CPE (all classes of carbapenemases, including MBL) MDR-PA CRAB	Siderophore cephalosporins, T > MIC 2 g q8h	FDA Approved for cUTI caused by susceptible Gram-negative microorganisms, who have limited or no alternative treatment options according to phase-3 RCT are infections due to carbapenem-resistant organisms in different sites (NCT02714595). Pivotal study on HAP/VAP finished (NCT03032380)
Ceftobiprole	MRSA VISA hVISA VRSA	Cephalosporins, T > MIC 500 mg q8 h	Approved for CAP and HAP (excluding VAP) *In vitro* and/or limited clinical data reporting a possible use as salvage therapy in combination with vancomycin or daptomycin for MRSA bacteremia

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Ceftolozane/ Tazobactam	ESBL-PE MDR-PA	Cephalosporins plus BLI, T > MIC 1.5 g q8h (3 g q8h for pneumonia)	Approved for cIAI (in combination with metronidazole) and cUTI Approved by FDA for VAP/HAP, with the CHMP of EMA also recently adopting a positive opinion recommending a change to the terms of the marketing authorization, including also VAP/HAP among approved indications
Ceftaroline	MRSA VISA hVISA VRSA	Cephalosporins, T > MIC 600 mg q12 h	Approved for ABSSSI and CAP In vitro and/or limited clinical data reporting a possible use as salvage therapy in combination with vancomycin or daptomycin for MRSA bacteremia
Ceftazidime		Cephalosporins, T > MIC 6 g q24h continuous infusion	Approved
Ceftazidime/ Avibactam	ESBL-PE CPE (class A and class D carbapenemases) MDR-PA	Cephalosporins plus BLI, T > MIC 2.5 g q8h	Approved for cIAI (in combination with metronidazole), cUTI, HABP/VABP, and infections due to aerobic Gram-negative organisms in adult patients with limited treatment options
Ceftriaxone		Cephalosporins, T > MIC 1–2 g q24h	Approved
Colistin	ESBL-PE CPE (all classes of carbapenemases, including MBL) MDR-PA CRAB	Polymyxins, AUC/MIC 9 MU loading dose, 4.5 MU every 8–12 h (modified according to TDM where available; higher dosages to be possibly considered in patients with ARC [58])	Approved Recommended for serious infections due to susceptible bacteria when other treatment options are limited
Daptomycin	MRSA VRE	Lipopeptides, AUC/MIC 8–10 mg/kg q24h	Approved for cSSTI and right-sided endocarditis

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Antibacterials	Activity against MDR pathogens	Class, PD index of choice Suggested dosage in critically–ill patients	Status
Eravacycline	MRSA VRE ESBL-PE CPE CRAB	Fluocyclines, AUC/MIC 1 mg/kg q12h	Approved for cIAI To be possibly used for BSI due to MDR organisms in absence of dependable alternative options, in combination with other agents (expert opinion)
Ertapenem	ESBL-PE	Carbapenems, T > MIC 1 g q12 h	Approved for IAI, CAP, acute gynecological infections, and diabetic food infections
Fosfomycin	ESBL-PE CPE (all classes of carbapenemases, including MBL) MDR-PA MRSA VRE	PEP analogues, unclear [144] 4–6 g q6h continuous infusion	Approved For BSI used in combination with other agents for the treatment of MDR infections with limited treatment options (also for CRAB), although in lack of high-level evidence
Gentamicin	Possibly active against MDR-GNB, although increased resistance to classical aminoglycosides has been reported [79, 143]	Aminoglycosides, AUC/MIC 5–7 mg/kg q24h (modified according to TDM)	Approved
Imipenem/ Cilastatin	ESBL-PE	Carbapenems, T > MIC 0.5–1 g q6h	Approved
Imipenem/ Relebactam	ESBL-PE CPE (class A carbapenemases) Some MDR-PA	Carbapenems plus BLI, T > MIC 500 mg/250–125 mg q6h	FDA approved for the treatment of cUTI and cIAI. The phase-3 RCT are HAP/VAP (NCT02493764) is ongoing.
Meropenem	ESBL-PE	Carbapenems, T > MIC 1–2 g q8h or extended infusion (over 4 h)	Approved
Meropenem/ Vaborbactam	ESBL-PE CPE (class A carbapenemases)	Carbapenems plus BLI, T > MIC 4 g q8h	Approved for cUTI, cIAI, HAP, VAP, and infections due to aerobic Gram-negative organisms in patients with limited treatment options

Comment optimisée l'administration des ATB

Antibacterials	Activity against MDR pathogens	Class, PD index of choice Suggested dosage in critically–ill patients	Status
Eravacycline	MRSA VRE ESBL-PE CPE CRAB	Fluocyclines, AUC/MIC 1 mg/kg q12h	Approved for cIAI To be possibly used for BSI due to MDR organisms in absence of dependable alternative options, in combination with other agents (expert opinion)
Ertapenem	ESBL-PE	Carbapenems, T > MIC 1 g q12 h	Approved for IAI, CAP, acute gynecological infections, and diabetic food infections
Fosfomycin	ESBL-PE CPE (all classes of carbapenemases, including MBL) MDR-PA MRSA VRE	PEP analogues, unclear [144] 4–6 g q6h continuous infusion	Approved For BSI used in combination with other agents for the treatment of MDR infections with limited treatment options (also for CRAB), although in lack of high-level evidence
Gentamicin	Possibly active against MDR-GNB, although increased resistance to classical aminoglycosides has been reported [79, 143]	Aminoglycosides, AUC/MIC 5–7 mg/kg q24h (modified according to TDM)	Approved
Imipenem/ Cilastatin	ESBL-PE	Carbapenems, T > MIC 0.5–1 g q6h	Approved
Imipenem/ Relebactam	ESBL-PE CPE (class A carbapenemases) Some MDR-PA	Carbapenems plus BLI, T > MIC 500 mg/250–125 mg q6h	FDA approved for the treatment of cUTI and cIAI. The phase-3 RCT are HAP/VAP (NCT02493764) is ongoing.
Meropenem	ESBL-PE	Carbapenems, T > MIC 1–2 g q8h or extended infusion (over 4 h)	Approved
Meropenem/ Vaborbactam	ESBL-PE CPE (class A carbapenemases)	Carbapenems plus BLI, T > MIC 4 g q8h	Approved for cUTI, cIAI, HAP, VAP, and infections due to aerobic Gram-negative organisms in patients with limited treatment options

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Piperacillin/ Tazobactam	Possibly active against ESBL-PE, although the results of the MERINO trial discourage the use of piperacillin/tazobactam for severe ESBL-PE infections [145]	Penicillins plus BLI, T > MIC 4.5 g q6h continuous infusion	Approved
Plazomicin	ESBL-PE CPE (all classes of carbapenemases, including MBL, although resistance has been described in NDM-1 producing strains, owing to co-expression of plazomicin-inactivating methyltransferases [146]) MDR-PA CRAB	Aminoglycosides, AUC/MIC 15 mg/kg q24h	An application has been recently submitted to EMA for approval of plazomicin for cUTI and other severe infections (plazomicin is approved by FDA for cUTI)
Tigecycline	MRSA VRE ESBL-PE CPE (all classes of carbapenemases, including MBL) CRAB	Glycylcyclines, AUC/MIC 100–200 mg loading those, then 50–100 mg q12h	Approved for cSSTI (excluding diabetic foot infections) and cIAI For BSI used only in combination with other agents for infections due to MDR organisms in presence of limited alternative therapeutic options
Vancomycin	MRSA	Glycopeptides, AUC/MIC 15–30 mg/kg loading dose, 30–60 mg/kg q12h, or continuous infusion (modified according to TDM)	Approved