SEPSIS: Importance de la précocité et la qualité de l'antibiothérapie initiale

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Liens d'intérêt

- **Conseil scientifique / financement recherche ou congrès**
  - ☐ Gilead
  - ☐ Astellas
  - ☐ Coreviome
  - ☐ Mylan
  - ☐ Pfizer

Au menu

- **Quelles sont les évidences ?**

- **Les dégâts collatéraux**

- **En pratique…**

Précocité de l'antibiothérapie

Cas clinique

- **Ginette M, 77 ans, EHPAD**
  - ☐ HTA, surpoids, troubles cognitifs, DNID => metformine + valsartan
  - ☐ **Admise aux urgences pour fièvre, diarrhée et asthénie (J5)**
  - ☐ Admission:
    - TA = 95/60 mmHg, T = 38,3° C, FC = 110/min
    - Désorientée, déshydratée
    - Pas de point d'appel infectieux
    - Creat 120 umol/L

Conduite à tenir ?

The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3)

QSOFA

Calcul du score SOFA	0 point	1 point	2 points	3 points	4 points
PaO_2/FiO_2	>400	301-400	201-300	101-200 et VA	≤ 100 et VA
Plaquettes $x10^3/mm^3$	>150	101-150	51-100	21-50	≤20
Bilirubine, mg/L (mmol/L)	<12 (<20)	12-19 (20-32)	20-59 (33-101)	60-119 (102-204)	>120 (>204)
Hypotension	PAM ≥70mmHG	PAM < 70mmHG	Dopamine ≤ 5 ou dobutamine (toute dose)	Dopa > 5 ou adrénaline ≤ 0,1 ou noradré ≤ 0,1	Dopamine > 15 ou adré > 0,1 ou noradré > 0,1
Score de Glasgow	15	13-14	10-12	6-9	<6
Créatinine, mg/L (µmol/L) ou diurèse	<12 (<110)	12-19 (110-170)	20-34 (171-299)	35-49 (300-440) ou <500mL/j	>50 (>440) ou <200mL/j

Singer M et al. JAMA 2016
Rhodes A et al. Intensive Care Med 2017
Levy MM et al. Intensive Care Med 2018

Antibiotics

- **We recommend that administration of IV antimicrobials be initiated as soon as possible after recognition and within 1 h for both sepsis and septic shock.**

(strong recommendation, moderate quality of evidence).

- **We recommend empiric broad-spectrum therapy with one or more antimicrobials to cover all likely pathogens.**

(strong recommendation, moderate quality of evidence).

The Surviving Sepsis Campaign Bundle:
2018 update

CrossMark

Pourquoi une reco aussi forte, pour un niveau de preuve aussi léger ?

- Measure lactate level. Remeasure if initial lactate is >2 mmol/L.
- Obtain blood cultures prior to administration of antibiotics.
- Administer broad-spectrum antibiotics.
- Begin rapid administration of 30ml/kg crystalloid for hypotension or lactate ≥4 mmol/L.
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mm Hg.

*"Time zero" or "time of presentation" is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis (formerly severe sepsis) or septic shock ascertained through chart review.

Fig. 1 Hour-1 Surviving Sepsis Campaign Bundle of Care

Levy MM et al. Intensive Care Med 2018

Does usage of a parachute in contrast to free fall prevent major trauma?: a prospective randomised-controlled trial in rag dolls

Czorlich P et al. Eur J Spine 2016
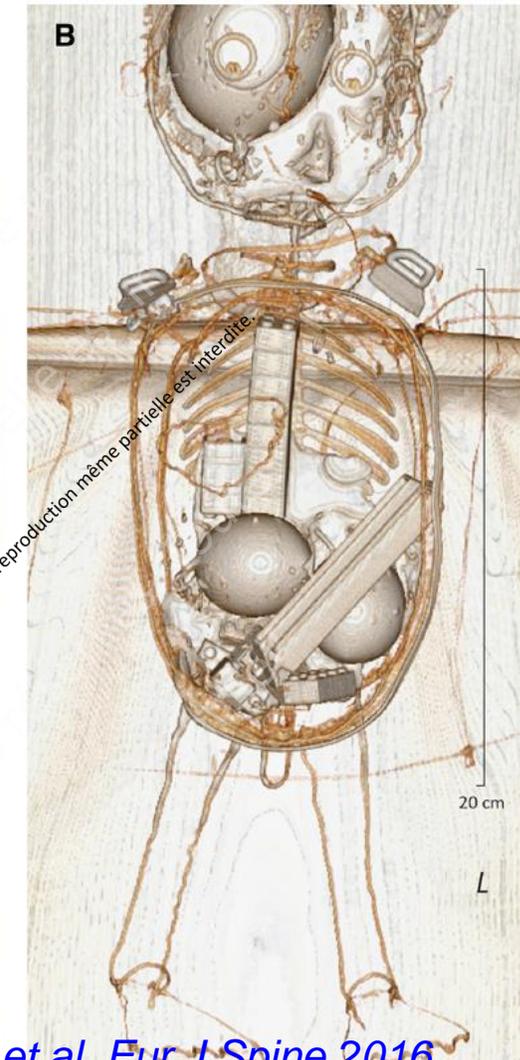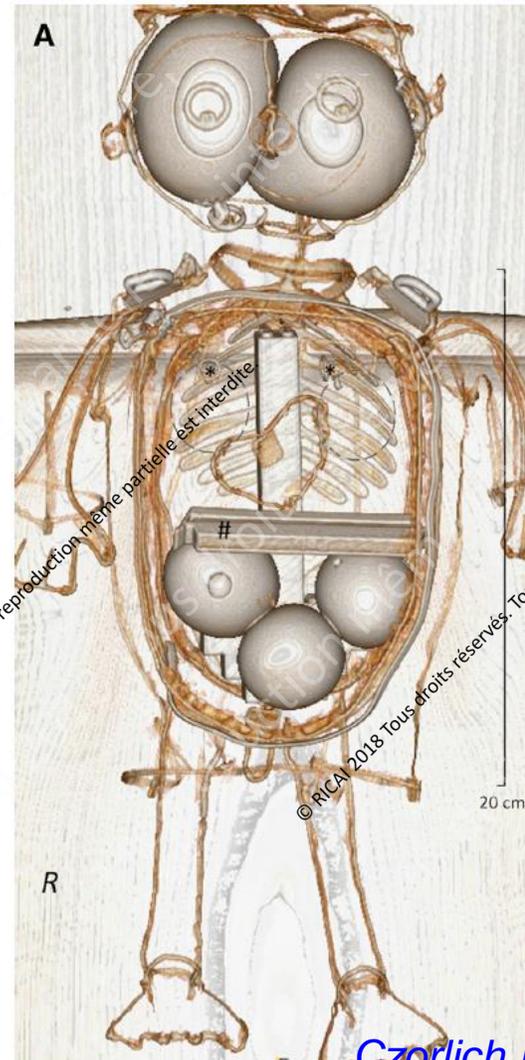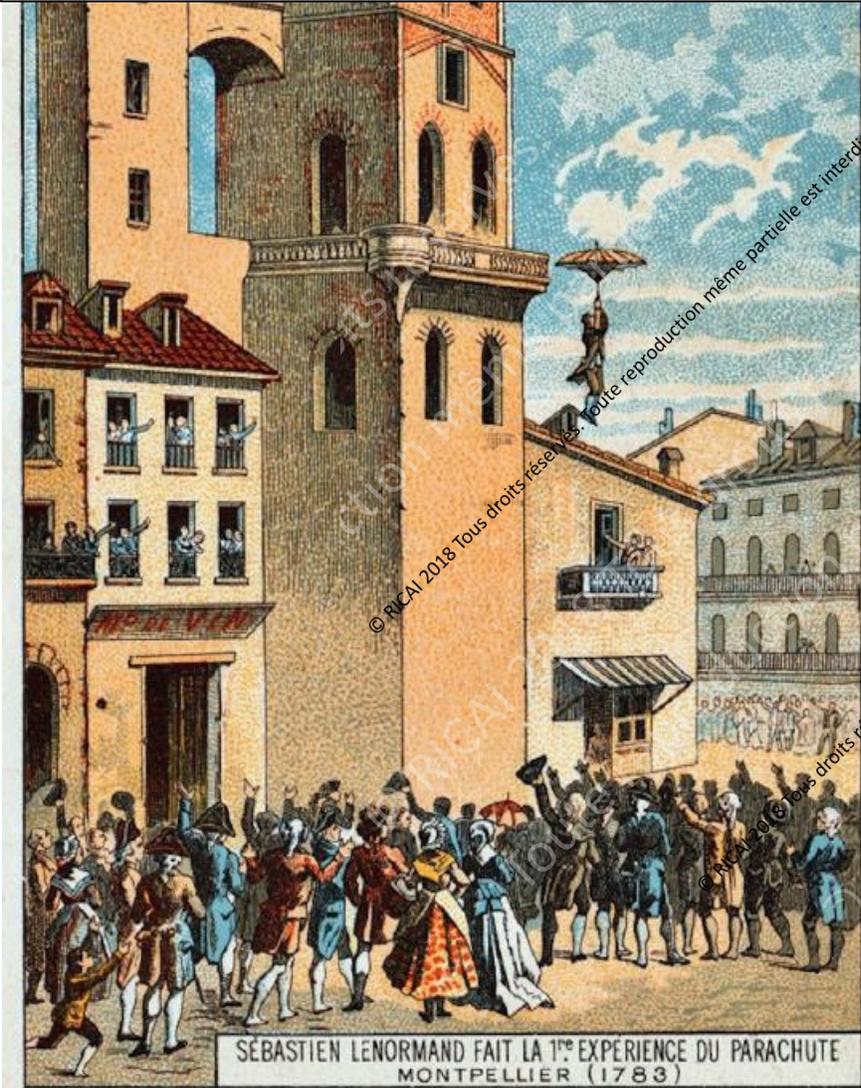
STROKE IS A BRAIN EMERGENCY
UPSTATE COMPREHENSIVE STROKE CENTER

Signs and Symptoms
- Anxiety
- Crushing chest pain
- Left arm pain (MEN)
- Arm, back, jaw pain (WOMEN)
- Diaphoresis
- Nausea
- SOB

AT LEAST 250,000 AMERICANS DIE FROM SEPSIS EACH YEAR.
GET AHEAD OF SEPSIS

GET AHEAD OF SEPSIS
KNOW THE RISKS. SPOT THE SIGNS. ACT FAST.

Cas clinique (épilogue)

- **Ginette M, 77 ans, EHPAD**
  - ☐ Réhydratation
  - ☐ **Abstention ATB sous surveillance aux urgences**
    - => H1, Ginette se sent mieux, les docteurs aussi
  - ☐ Amélioration progressive (hémodynamique, état cognitif)
  - ☐ **Diagnostic final = gastro-entérite + hypovolémie**
  - ☐ **Retour en EHPAD après 24 h**

The Timing of Early Antibiotics and Hospital Mortality in Sepsis

Vincent X. Liu[1], Vikram Fielding-Singh[2], John D. Greene[1], Jennifer M. Baker[1], Theodore J. Iwashyna[3,4], Jay Bhattacharya[5], and Gabriel J. Escobar[1]

Etude rétrospective **35 000 patients**, 21 urgences, Californie 2010-2013

La corrélation précocité/pronostic n'est significative que pour le choc septique
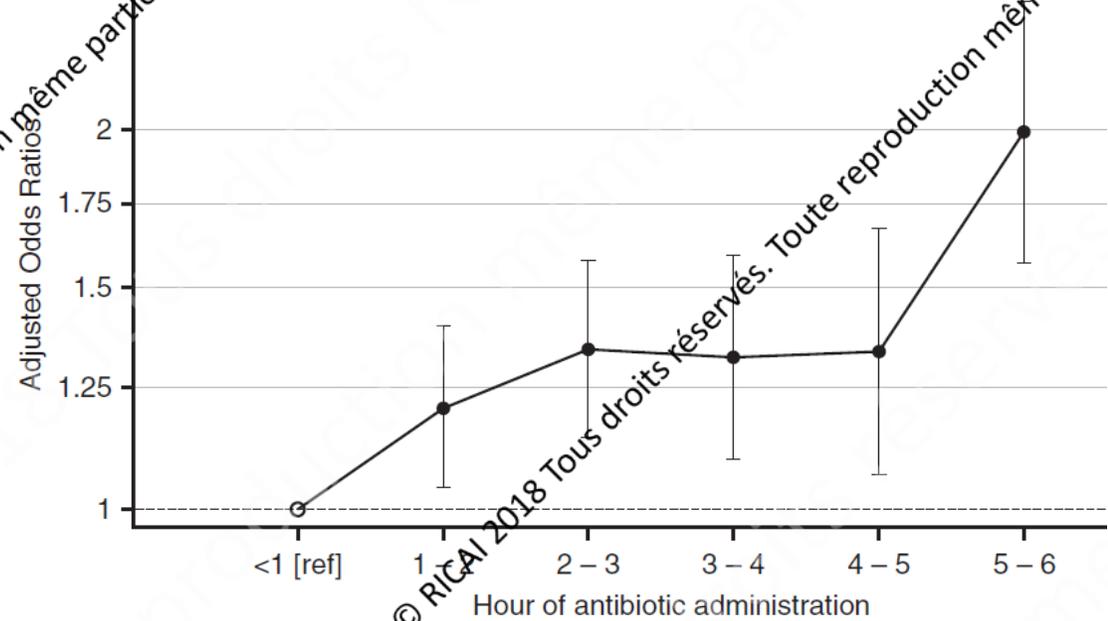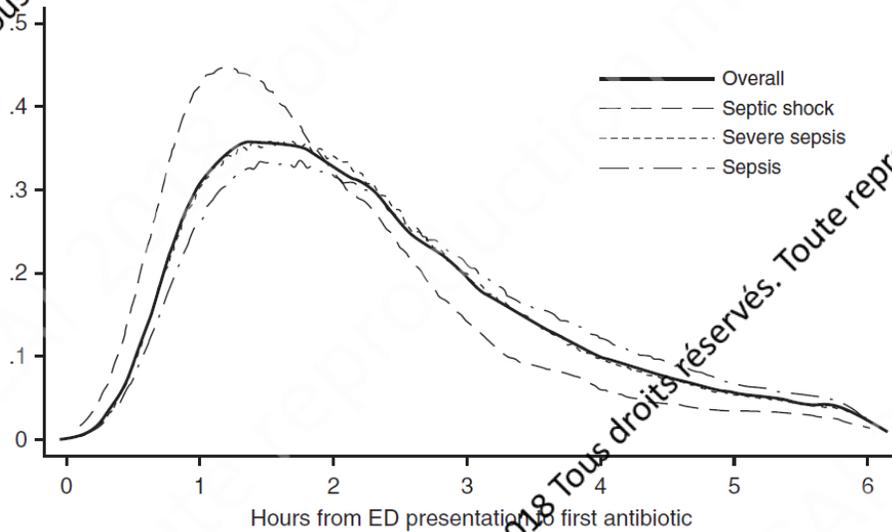
Liu V et al. AJRCCM 2017

Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial

- **Etude randomisée, Pays Bas, 2014-16**
  - ☐ ATB en pré-hospitalier (ceftriaxone, 2 g)
  - ☐ Prise en charge usuelle (évaluation Urgences)

- **2672 patients inclus**
  - ☐ **60% sepsis (def. Sepsis-3)**
  - ☐ **<5% choc septique**

- **Critère principal** = survie J28

Alam N et al. Lancet Respir Med 2018

Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial

	Usual care group (n=1137)	Intervention group (n=1535)	Relative risk (95% CI)	Risk difference (%, 95% CI)	p value
TTA before arriving at the ED (min)	..	26 (19–34)			
Median TTA in the ED (min)	70 (36–128)	..	..	..	..
28 day mortality	93 (8%)*	120 (8%)	0·95 (0·74 to 1·24)	–0·37 (–2·5 to 1·7)	0·78
90 day mortality	134 (12%)*	178 (12%)	0·98 (0·80 to 1·21)	–0·20 (–2·7 to 2·3)	0·87
Intensive care unit admission	98 (9%)	155 (10%)	1·17 (0·92 to 1·49)	1·5 (–0·73 to 3·8)	0·19

*Alam N et al. Lancet Respir Med 2018*

Prehospital antibiotics in the ambulance for sepsis: a multicentre, open label, randomised trial

	Usual care group (n=1137)	Intervention group (n=1535)
Age (years)		
<65	12/276 (4%)	6/336 (2%)
≥65	81/860 (9%)	114/1199 (10%)
qSOFA (prehospital)		
<2	59/872 (7%)	71/1132 (6%)
2	25/180 (14%)	45/318 (14%)
NEWS (prehospital)		
<5	7/146 (5%)	7/192 (4%)
≥5	53/622 (9%)	71/827 (9%)
SBP (prehospital)		
≤100	15/112 (13%)	25/181 (14%)
>100	75/1001 (7%)	95/1337 (7%)
Severity of sepsis		
Sepsis	8/424 (2%)	13/579 (2%)
Severe sepsis	74/656 (11%)	88/868 (10%)
Septic shock	10/37 (27%)	19/66 (29%)
Overall	93/1136 (8%)	120/1535 (8%)
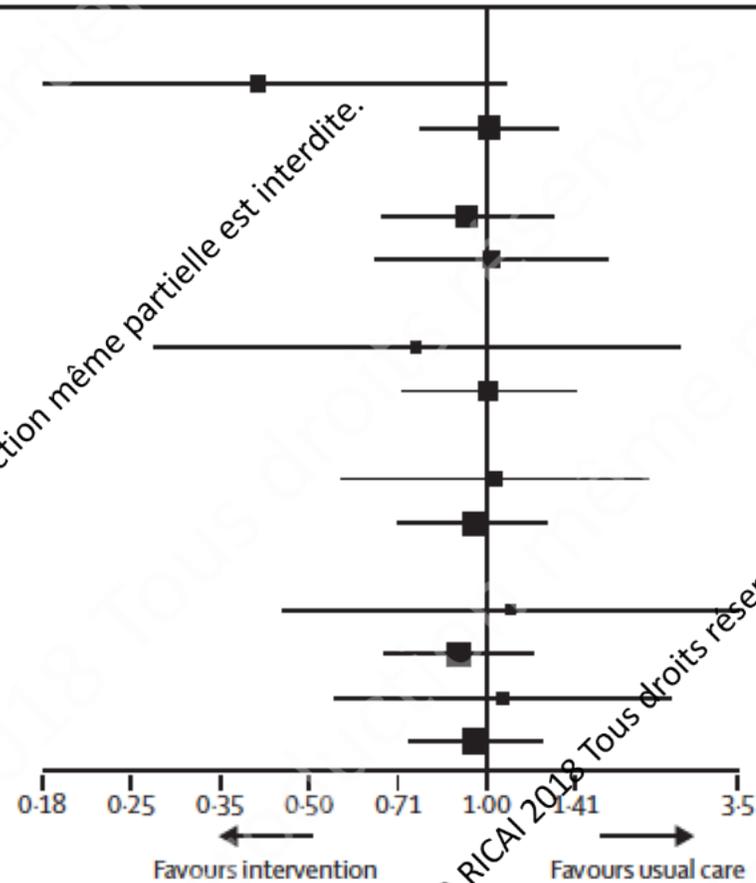
Antibiotics for Sepsis—Finding the Equilibrium

The time has come to balance the recommendation for early and aggressive antibiotics for all patients with possible sepsis with the diagnostic uncertainty regarding sepsis and the possible harm associated with unnecessary antibiotics.

conflating sepsis and septic shock is a mistake. Time to instituting effective treatment is important for patients with septic shock, but the data are less clear for patients with possible sepsis alone who are not in shock.

Golden hour:

OK pour choc septique, mais pas pour 'suspicion sepsis' !

Klompas M et al. JAMA 2018

Golden hour:

OK pour méningite bactérienne

Detrimental role of delayed antibiotic administration and penicillin-nonsusceptible strains in adult intensive care unit patients with pneumococcal meningitis: The PNEUMOREA prospective multicenter study*

Marc Auburtin, MD; Michel Wolff, MD; Julien Charpentier, MD; Emmanuelle Varon, MD; Yves Le Tulzo, MD, PhD; Christophe Girault, MD; Ismaël Mohammedi, MD; Benoît Renard, MD; Bruno Mourvillier, MD; Fabrice Bruneel, MD; Jean-Damien Ricard, MD; Jean-François Timsit, MD, PhD

Etude prospective **156 patients**, 56 réanimations, France 2001-2003

Table 2. Multivariate analysis of baseline factors at intensive care unit admission associated with 3-month mortality

Variable	Odds Ratio	95% Confidence Interval	p Value
SAPS II	1.12	1.072–1.153	.002
Penicillin-nonsusceptible *Streptococcus pneumoniae*	6.83	2.94–20.8	$<10^{-4}$
Interval >3 hrs between hospital admission and antibiotic treatment	14.12	3.93–50.9	$<10^{-4}$

Auburtin M et al. Crit Care Med 2006

Les effets collatéraux des incitations à dégainer les ATB 'tôt'

- **Programme 'pay for performance',** USA, 2006**:** Incitation à la prescription précoce d'ATB aux urgences en cas de pneumonie

- **Intéressement financier pour les hôpitaux,** basé sur le % de patients codés 'pneumonie' qui auront reçu les ATB <4 h après l'arrivée aux urgences

- Données disponibles pour le public…

The Centers for Medicare and Medicaid Services (CMS) Community Acquired Pneumonia Core Measures Lead to Unnecessary Antibiotic Administration by Emergency Physicians

Bret A. Nicks, MD, David E. Manthey, MD, and Michael T. Fitch, MD, PhD

Public Reporting of Antibiotic Timing in Patients with Pneumonia: Lessons from a Flawed Performance Measure

Original Investigation

February 25, 2008

Antibiotic Timing and Errors in Diagnosing Pneumonia

James A. Welker, DO; Michelle Huston, MD; Jack D. McCue, MD

» Author Affiliations | Article Information

National Hospital Antibiotic Timing Measures for Pneumonia and Antibiotic Overuse

Douglas E. Drake; Abigail Cohen; Jeffrey Cohn

THE MEASUREMENT OF TIME TO FIRST ANTIBIOTIC DOSE FOR PNEUMONIA IN THE EMERGENCY DEPARTMENT: A WHITE PAPER AND POSITION STATEMENT PREPARED FOR THE AMERICAN ACADEMY OF EMERGENCY MEDICINE

Jesse M. Pines, MD, MBA, MSCE,*†‡ Joshua A. Isserman, MS,* and Patrick B. Hinfey, MD§

ARTICLE SUMMARY

1. Why is this topic important?

The use of time to first antibiotic dose (TFAD) as a core measure for patients admitted with community-acquired pneumonia (CAP) in the ED has been controversial. Despite this controversy, it continues to be measured across US EDs and reported publicly.

2. What does this review attempt to show?

This review is aimed at assessing the evidence that reports outcome data on specific interventions on the implementation of programs that measure or improve TFAD in the ED for patients with CAP.

3. What are the key findings?

The strength of evidence is variable on whether the measurement of TFAD in CAP improves outcomes, however, recent studies show that implementing this core measure may lead to antibiotic overuse. The AAEM does not support continued measurement of TFAD for CAP in US EDs.

Pines J et al. J Emerg Med 2009

Endocardites, évolution des guidelines

Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications

A Scientific Statement for Healthcare Professionals From the American Heart Association

Endorsed by the Infectious Diseases Society of America

Larry M. Baddour, MD, FAHA, Chair; Walter R. Wilson, MD; Arnold S. Bayer, MD;

Recommendations

1. Infectious diseases consultation should be obtained to define an optimal empirical treatment regimen at the time of initiation of antimicrobial therapy (*Class I; Level of Evidence B*).

Baddour L et al. Circulation 2015

Qualité de l'antibiothérapie initiale

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

- **Etude randomisée, Israël, 2015-17**
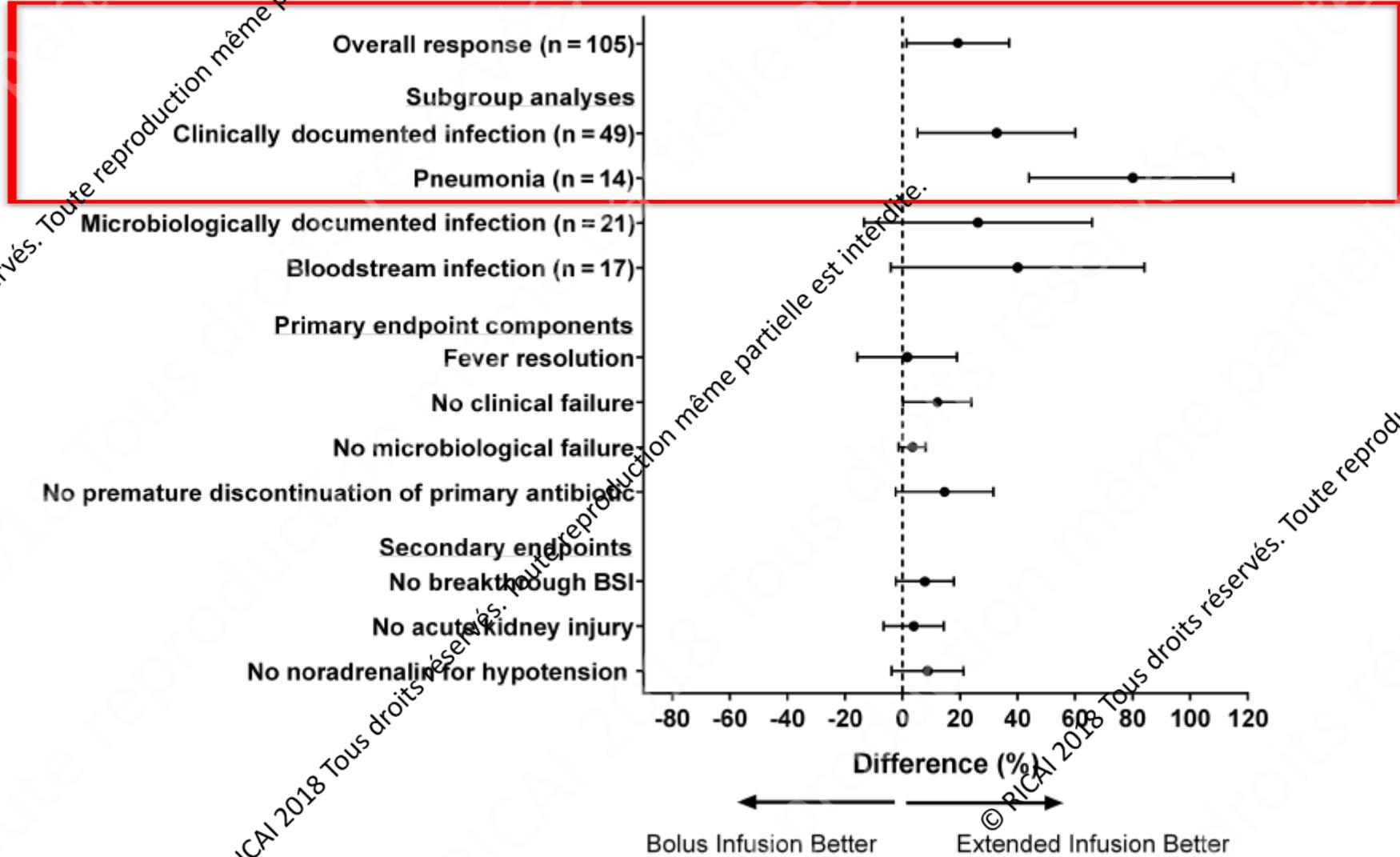
- **Neutropénie fébrile à haut risque**
  - Greffe CSH ou LA en induction/consolidation
  - PNN < 500/mm3

- **Randomisation sur durée de perf. (30' vs. 4 h)**
  - **90% pipé/tazo**
  - **+ 40% vanco**

- **Critère principal composite J4**

Ram R et al. Clin Infect Dis 2018

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

Ram R et al. Clin Infect Dis 2018

Are all beta-lactams similarly effective in the treatment of methicillin-sensitive *Staphylococcus aureus* bacteraemia?

M. Paul[1,2], N. Zemer-Wassercug[1], O. Talker[1], Y. Lishtzinsky[1], B. Lev[3], Z. Samra[3,2], L. Leibovici[4,2] and J. Bishara[1,2]

TABLE 2. Multivariable logistic regression analysis for 30-day mortality: empirical antibiotic treatment[a]

Variable[b]	OR, 95% CI n = 541 patients, deaths = 202	p value
Empirical antibiotic treatment		
Oxacillin/cefazolin	Reference	
Cefuroxime	1.98 (0.98–4.01)	0.058
Ceftriaxone/cefotaxime	2.24 (1.23–4.08)	0.008
Beta-lactam-beta-lactamase	2.68 (1.23–5.85)	0.013

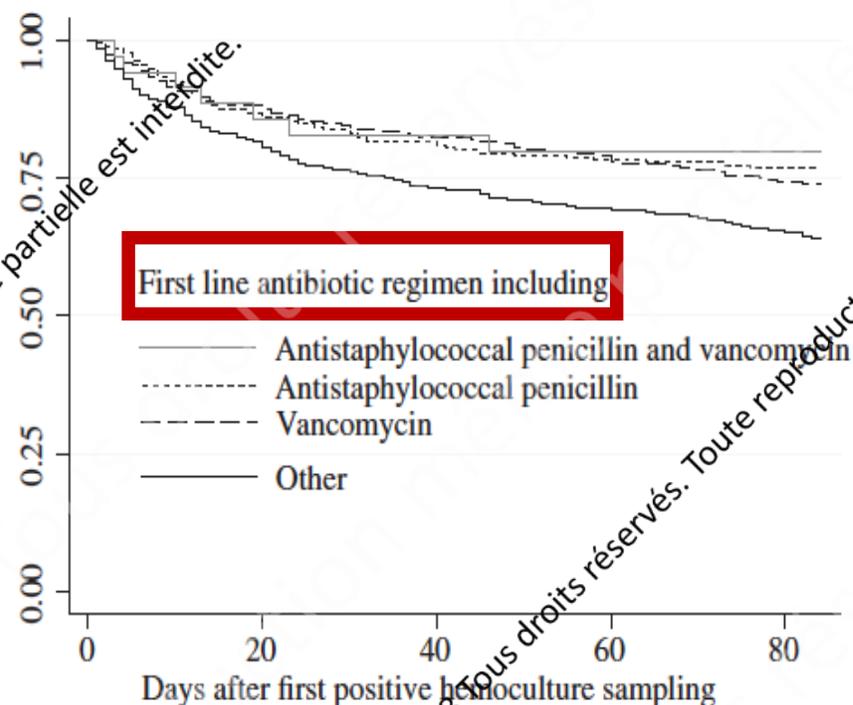**Factors associated with 12-week case-fatality in *Staphylococcus aureus* bacteraemia: a prospective cohort study**

P. Braquet [1,2,*], F. Alla [3,4,5], C. Cornu [6,7,8], F. Goehringer [9], L. Piroth [10], C. Chirouze [11], M. Revest [12], C. Lechiche [13], X. Duval [14,15,16], V. Le Moing [1,2,*], on behalf of the VIRSTA-AEPEI study group

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MICROBIOLOGY
AND INFECTION
ESCMID
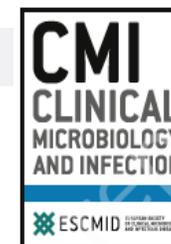
Cohorte VIRSTA

- Prospective, observationnelle

- France, 2009-2011

- 2091 bactériémies *S. aureus*

- **Létalité**
  - **23% à S4**
  - **34% à S12**

First line antibiotic regimen including
- Antistaphylococcal penicillin and vancomycin
- Antistaphylococcal penicillin
- Vancomycin
- Other

Days after first positive hemoculture sampling

Braquet P et al. Clin Microbiol Infect 2016

Traitements ATB 'progressifs' et résistances

Kisheny R et al. Science 2016

Les messages

- L'importance du timing est prouvée pour les infections graves & rapidement évolutives **uniquement**
  - ☐ **Choc septique**
  - ☐ **Méningites pneumocoque/méningocoque**

- De nombreuses situations 'sepsis-like' ne justifient pas la prescription d'ATB en urgence

- **Temporiser permet souvent de ne pas prescrire d'ATB du tout !**

- Si on prescrit, il faut que ce soit non seulement rapide, **mais parfait (molécules, doses, modalités de perfusion)**

Les pistes pour un meilleur usage des ATB dans le sepsis

- Investir sur le **diagnostic**
  - clinique ⇔ formation des médecins
  - tests diagnostics rapides

- **Filière 'sepsis',** avec expertises

- **Permettre et valoriser la non-prescription**
  - lever les angoisses des médecins de 1ère ligne
  - rendre possible l'abstention initiale avec ré-évaluation