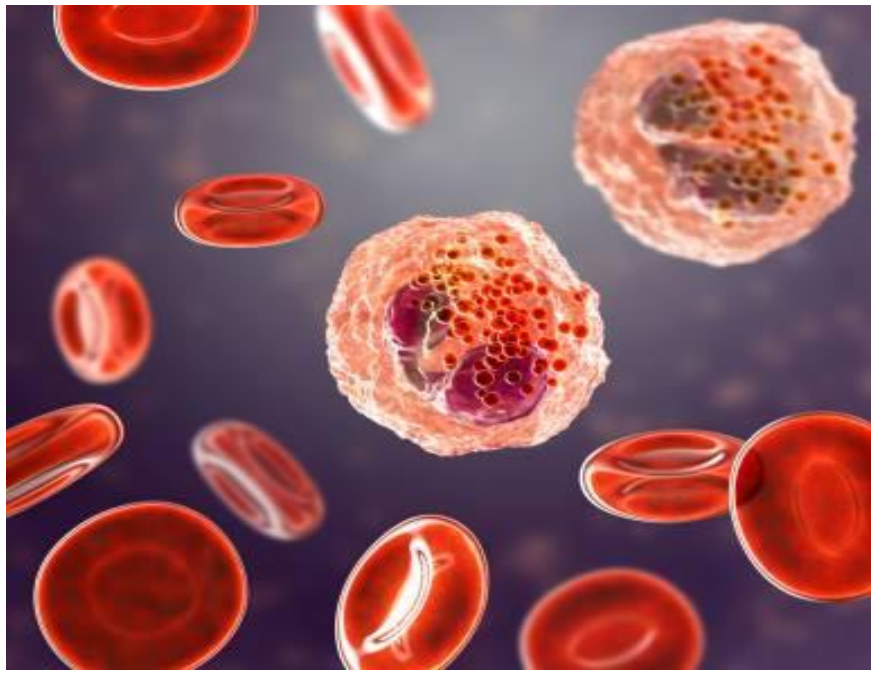
BACTÉRIÉMIES ET CHOC SEPTIQUE

Une biantibiothérapie pour qui ?



Pr Benjamin GABORIT

Service de Maladies Infectieuses CHU Nantes

CRT2I eq.6, *Impact of acute inflammation on host pathogen interactions and Lung homeostasis.*

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Objectifs

- Stratégie d'antibiothérapie au cours de la bactériémie
- Évaluer le rapport bénéfice/risque à la **bithérapie** au cours du sepsis, choc septique, chez l'immunodéprimé
- Optimiser les stratégies d'administration

1 Allez sur wooclap.com

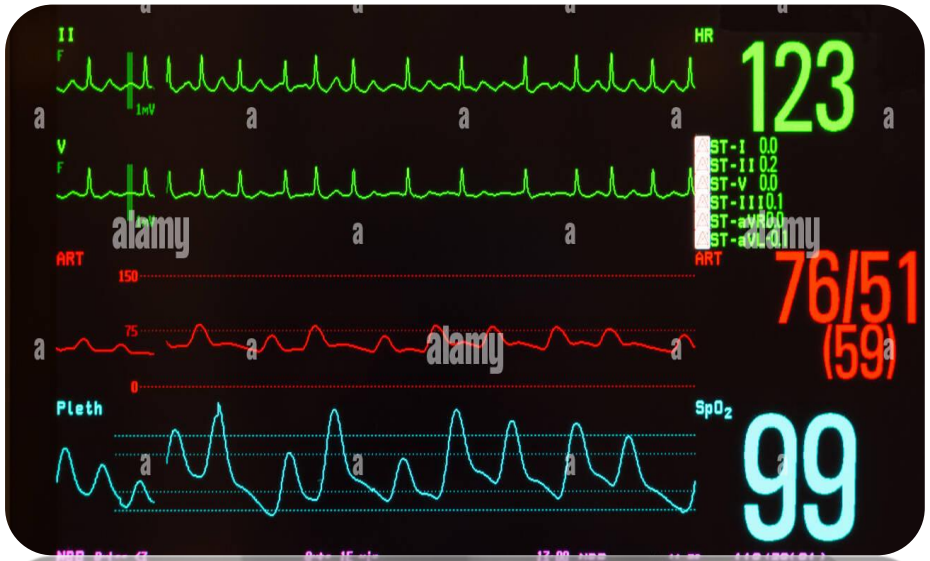
2 Entrez le code d'événement dans le bandeau supérieur

Code d'événement
UYCGCK

Activer les réponses par SMS

https://app.wooclap.com/UYCGCK?from=instruction-slide

Cas clinique



Mme M., 40 ans, sans antécédents médicaux notables, consulte aux urgences pour **fièvre** évoluant depuis **4 jours**, associée à des **douleurs abdominales diffuses**.

Vue par son médecin traitant deux jours plus tôt, il lui prescrit **un bilan biologique**, sans traitement instauré.
Elle **consulte au SAU** car la fièvre (T° max 39,5°C) persiste et ses douleurs se majorent.

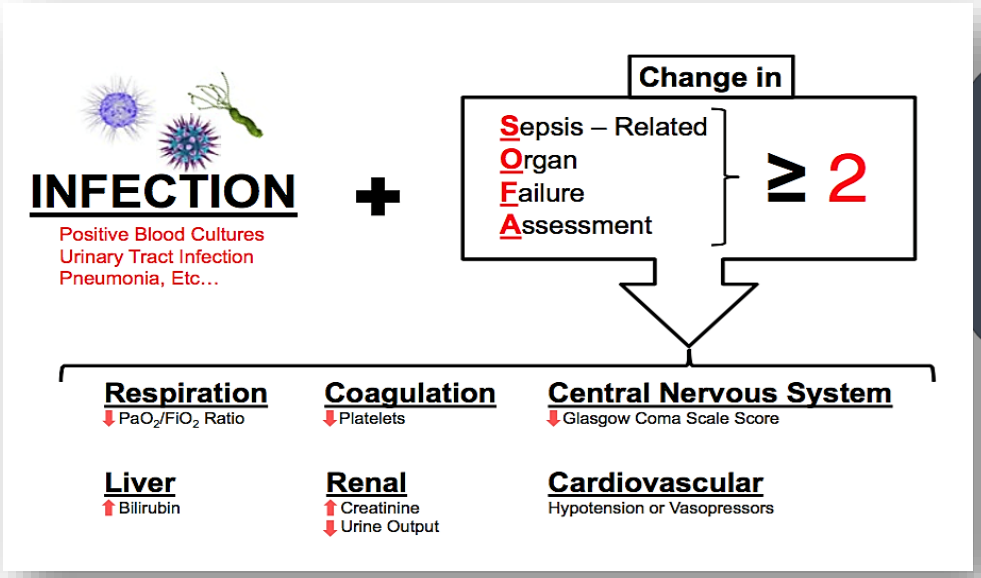
À l'examen au SAU :
- T° **39°C**, FC **123 bpm**, PA **76/51** mmHg.
- Sensibilité **abdominale**, pas de défense abdominale.
- Pas de syndrome méningé ni de foyer pulmonaire.

Bilan biologique en ville :

- Leucocytes 15,8 G/L, PNN 85 %; **CRP 250 mg/L**; **Créatinine 120 µmol/L**; Iono : Na 136, K 4,0 mmol/L; BH et TP normaux.

1- Quelles informations complémentaires sont nécessaires à ce stade pour adapter votre stratégie antibiothérapie probabiliste ?

Cas clinique



1- Quelles informations complémentaires sont nécessaires à ce stade pour adapter votre stratégie antibiothérapie probabiliste ?

Cas clinique

- Concernant **le diagnostic : suspicion d'infection bactérienne (BU…)**
- Signes de sepsis/choc (lactates..)
- Contrôle de la source (Uro-TDM, PNA obstructive ect..)

- Concernant **le risque de BMR (et TDR)**
  - Infection / colonisation **BMR** (12 mois)
  - **Ecologie** locale
  - Contexte **d'infection nosocomiale**
  - Utilisation **d'ATB à large spectre** (<90j)
  - **Voyage** dans une zone à risque MDR (<90j)

La suite,
Arguments MDR = NON
Signes de sepsis/CHOC ?

Dans la vraie vie diagnostic parfois difficile ..

Cas clinique

2- Au SAU lorsqu'un sepsis est suspecté en population générale, a combien (en %) estimez vous la part d'erreur c'est-à-dire sans infection bactérienne (avec ATB inutile) ?

Quel état des lieux au SAU ?

JOURNAL ARTICLE

Frequency of Antibiotic Overtreatment and Associated Harms in Patients Presenting With Suspected Sepsis to the Emergency Department: A Retrospective Cohort Study

Get access >

Claire N Shappell ✉, Tingting Yu, Michael Klompas, Anna A Agan, Laura DelloStritto, Brett A Faine, Michael R Filbin, Nicholas M Mohr, Steven T Park, Kamryn Plechot ... Show more

Clinical Infectious Diseases, Volume 80, Issue 6, 15 June 2025, Pages 1197–1207, https://doi-org.proxy.insermbiblio.inist.fr/10.1093/cid/ciaf118

Published: 15 April 2025 **Article history** ▾

Conclusions

Among 600 patients treated with broad-spectrum antibiotics for possible sepsis, 1 in 3 most likely did not have a bacterial infection, 4 in 5 of those with bacterial infections were treated with regimens that were broader than necessary in retrospect, and 1 in 6 developed antibiotic-associated complications.

7 SAU (USA) avec suspicion de sepsis

46 245 patients « sepsis », 26 550 (57%) ATB large spectre (PYO/SARM)

Analyse de 600 patients (aléatoire): 68% Vs 32%

- **48%** infection bactérienne **certaine**
- **20 % probable**
- **18% peu probable**
- **14% aucune infection bactérienne a posteriori**
- **20% virale/fungique**

Parmi les patients avec infection **certaine/probable (62% doc+)** :

79% ont reçu **une antibiothérapie trop larges (C3G sufisante)**
8% une atb trop **« étroite »**
17% de **complications liées** aux ATB dans les 90 jours
8 % nouvelle infection par des bactéries résistantes

Un diagnostic difficile (étiologies non bactériennes)

Réflexion guidée par la gravité et le risque de résistance

Cas clinique

-> **BU+ et l'Hémoculture** en ville est positive à **bacilles à Gram négatif**.

Le diagnostic d'uro-sepsis est confirmé, vous débutez un remplissage vasculaire, quelle stratégie thérapeutique antibiotique immédiate vous parait indiquée ?

1- Vous réalisez **de nouveaux prélèvements infectiologique** et **temporiser** l'initiation des antibiotiques

2- Vous débutez un traitement par **fluoroquinolone** (Ciprofloxacine) par voie orale

3- Vous débuter un traitement par **C3G (Ceftriaxone)**

4- Vous débutez un traitement par **C3G (Ceftriaxone) associé à un aminoside (Amikacine)**

5- Vous débutez un traitement par **carbapénème (Imipenem / Cilastatin) associé à un aminoside (Amikacine)**

Cas clinique

-> l'**Hémoculture** en ville est positive à **bacilles à Gram négatif**.

3- Le diagnostic d'uro-sepsis est confirmé, vous débutez un remplissage vasculaire, quelle stratégie thérapeutique antibiotique immédiate vous parait indiquée ?

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5- Vous débutez un traitement par **carbapénème (Tienam) associé à un aminoside (Amikacine)**

Quels objectifs pour le sepsis ?

Les recommandations ?

	Shock is present	Shock is absent
Sepsis is definite or probable	Administer antimicrobials ***immediately***, ideally within 1 hour of recognition.	Administer antimicrob ***immediately***, ideally 1 hour of recognition.
Sepsis is possible	Administer antimicrobials ***immediately***, ideally within 1 hour of recognition.	Rapid assessment* of infectious vs. noninfectious causes of acute illness.
		Administer antimicrobials ***within 3 hours*** if concern for infection persists.

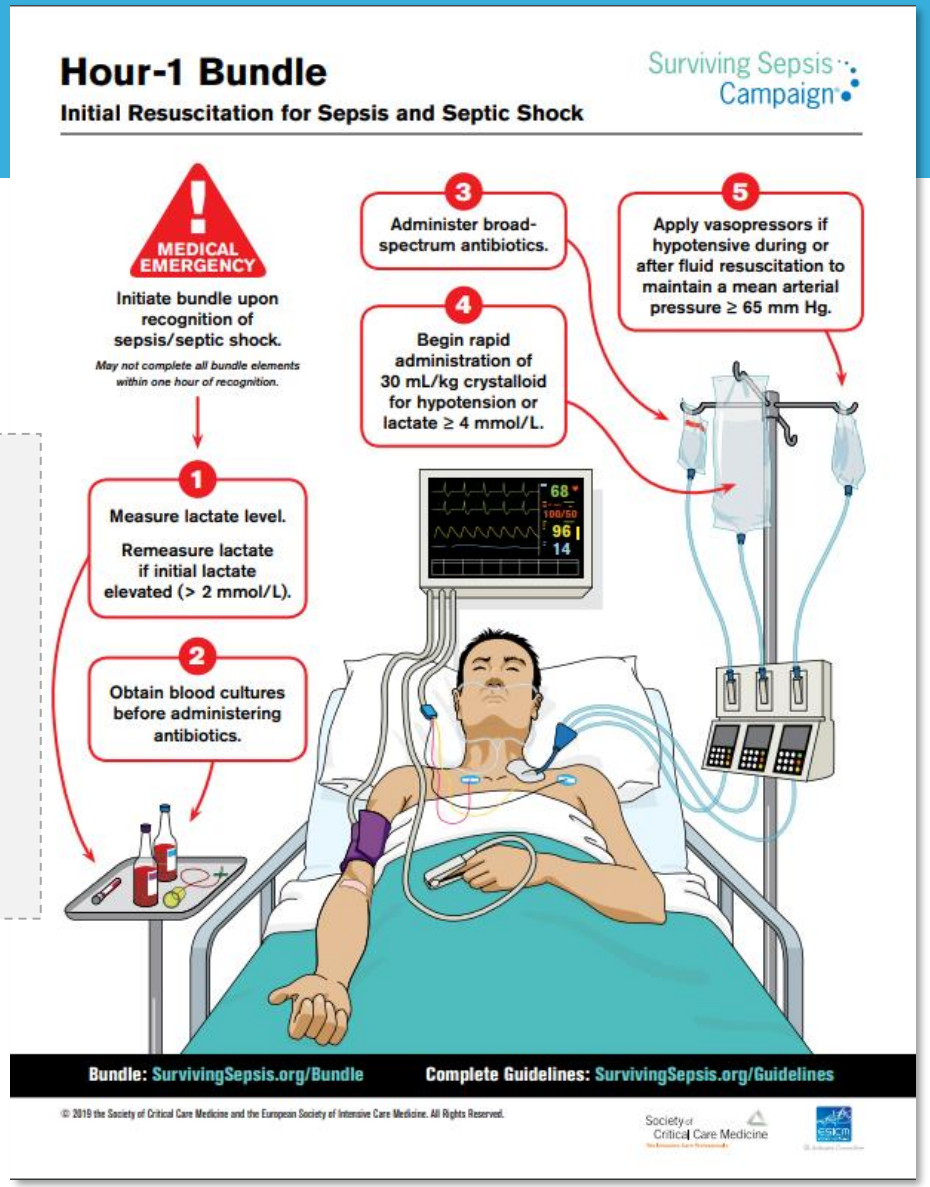
**Rapid assessment includes history and clinical examination, tests for both infectious and noninfectious causes of acute illness, and immediate treatment of acute conditions that can mimic sepsis. Whenever possible, this should be completed within 3 hours of presentation so that a decision can be made as to the likelihood of an infectious cause of the patient's presentation and timely antimicrobial therapy provided if the likelihood is thought to be high.*

- **La place de bi-antibiothérapie**

1- <u>Pourquoi ?</u>

2- <u>Pour qui ?</u>

3- <u>Comment ?</u>



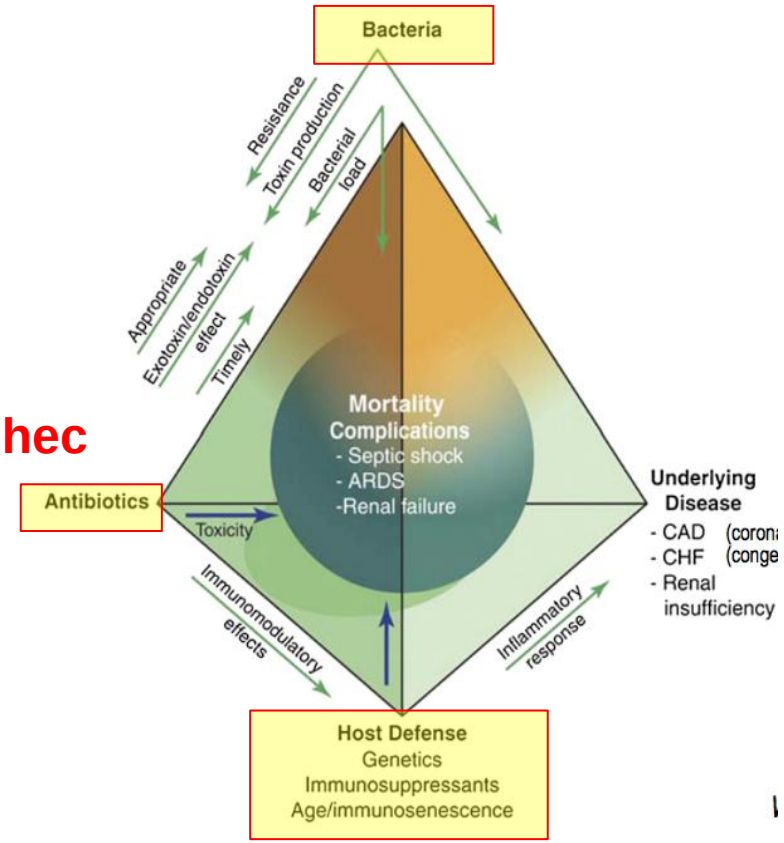
Surviving Sepsis Campaign

Society of Critical Care Medicine

ESICM

Si le sepsis est confirmé, comment faire mieux ?

↗ **Résistance au ATB**



↗ **échec**

Immunodépression/ infections liées aux soins

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

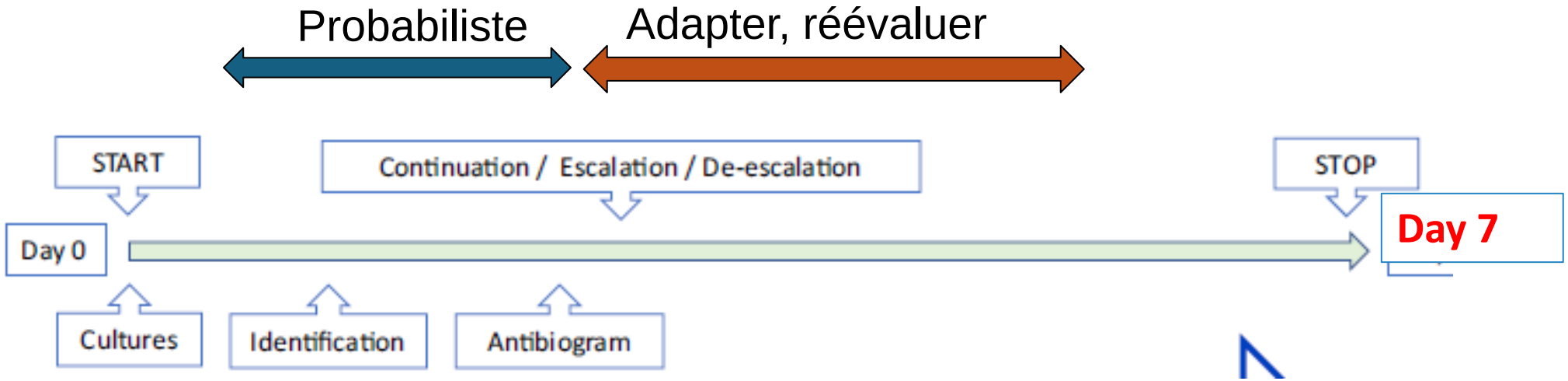
impacts sur le microbiote dès J3

Sous-traitement

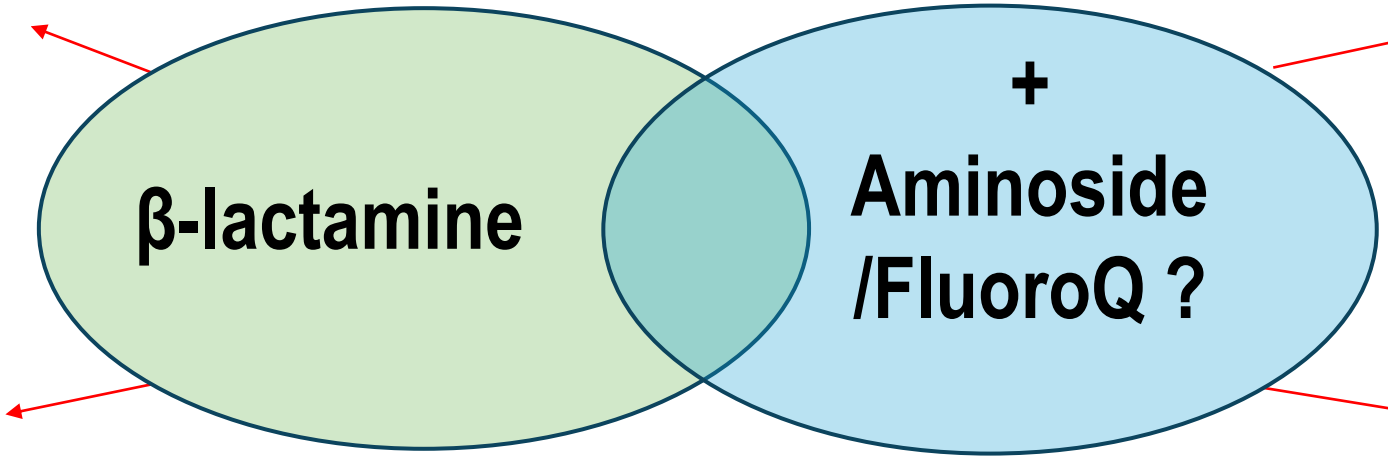
~ 10-20 % nécessitant une adaptation

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** ?



Le **spectre** ?



Effet **synergique** ?

La **toxicité** ?

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

Jan J. De Waele ICM 2020

4- Quel est le taux de traitement inapproprié (inefficace) au SAU en cas de choc sepsis confirmé (et quel impact) ?

Cas clinique

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

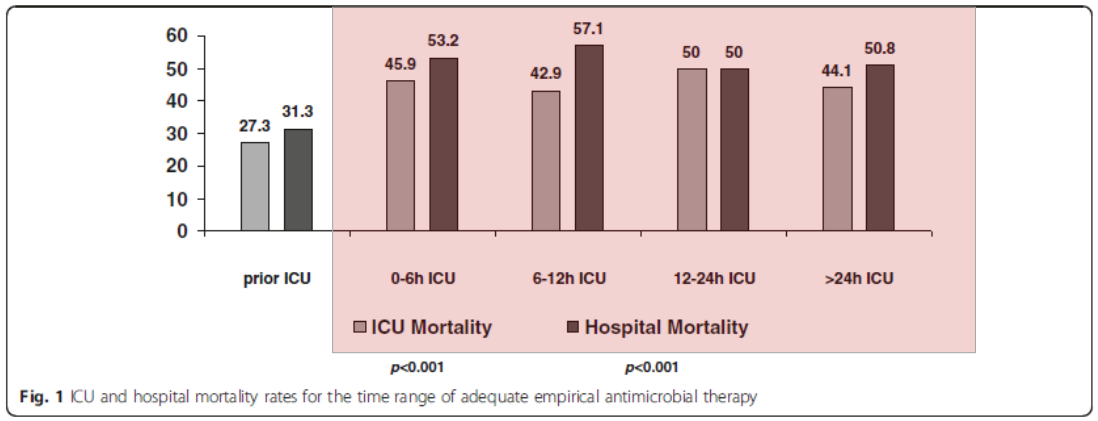


Fig. 1 ICU and hospital mortality rates for the time range of adequate empirical antimicrobial therapy

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

- **30% de « sous traitement » et effet protecteur d'un traitement adapté précoce (>6h)**

Garnacho et al. 2015 Crit Care

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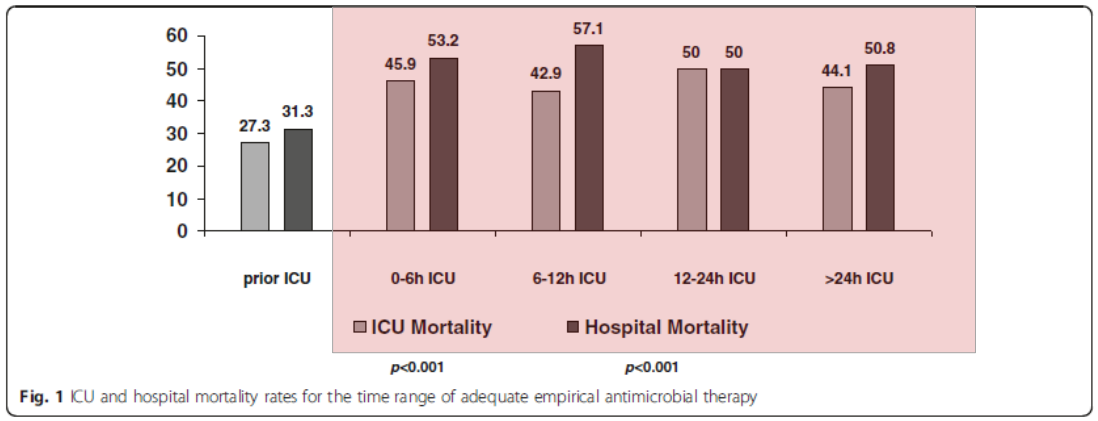

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Garnacho et al. 2015 Crit Care

Le bénéfice est-il aussi net pour tous les patients au SAU ?

J Antimicrob Chemother 2013; **68**: 947–953
doi:10.1093/jac/dks475 Advance Access publication 21 December 2012

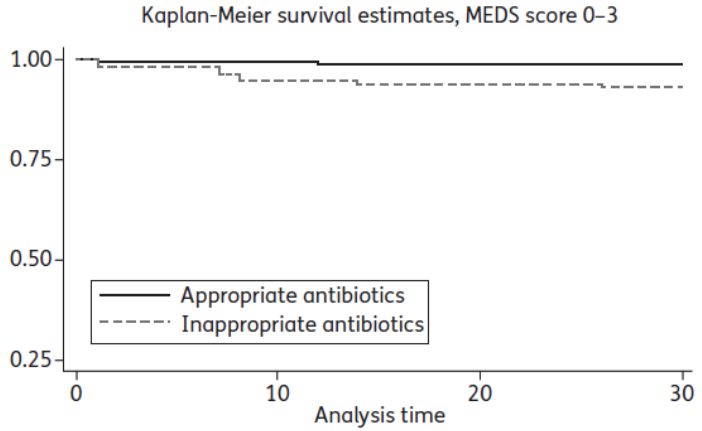
Journal of Antimicrobial Chemotherapy

Outcome of inadequate empirical antibiotic therapy in emergency department patients with community-onset bloodstream infections

Hang-Cheng Chen[1], Wen-Ling Lin[2], Chi-Chun Lin[1], Wen-Han Hsieh[3], Cheng-Hsien Hsieh[1], Meng-Huan Wu[2], Jiunn-Yih Wu[1†] and Chien-Chang Lee[4,5*†]

Etude prospective observationnelle
Taiwan, 2008-2009
937 bactériémies au SAU ++
27% d'ATB probabiliste inadéquate (24h)

	Adequate antibiotics (n=682)	Inadequate antibiotics (n=255)	P^a
Outcome			
30 day mortality, n (%)	62 (9.1)	97 (38.0)	<0.001
length of hospital stay (days), median (IQR)	14 (6–28)	13 (7–23)	0.404



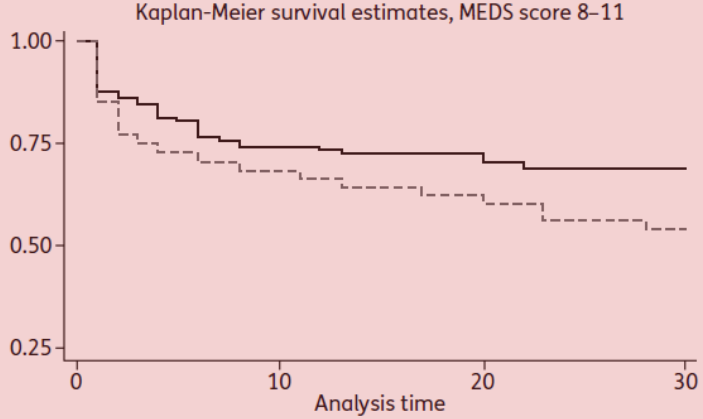


Figure 1. Effect of inappropriate empirical antibiotics on 30 day mortality

Bénéfice de survie à une ATB probabiliste adapté aux SAU pour <u>les patients sévères</u>

Cas clinique

5- La **bithérapie** présente-elle un avantage sur un **germe sensible** (**synergie ++**) chez le malade en choc septique ?

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**

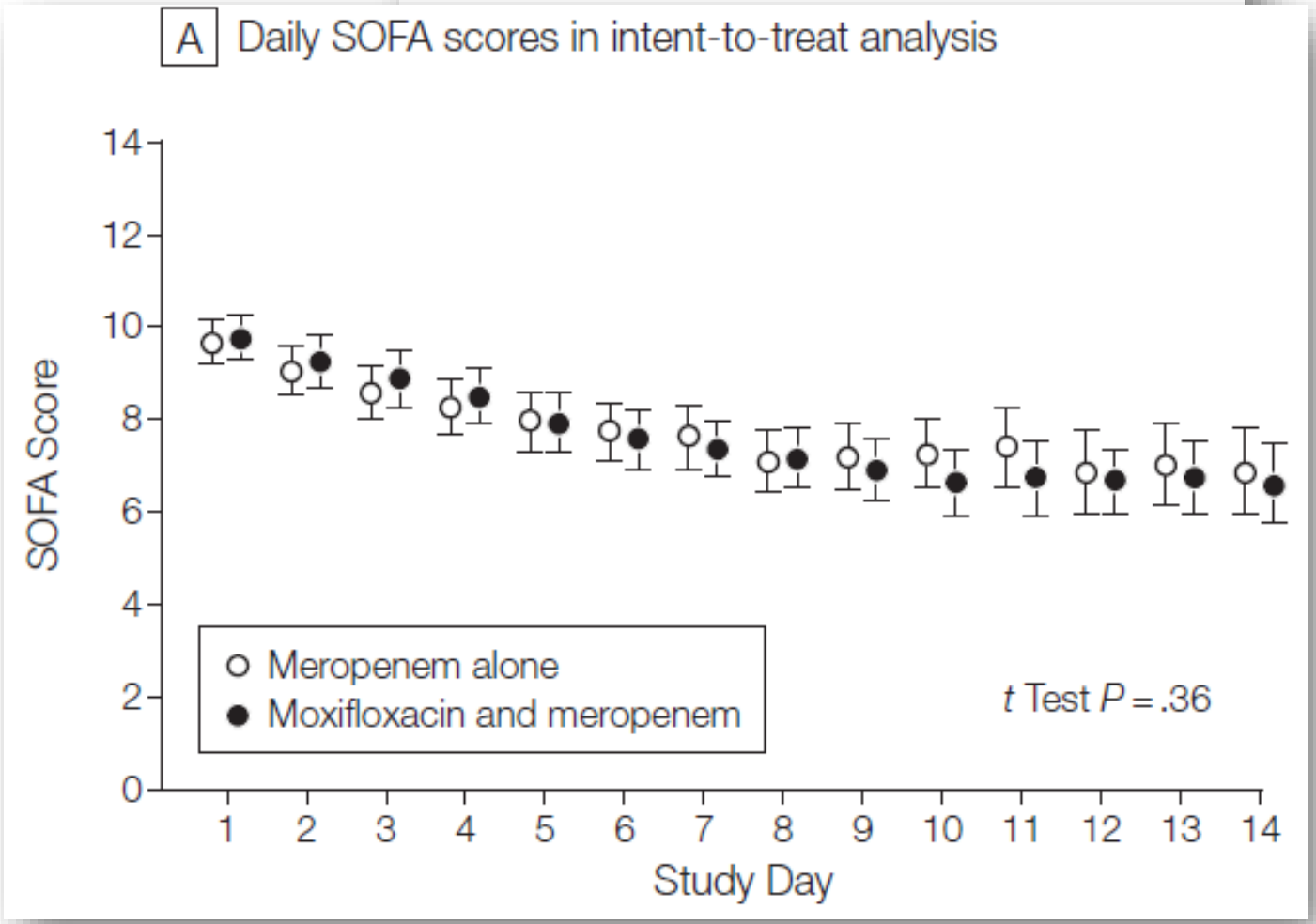
Pas d'impact: SOFA, mortalité, durée d'hospitalisation, infection secondaires ..

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**

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A Daily SOFA scores in intent-to-treat analysis

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

Cas clinique

6- Quelles populations pourraient bénéficier d'une bithérapie au cours du choc septique ?

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, peut etre un impact chez ID et MDR (spectre++)**

Ripa et al. JAC **2017**

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

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Table 5. P

Subgroup			y mortality 95% CI)	*P* value
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Haematolo				
malign				
	DACT		29)	0.138
	PS		74)	0.521
Unknown f				
infectio				
	DACT		14)	0.090
	PS		33)	**0.004**
Pulmonary				
infectio				
	DACT		65)	0.396
	PS		38)	0.625
Time to bl				
positivit				
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Pseudomo				
aerugin				
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Empirical				
β-lactar				
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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, peut etre un impact chez ID et MDR (spectre++)**

Ripa et al. JAC **2017**

Que disent les recommandations ?

Cas clinique

Que disent les recommandations ?

Surviving Sepsis Campaign

Society of Critical Care Medicine
The Intensive Care Professionals

ESICM
The Intensive Connection

Recommendations

19. For adults with sepsis or septic shock and high risk for multidrug resistant (MDR) organisms, we **suggest** using two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent

Weak recommendation, very low quality of evidence

20. For adults with sepsis or septic shock and low risk for MDR organisms, we **suggest against** using two Gram-negative agents for empiric treatment, as compared to one Gram-negative agent

Weak recommendation, very low quality of evidence

21. For adults with sepsis or septic shock, we **suggest against** using double gram-negative coverage once the causative pathogen and the susceptibilities are known

Weak recommendation, very low quality of evidence

VERY LOW

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21 For adults with sepsis or septic shock, we **suggest against** using double gram-negative coverage once the causative pathogen and the susceptibilities are known.

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*)

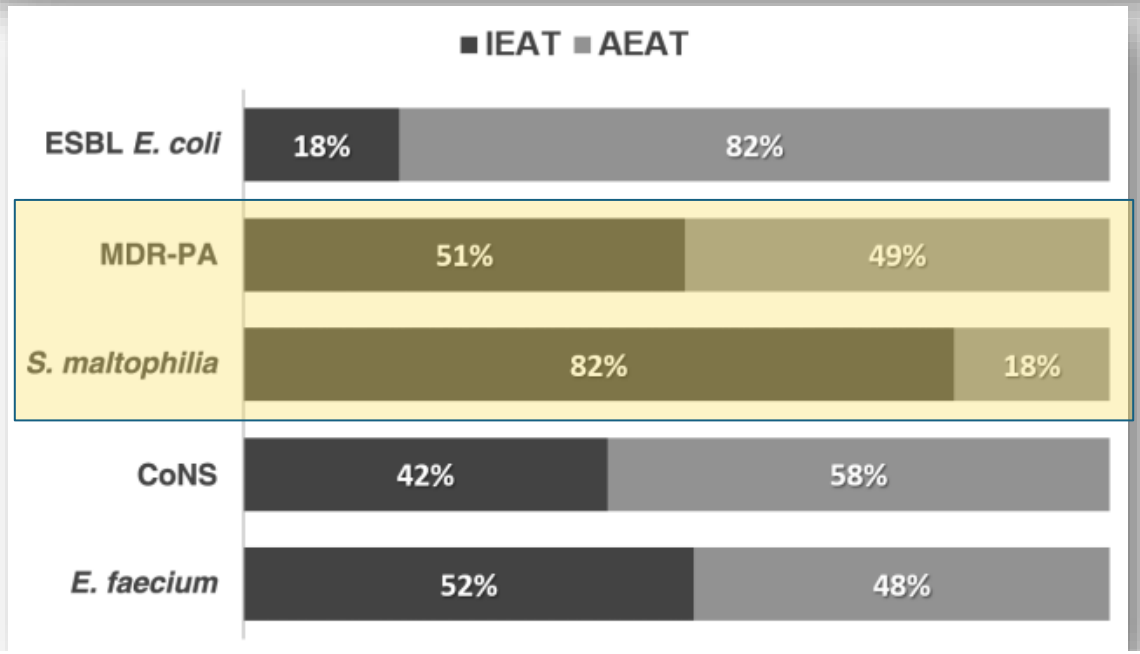
***P.A* 48%** (Vs 31%, *P.02*)

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

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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*.

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Plan

Au cours de la neutropénie fébrile ?

En pratique : au cours de la Neutropénie Fébrile ?

10th EUROPEAN CONFERENCE on INFECTIONS in LEUKAEMIA

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 ?

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

En pratique : au cours de la NF ?

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**

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 sévère ou ID, mais intérêt de la bithérapie pour**
  - **Intérêt d'ELARGIR le spectre** pour **les patients « critiques » (>25% décès) en cas FDR de résistances atb**
  - **Pour la neutropénie avec Bactériémie à BGN (et BMR)**
- **En pratique :**
  - **Choc septique/sepsis : pas d'intérêt à bi-thérapie sur germes sensibles**
  - **Aminosides** pour le choc septique et bactériémie : colonisation (MDR), écologie locale, nosocomiale, atb large spectre <90j, voyage zone à risque <90j
  - **Peu de preuves pour la synergie (quand on utilise des molécules efficaces)**
- **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
AUX NOUVELLES FRONTIÈRES DE LA SANTÉ

benjamin.gaborit@chu-nantes.fr

Nantes Université

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

Comment optimisée l'administration des ATB

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

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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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

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