Bactériémies à *Staphylococcus aureus*

Prof. Pierre Tattevin [1,2]

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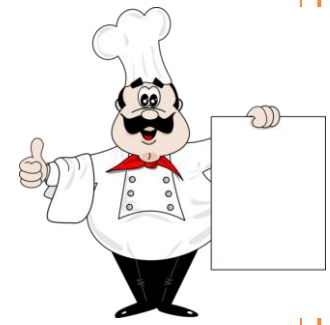
- [2] **Société de Pathologie Infectieuse de Langue Française (SPILF)**

Objectifs du cours



- Vous convaincre que les bactériémies à *S. aureus* sont une des meilleures justifications du métier d'infectiologue

1. fréquentes et graves
2. les bonnes pratiques sauvent des vies

- Faire le tour de quelques bonnes pratiques 'de base'

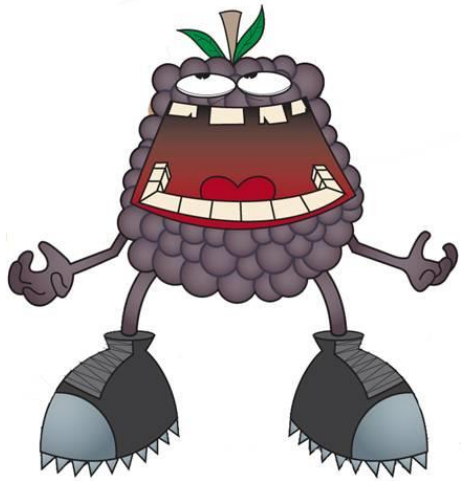
1. **antibiothérapie optimale**
2. **monitoring des hémocultures sous traitement**

- Traitements de sauvetage des bactériémies persistantes (SASM & SARM)

- Pistes de recherche

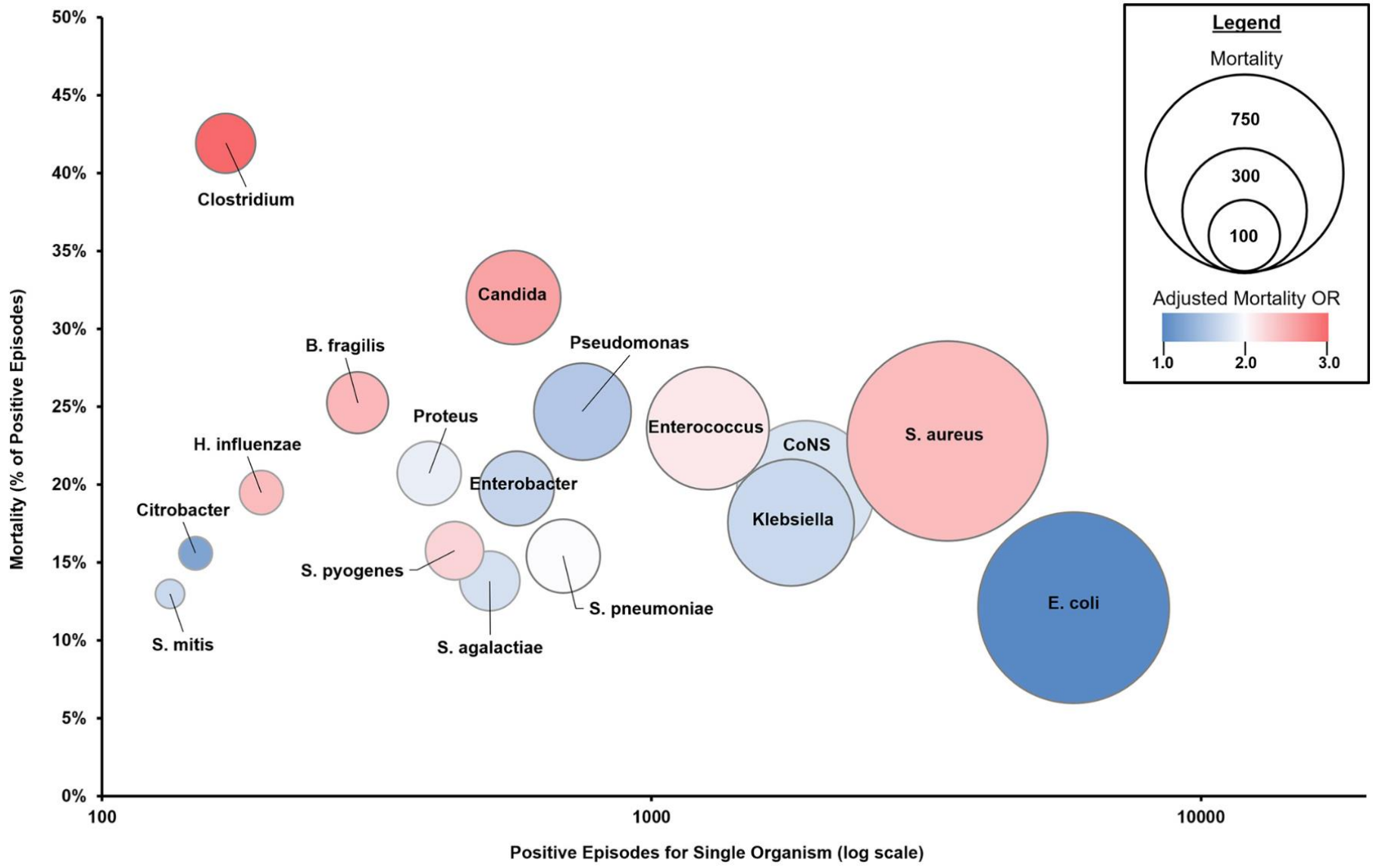
INTRODUCTION – *Staphylococcus aureus*

- **Pathogène majeur pour l 'Homme**
  - **Colonise 1/3 de la population en bonne santé**
  - **Mortalité spontanée 80%** si bactériémie (Boston, 1940)



Chambers, EID 2001; Lowy, NEJM 1998; Diep et al. Annals 2008

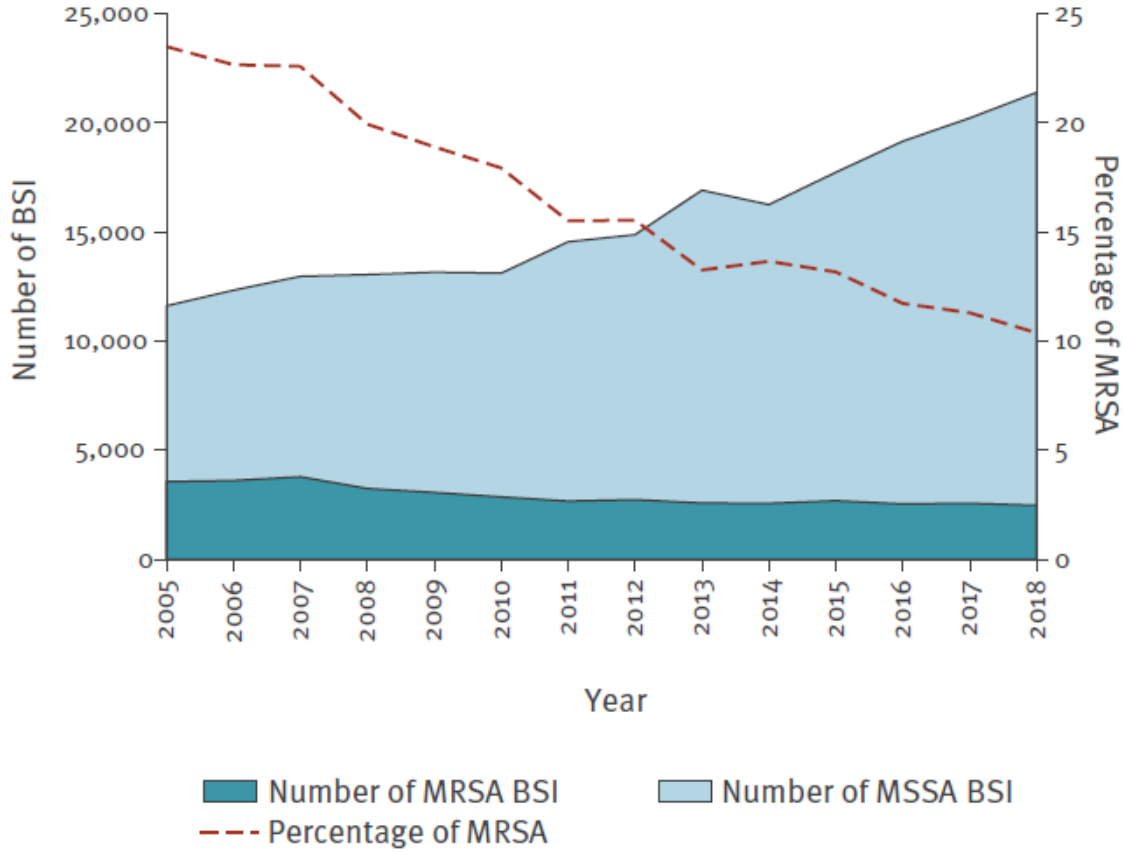
Le fardeau des bactériémies à *Staphylococcus aureus*



Verway et al. J Clin Microbiol 2022

Une vraie maladie infectieuse émergente (MIE)

Bloodstream infections caused by meticillin-resistant and meticillin-susceptible *Staphylococcus aureus*, EU/EEA, 2005–2018 (n = 258,448)



Cagliotti C et al. Eurosurv 2021

Clinical Microbiology Reviews

Predictors of Mortality in Staphylococcus aureus Bacteremia

Sebastian J. van Hal, Slade O. Jensen, Vikram L. Vaska, Björn A. Espedido, David L. Paterson and Iain B. Gosbell
Clin. Microbiol. Rev. 2012, 25(2):362. DOI:

1. Antibiothérapie **initiale**
   - **Délai d'introduction d'un agent actif *in vitro*** *(48 h)*
   - **Bêta-lactamines > vancomycine si SAMS**
   - **Péni M (anti-staph) ou céfazoline > autres Beta-lactamines si SAMS**

2. **Eradication de la source / foyer(s) secondaire(s)**
   - **Cathéter** si responsable
   - **Drainage collections, etc.**

3. **Divers**
   - **Monitoring durée bactériémie => traitement adapté**
   - Avis spécialisé**: les infectiologues !**

NB: Associations démontrées dans études observationnelles multivariées

Van Hal S et al. Clin Microbiol Rev 2012

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

Paul M et al. Clin Microbiol Infect 2011

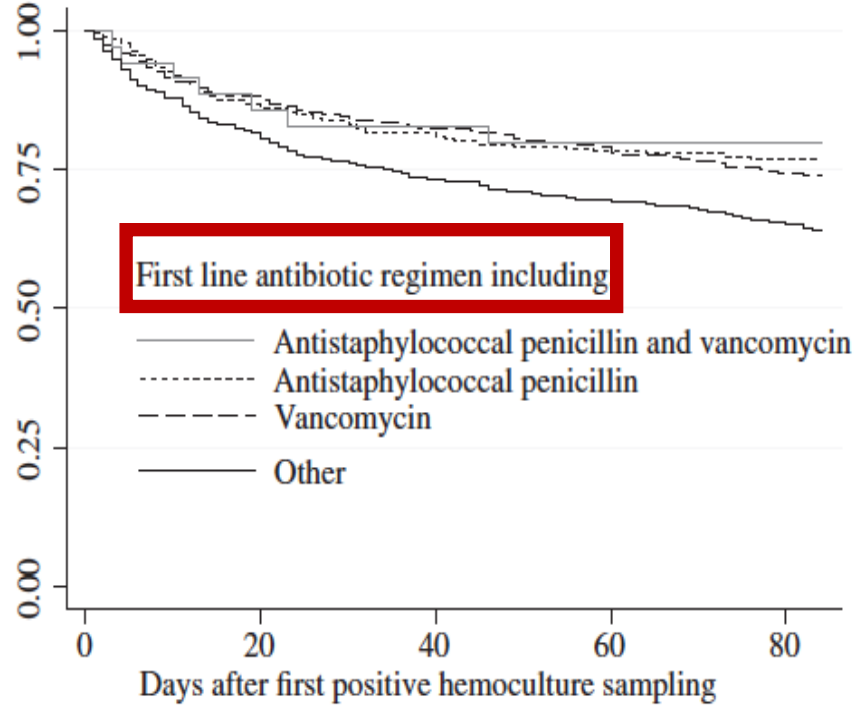
Factors associated with 12 week case-fatality in *Staphylococcus aureus* bacteraemia: a prospective cohort study

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

CMI CLINICAL MICROBIOLOGY AND INFECTION
ESCMID

- **Cohorte VIRSTA**

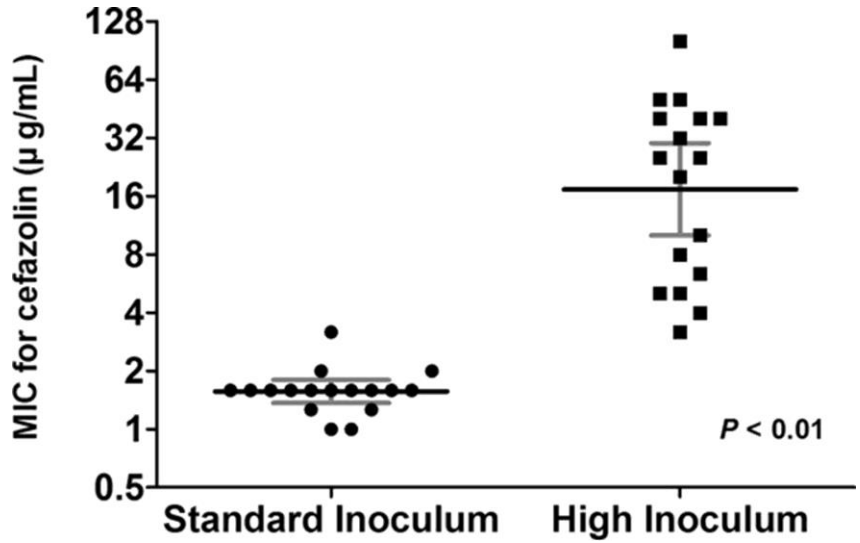
  - Prospective, observationnelle
  - France, 2009-2011
  - 2091 bactériémies *S. aureus*
  - **Létalité**
    - **23% à S4**
    - **34% à S12**



Braquet P et al. Clin Microbiol Infect 2016

Bactériémie à SAMS: Céfazoline ou (cl)oxacilline ?

1. cefazoline moins efficace si gros inoculum ?



Brief Report

Unsuccessful Treatment of Staphylococcal Endocarditis With Cefazolin

Richard E. Bryant, MD, Robert H. Alford, MD

• Two patients with staphylococcal endocarditis were treated unsuccessfully with cefazolin sodium. One patient relapsed after 52 days of therapy.

fects believed to be splenic infarcts led to splenectomy. Gross and microscopic exam-

Cefazolin and *Staphylococcus aureus* Endocarditis

To the Editor.—Bryant and Alford (237:569, 1977) suggest that cefazolin sodium should not be used for treatment of *Staphylococcus aureus* endocarditis. We disagree. Because of its

Lee et al. AAC 2016
Bryant et al. JAMA 1977
Kaye et al. JAMA 1977
Carvajal et al. AAC 2020

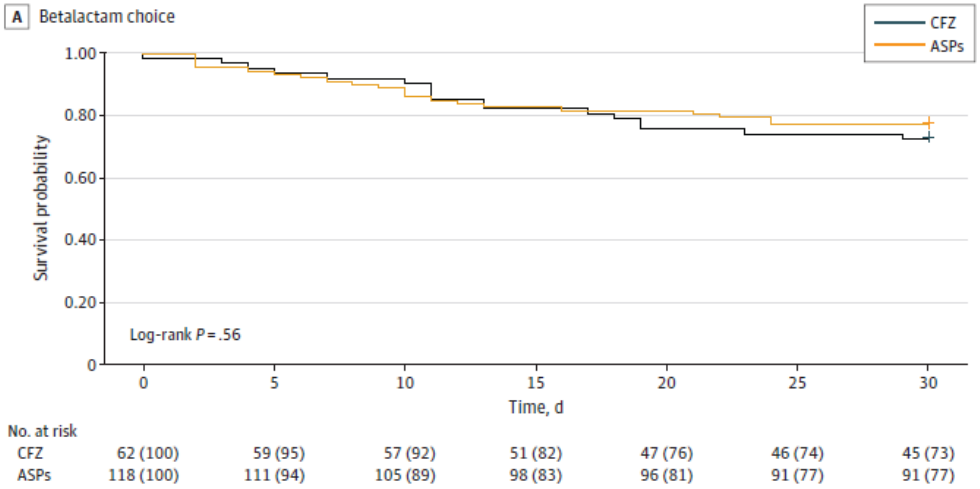
JAMA Network Open

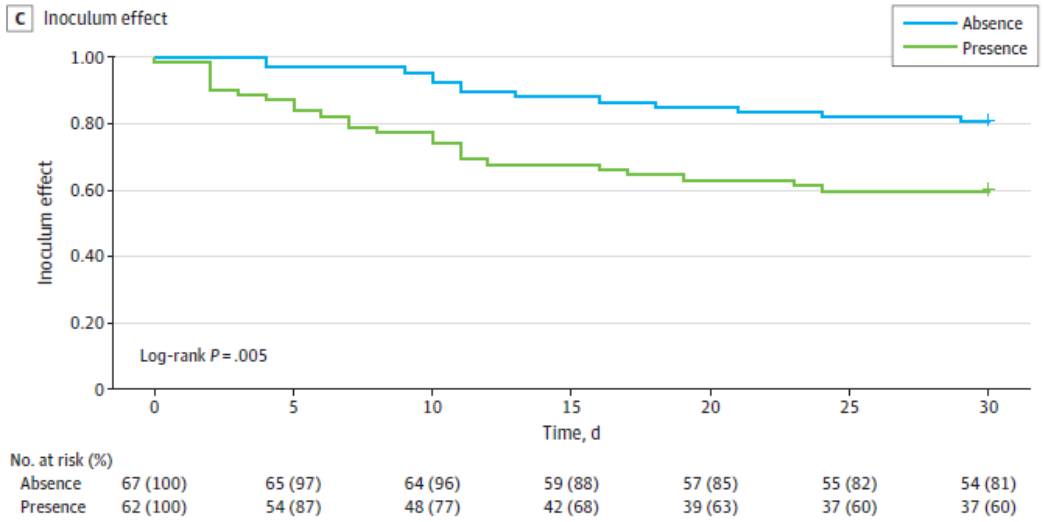
Original Investigation | Infectious Diseases

β-Lactam Inoculum Effect in Methicillin-Susceptible *Staphylococcus aureus* Infective Endocarditis

Baptiste Jean, MD; Maelys Crolle, PharmD; Candice Pollani, PharmD; Adèle Le Guilloux; Guillaume Martin-Blondel, PhD; Pierre Tattevin, PhD; Audrey Le Bot, MD; David Luque Paz, MD; François Guérin, PhD; Vincent Cattoir, PhD; Laurence Armand-Lefevre, PhD; Signara Gueye; François-Xavier Lescure, PhD; Xavier Duval, PhD; Clémence Massip, PhD; Pierre Delobel, PhD

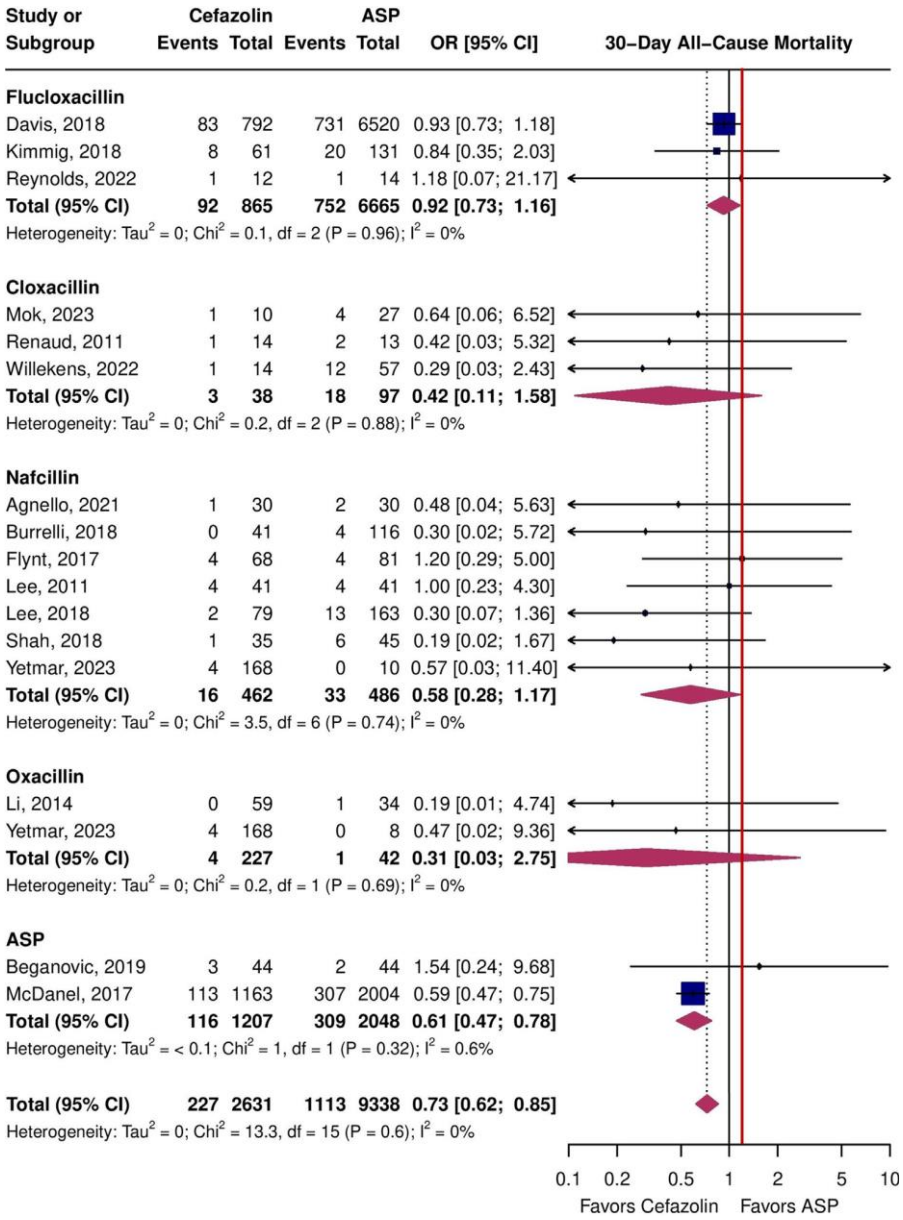
Figure 3. One-Month Survival Curves in Methicillin-Susceptible Staphylococcus aureus Left-Sided Infective Endocarditis

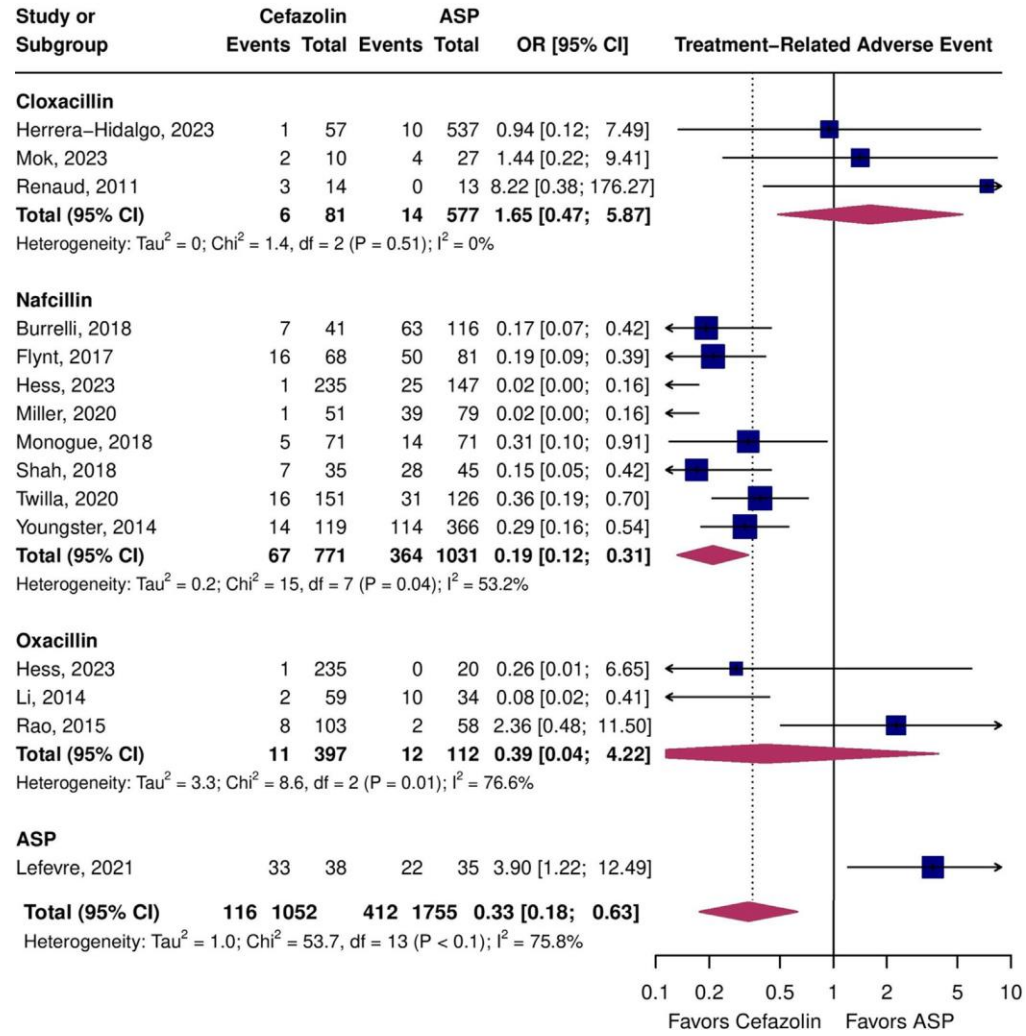




Jean B et al JAMA Network Open 2024

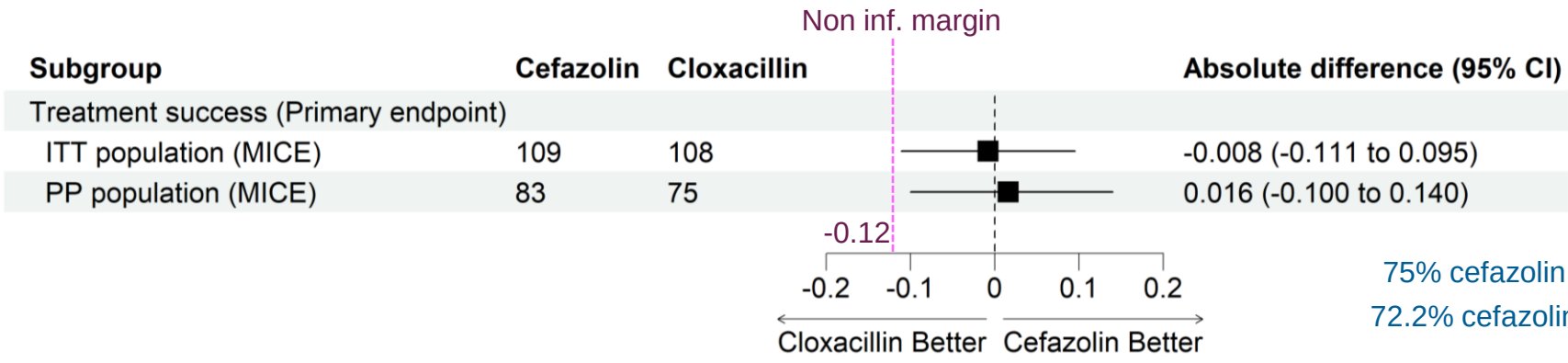
2. Etudes observationelles: mortalité idem, mais tolerance cefazoline nettement meilleure





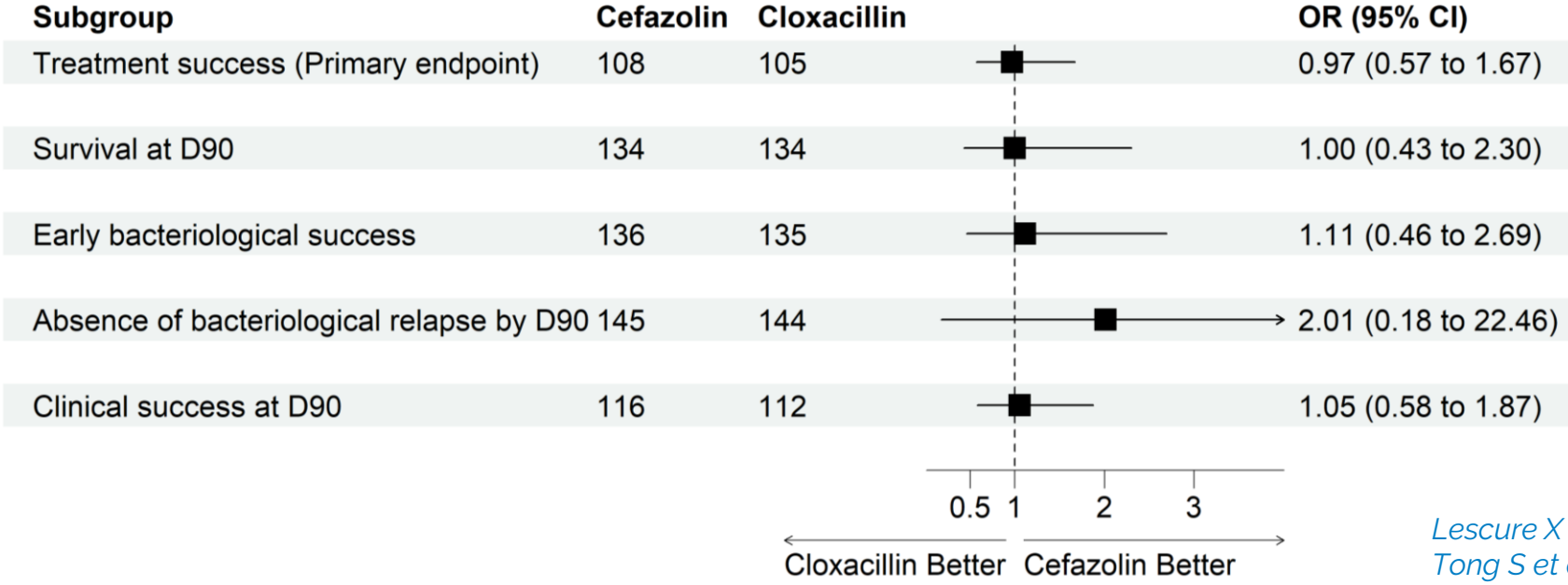
Prosty C et al. Clin Microbiol Infect 2025

3. Etudes randomisées (CLOCEBA, SNAP): efficacité idem, mais tolerance cefazoline meilleure



75% cefazolin vs 75.5% cloxacillin

72.2% cefazolin vs 70.1% cloxacillin

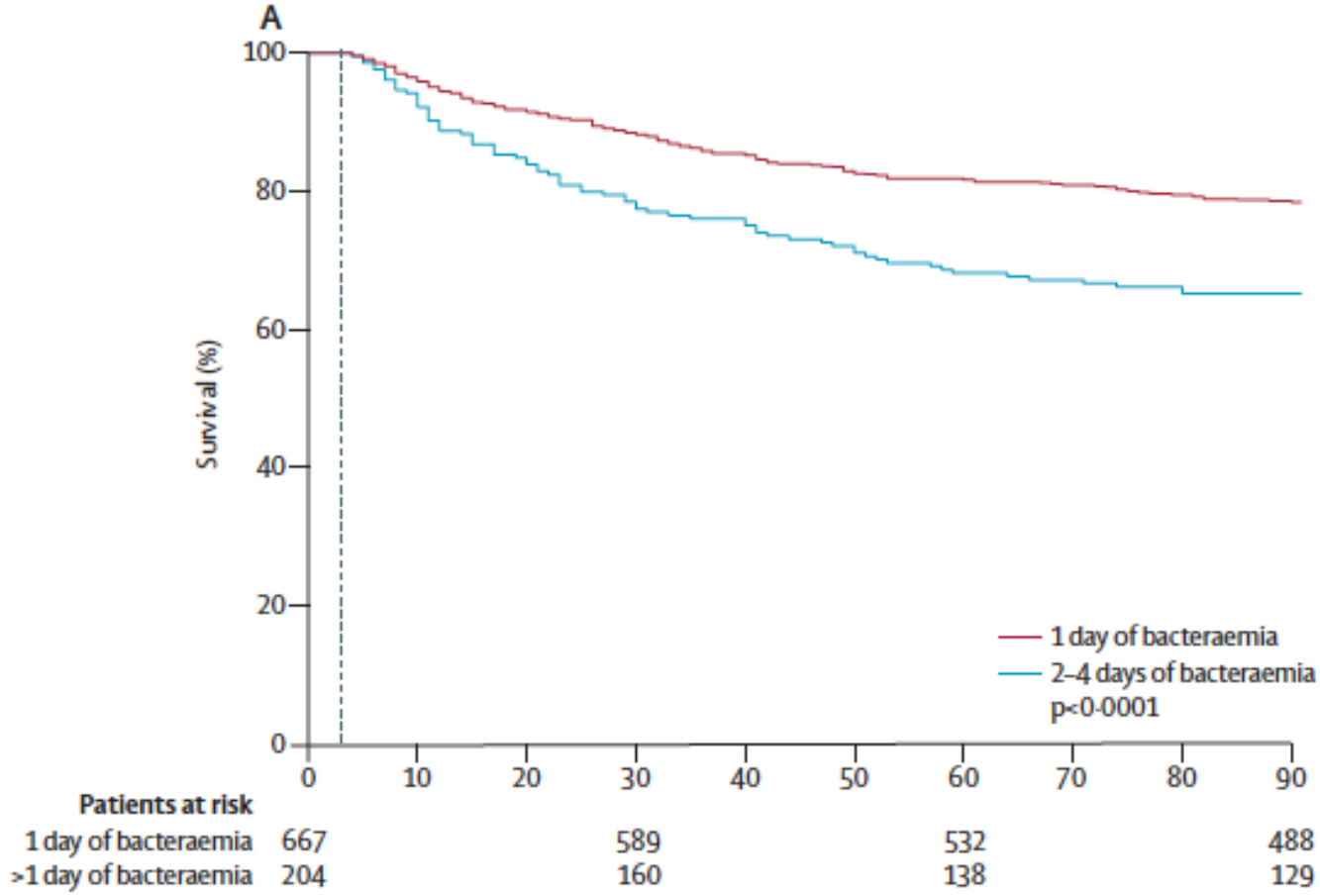


Lescure X et al (Lancet, in press).
Tong S et al. (New Eng J Med, in press)

Defining persistent *Staphylococcus aureus* bacteraemia: secondary analysis of a prospective cohort study

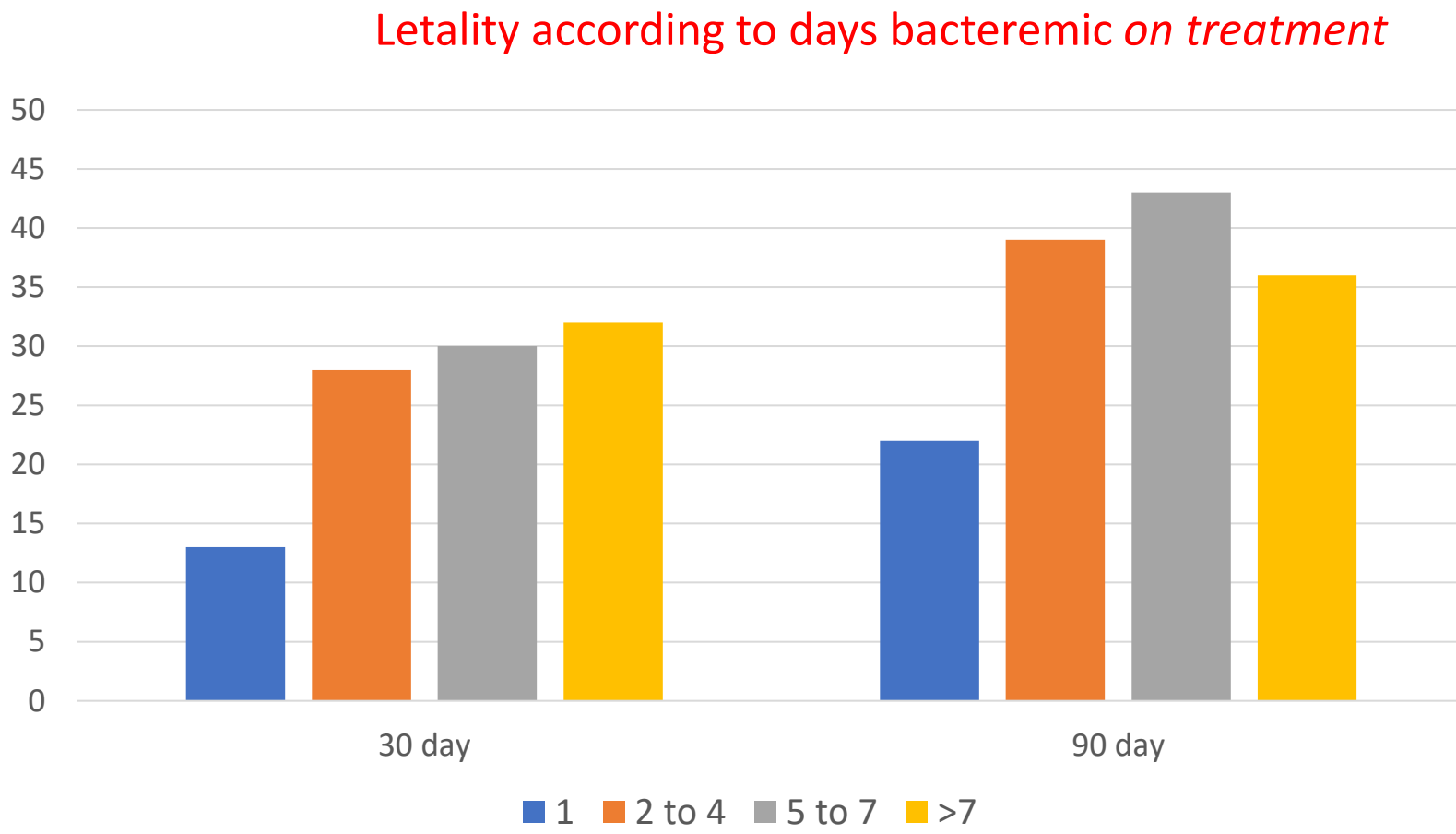
*Richard Kuehl, Laura Morata, Christian Boeing, Isaac Subirana, Harald Seifert, Siegbert Rieg, Winfried V Kern, Hong Bin Kim, Eu Suk Kim, Chun-Hsing Liao, Robert Tilley, Luis Eduardo Lopez-Cortés, Martin J Llewelyn, Vance G Fowler, Guy Thwaites, José Miguel Cisneros, Matt Scarborough, Emmanuel Nsutebu, Mercedes Gurgui Ferrer, José L Pérez, Gavin Barlow, Susan Hopkins, Hugo Guillermo Ternavasio-de la Vega, M Estée Török, Peter Wilson, Achim J Kaasch, Alex Soriano, on behalf of the International Staphylococcus aureus collaboration study group and the ESCMID Study Group for Bloodstream Infections, Endocarditis and Sepsis**

987 patients with F-U blood cultures



Kuehl et al. Lancet Infect Dis 2020

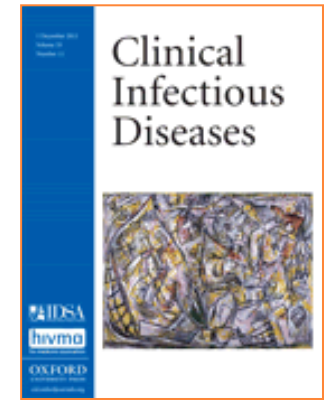
Quel seuil pour une bactériémie ‘à risque’ ?



Kuehl et al. Lancet Infect Dis 2020

Impact of an Evidence-Based Bundle Intervention in the Quality-of-Care Management and Outcome of *Staphylococcus aureus* Bacteremia

Luis E. López-Cortés,[1,a] Maria Dolores del Toro,[1,2] Juan Gálvez-Acebal,[1,2] Elena Bereciartua-Bastarrica,[3] María Carmen Fariñas,[4] Mercedes Sanz-Franco,[5] Clara Natera,[6] Juan E. Corzo,[7] José Manuel Lomas,[8] Juan Pasquau,[9] Alfonso del Arco,[10] María Paz Martínez,[11] Alberto Romero,[12] Miguel A. Muniain,[1,2,14] Marina de Cueto,[1,2] Álvaro Pascual,[1,2,13] and Jesús Rodríguez-Baño,[1,2,14] for the REIPI/SAB group[b]



Méthodes

- Définition de **critères de qualité de prise en charge (littérature)**
    1. associés au **pronostic**
    2. **modifiables**

- **Intervention**
    1. **formation des prescripteurs** (12 CHU/CHG) sur ces 6 critères
    2. **visite systématique infectiologues** si hémocultures isole '*S. aureus*'

- **Mesure 'avant-après'**
    1. **indicateurs** de qualité de prise en charge
    2. **survie** (J14, J30)

Lopez-Cortés L et al. Clin Infect Dis 2013

Critères de qualité de la prise en charge:
1. antibiothérapie

Early use of intravenous cloxacillin for MSSA as definitive therapy	Definitive therapy with intravenous cloxacillin (at least 2 g every 6 h or adjusted based on renal function in renal failure) in cases of methicillin-susceptible strains (allergic patients excluded). Treatment should be started within the first 24 h after methicillin sensitivity was available. For hemodialysis patients, cefazolin 2 g after each hemodialysis session was acceptable

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Adjustment of vancomycin dose according to trough levels	Measurement of trough levels of vancomycin in patients treated for at least 3 d with this antibiotic and adjustment of dose in order to achieve plasma trough levels between 15 and 20 mg/L in survivors

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Adjustment of vancomycin dose according to trough levels	Measurement of trough levels of vancomycin in patients treated for at least 3 d with this antibiotic and adjustment of dose in order to achieve plasma trough levels between 15 and 20 mg/L in survivors
Treatment duration according to the complexity of infection	Duration of antimicrobial therapy of at least 14 d for uncomplicated bacteremia and 28 d for complicated bacteremia. Sequential oral treatment with fluoroquinolone plus rifampin, trimethoprim-sulfamethoxazole, or linezolid was considered accepted in selected cases

Critères de qualité de la prise en charge:
2. autres mesures

Quality-of-Care Indicator	Definition
Follow-up blood cultures	Performance of control blood cultures 48–96 h after antimicrobial therapy was started regardless of clinical evolution

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2. autres mesures

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Critères de qualité de la prise en charge: 2. autres mesures

Quality-of-Care Indicator	Definition
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Early source control	Removal of nonpermanent vascular catheter whenever the catheter was suspected or confirmed as the source of SAB, or drainage of an abscess in <72 h
Echocardiography in patients with clinical indications	Performance of echocardiography in patients with complicated bacteremia (see definition in Methods) or predisposing conditions for endocarditis

'**Bactériémie compliquée**': **endocardite**, foyers **infectieux 'métastatiques', hémoc + après 72 h ATB efficace *in vitro***, matériel **endovasculaire maintenu**

Lopez-Cortés L et al. Clin Infect Dis 2013

Table 4. Adherence to Quality-of-Care Indicators

Quality-of-Care Indicator	Preintervention Period	Intervention Period
Follow-up blood culture	131/214 (61.2)	159/198 (80.3)
Source control	86/122 (70.2)	105/115 (91.3)
Echocardiography	76/144 (52.8)	74/101 (73.3)
Early cloxacillin in MSSA	120/211 (56.9)	124/174 (71.3)
Vancomycin dosing	23/49 (46.9)	30/54 (55.6)
Treatment duration	151/207 (72.9)	161/189 (85.2)

Lopez-Cortés L et al. Clin Infect Dis 2013

Table 7. Multivariate Analyses of Variables Associated With 14- and 30-Day Mortality Among Patients With *Staphylococcus aureus* Bacteremia

Variables	OR (95% CI)	*P* Value
14-day mortality		
Age >60 y	2.97 (1.51–5.87)	.002
Pitt score >2	3.04 (1.74–5.33)	<.001
High-risk source[a]	2.80 (1.32–5.92)	.007
Intervention	0.49 (.28–.87)	.016
30-day mortality		
Age >60 y	3.48 (1.89–6.41)	<.001
Pitt score >2	2.34 (1.40–3.92)	.001
High-risk source[a]	3.11 (1.54–6.26)	.001
Intervention	0.59 (.36–.97)	.04

Pitt score = score gravité adapté aux bactériémies

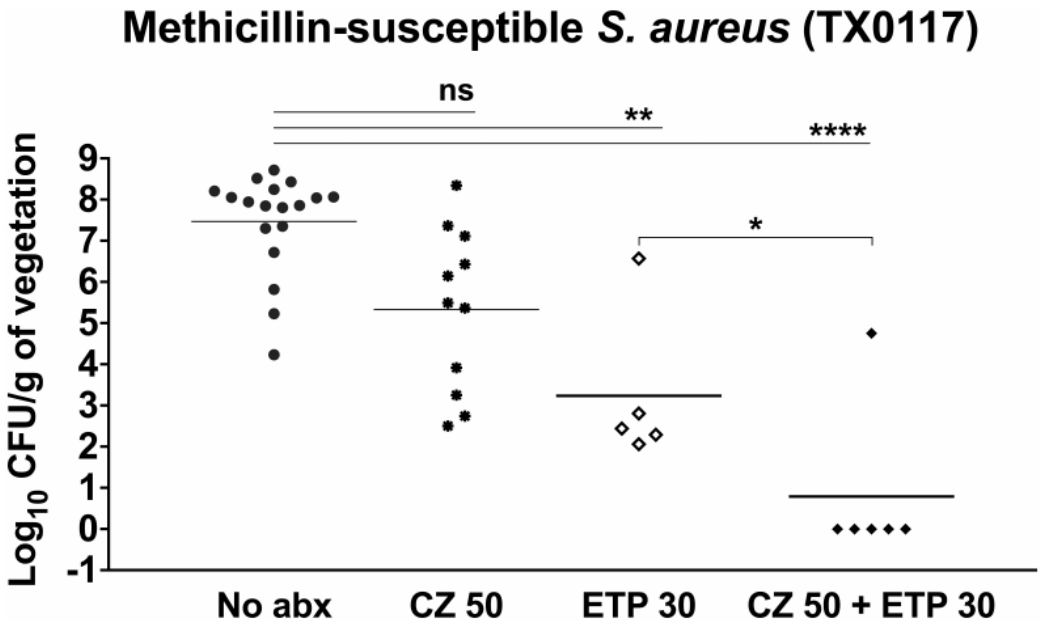
[a]High-risk source includes endovascular sources different than catheter, endocarditis, nervous central system infections, intra-abdominal infections,

Lopez-Cortés L et al. Clin Infect Dis 2013

Traitement de sauvetage des bactériémies à SAMS persistantes à J7 de traitement optimisé

Cefazolin and Ertapenem Salvage Therapy Rapidly Clears Persistent Methicillin-Susceptible *Staphylococcus aureus* Bacteremia

Erlinda R. Ulloa,[1,2] Kavindra V. Singh,[3,4] Matthew Geriak,[5] Fadi Haddad,[6] Barbara E. Murray,[3,4] Victor Nizet,[1,7] and George Sakoulas[1,5]



- Petite série retrospective (n=11)

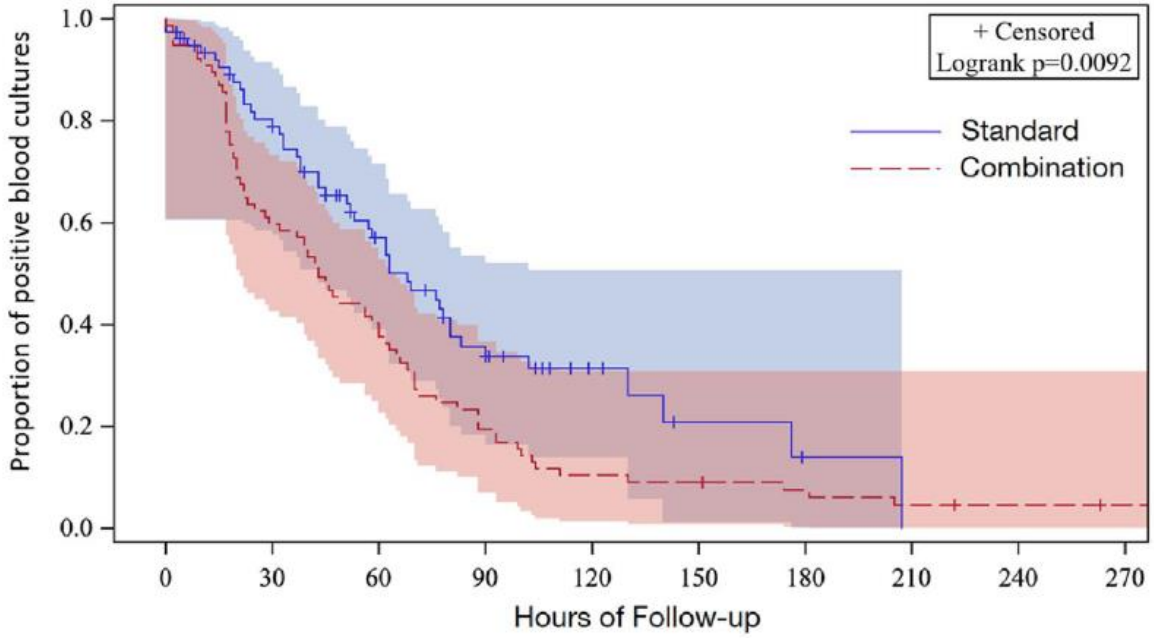
- Données très spectaculaires dans l'endocardite expérimentale à SAMS

Ulloa CID 2020
Smelter AAC 2022

Sauvetage des bactériémies persistantes à SAMS

Carbapenem combination therapy versus standard of care for persistent methicillin-susceptible *Staphylococcus aureus* bacteraemia

Sunish Shah [1,2]*, Lloyd G. Clarke[1,2], Justin Ludwig[3], Sarah Burgdorf[4], Ricardo D. Arbulu Guerra[4] and Ryan K. Shields [1,4]



Rétrospective, multicentrique (n=238)

Appariement

- **Stérilisation + rapide des hémocultures si ertapeneme rajouté à cefazoline ou péni anti-staphylocoque**

- **Pas de difference sur la survie**

Shah S et al, J Antimicrob Chemother 2024

Traitement de sauvetage des bactériémies persistantes à SARM

Use of Antistaphylococcal β-Lactams to Increase Daptomycin Activity in Eradicating Persistent Bacteremia Due to Methicillin-Resistant *Staphylococcus aureus*: Role of Enhanced Daptomycin Binding

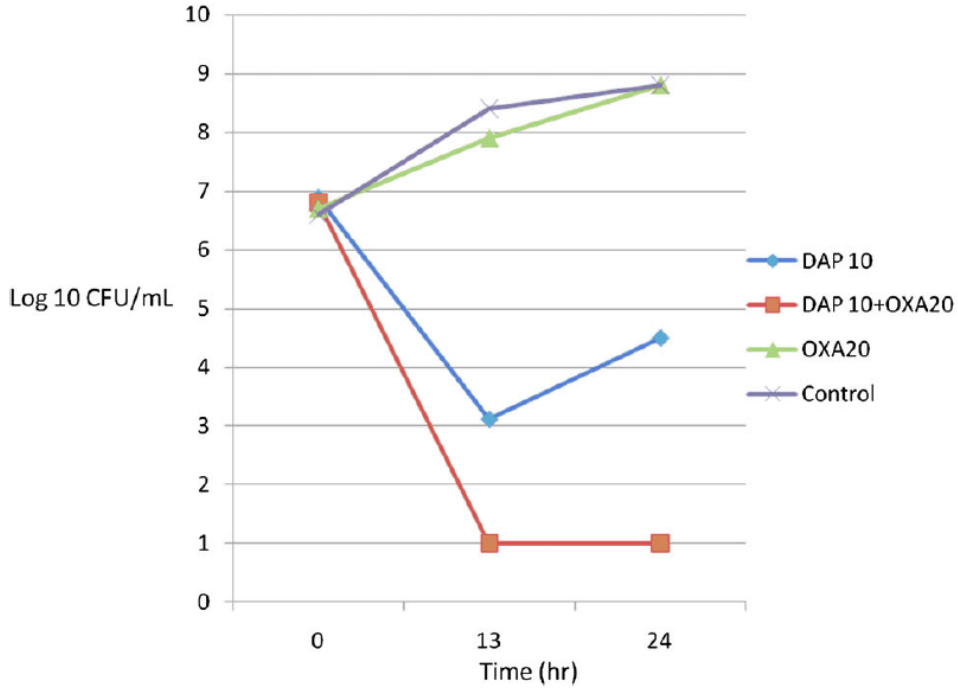
Abhay Dhand,[1] Arnold S. Bayer,[3,4] Joseph Pogliano,[5] Soo-Jin Yang,[3,4] Michael Bolaris,[3] Victor Nizet,[5] Guiquing Wang,[2] and George Sakoulas[1,5,6]

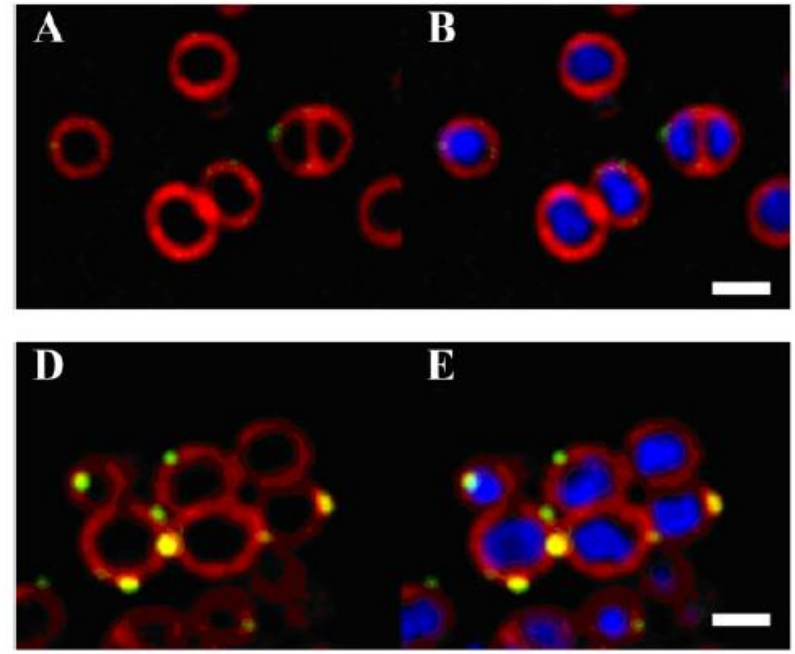
- **7 patients with persistent MRSA bacteremia (7-22 days)**
  - No issue with source control or foreign devices
  - MIC daptomycin & vancomycin ≤ 1 mg/L (6/7)
  - 'optimal' antistaphylococcal combinations

  => *All successfully controlled with oxacillin + daptomycin*

Dhand A et al. Clin Infect Dis 2011

Traitement de sauvetage des bactériémies persistantes à SARM





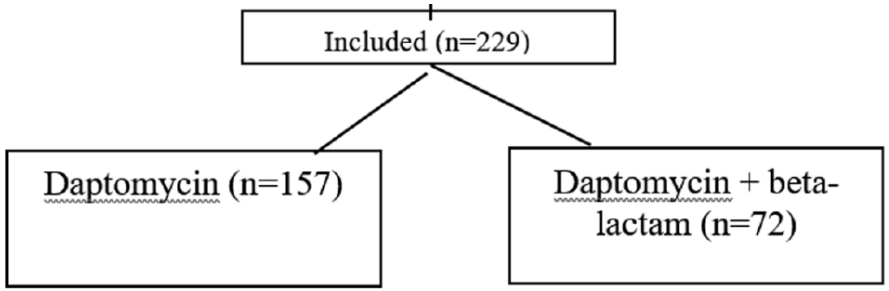
Dhand A et al. Clin Infect Dis 2011

Traitement de sauvetage des bactériémies à SARM

Daptomycin Plus β-Lactam Combination Therapy for Methicillin-resistant *Staphylococcus aureus* Bloodstream Infections: A Retrospective, Comparative Cohort Study

Sarah C. J. Jorgensen,[1] Evan J. Zasowski,[1,2] Trang D. Trinh,[1,3] Abdalhamid M. Lagnf,[1] Sahil Bhatia[1] Noor Sabagha,[1] Jacinda C. Abdul-Mutakabbir,[1] Sara Alosaimy,[1] Ryan P. Mynatt,[4] Susan L. Davis,[1,5] and Michael J. Rybak[1,4,6]

- Observational study, 2008-2018
- Primary criteria = day 60 mortality or relapse

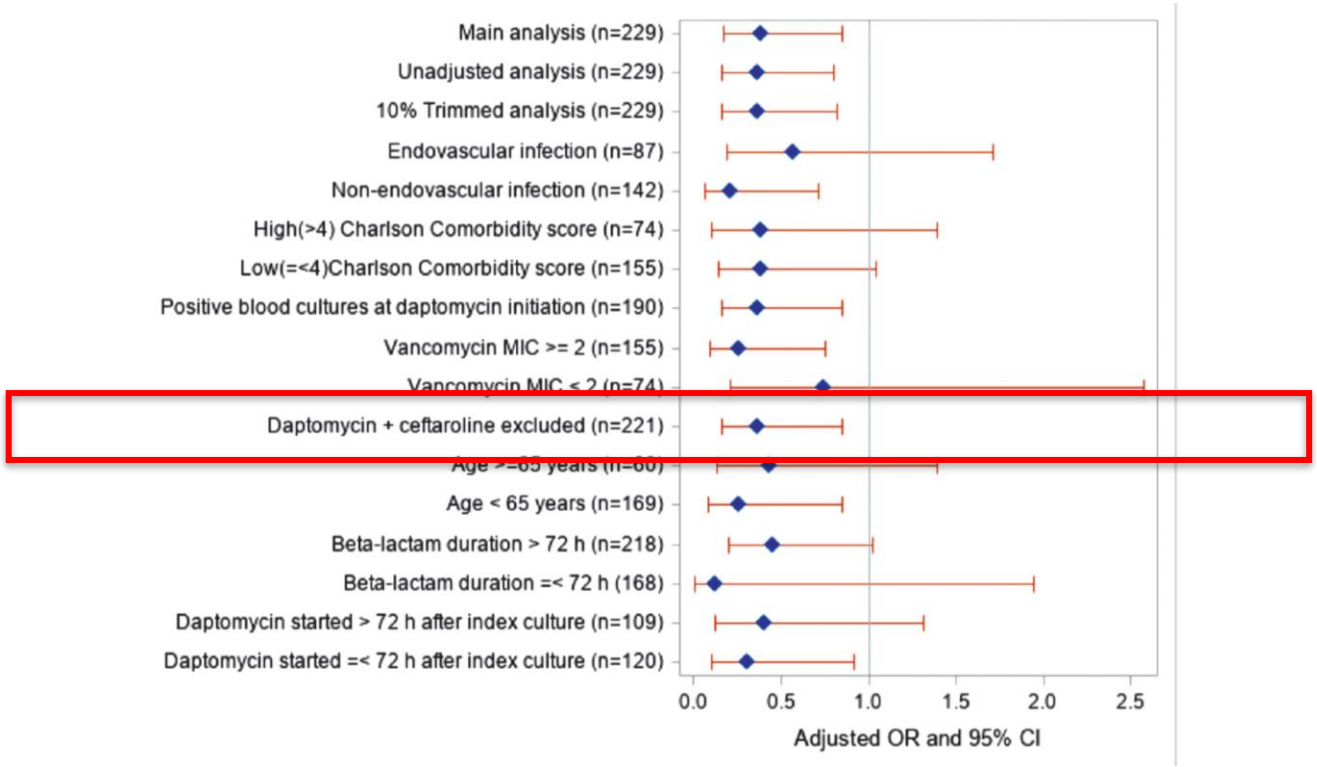


Reason for the addition of a β-lactam, n (%)	…
Empiric	33 (45.8)
Anticipated synergy	25 (34.7)
Concurrent infection	14 (19.4)

β-Lactam, n (%)	…
Cefepime	31 (43.1)
Cefazolin	18 (25.0)
Ceftaroline	7 (9.7)
Ceftriaxone	7 (9.7)

Jorgensen SCJ et al. Clin Infect Dis 2020

Traitement de sauvetage des bactériémies à SARM



Jorgensen SCJ et al. Clin Infect Dis 2020

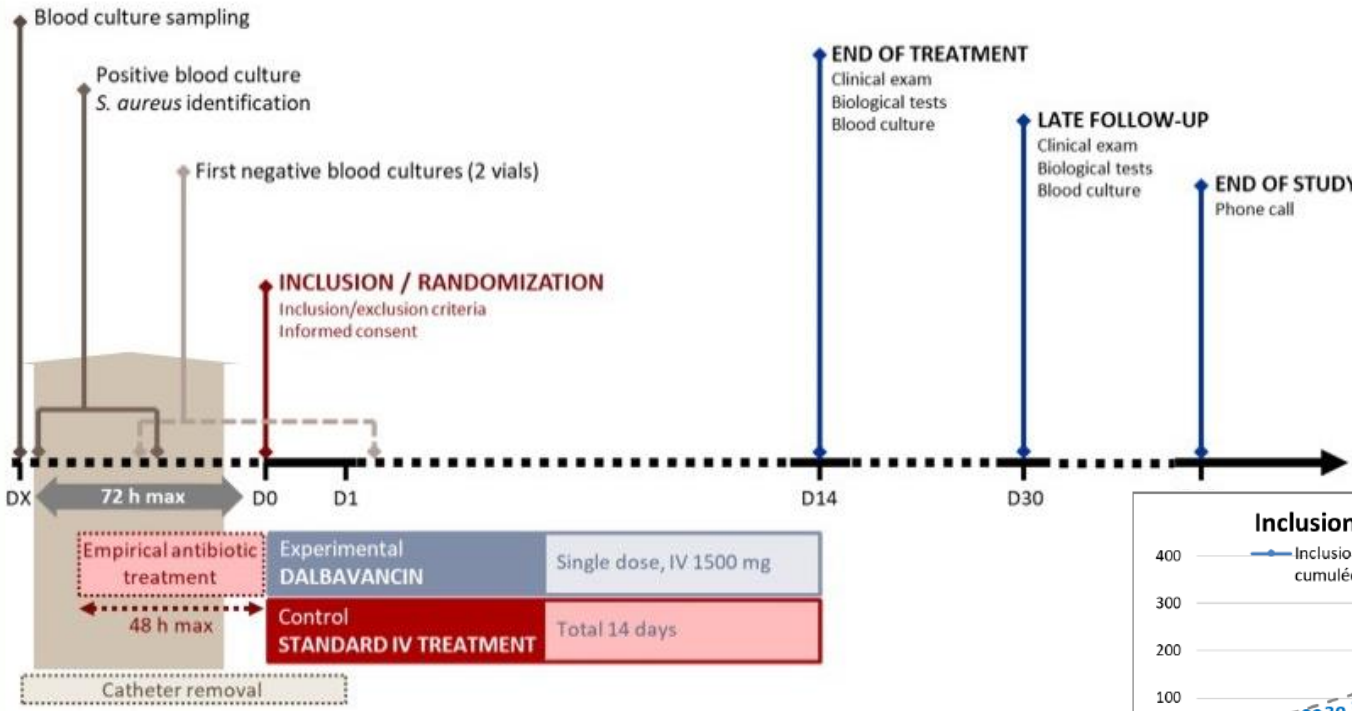
Perspectives

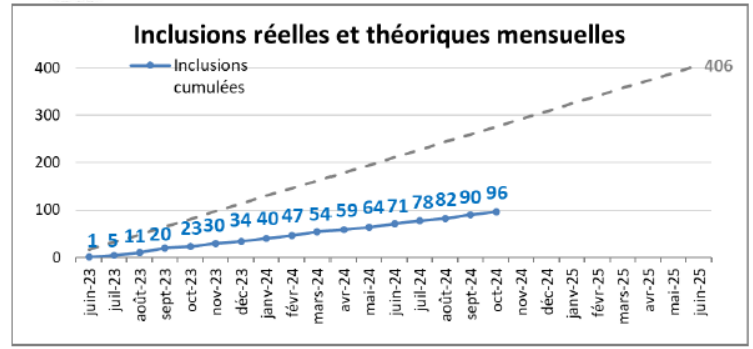
Newsletter n°16 - Octobre 2024

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

DALICATH

Essai contrôlé en ouvert randomisé évaluant une dose unique de Dalbavancine vs antibiothérapie standard pour le traitement des bactériémies à Staphylococcus aureus associées à un cathéter





CORE PROTOCOL

Staphylococcus aureus Network Adaptive Platform trial (SNAP)

Essai adaptatif en plateforme: Kézako

Répondre vite à des questions de recherche prioritaires

Inclusions faciles et à haut débit

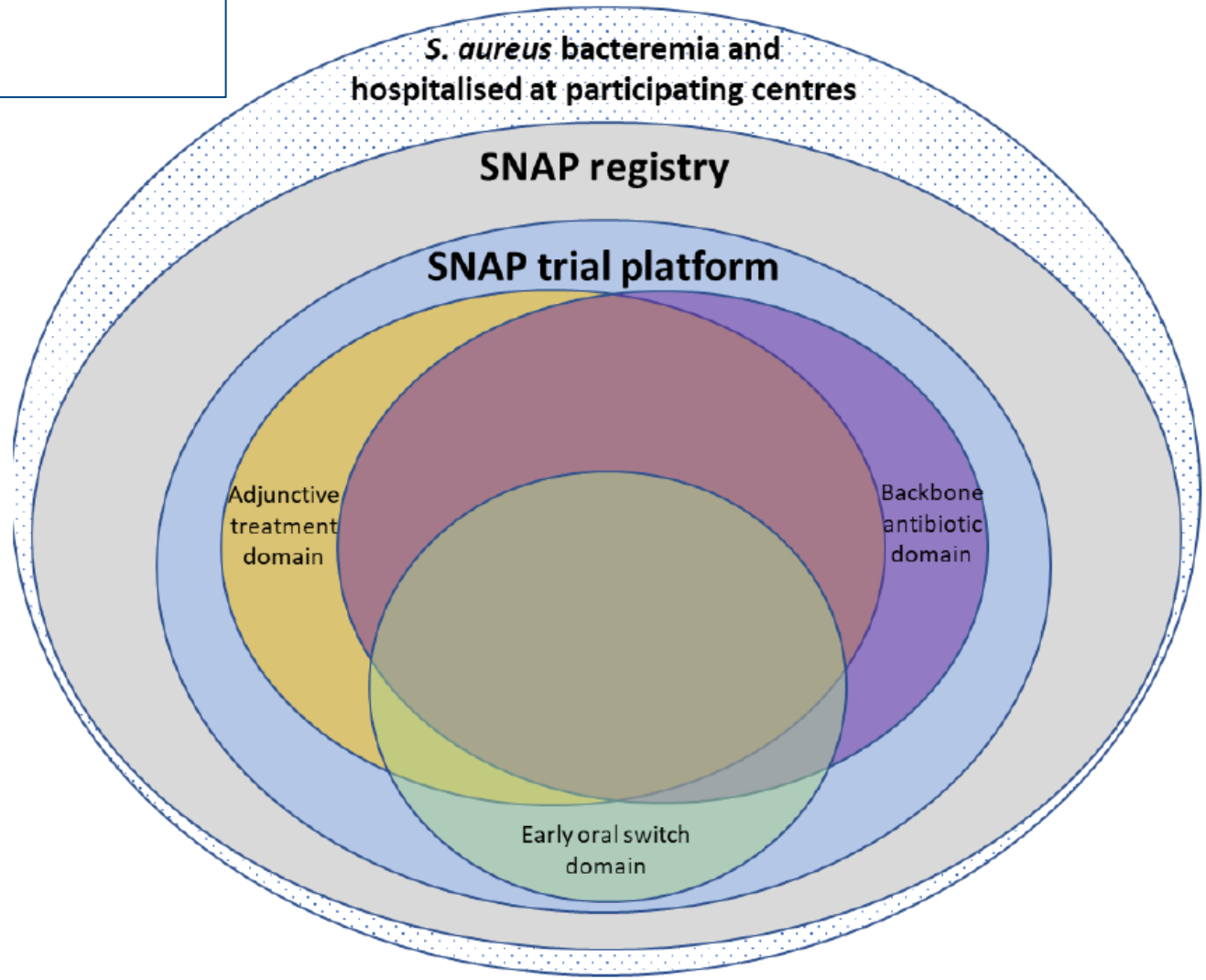
- Maladie non rare
- Critères inclusion simples
- Gestion de l'étude nichée dans le soin courant
- Plateforme de recherche durable

Adaptabilité

- Possibilité de changer les questions de recherche en cours de route
- Analyses intermédiaires multiples pré-programmées
- veille active de la littérature
- Conseils scientifiques multiples

Critères inclusion:

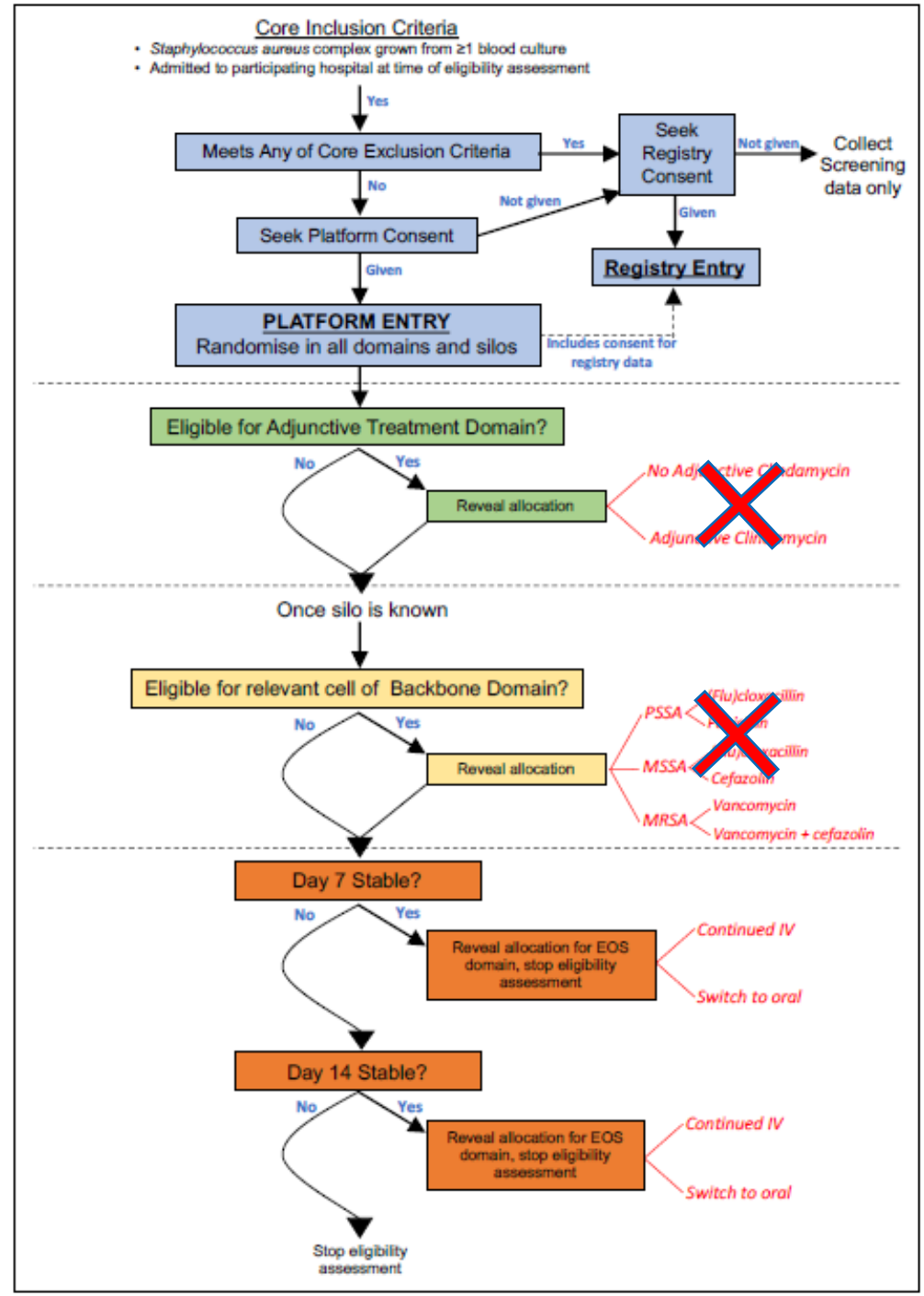
- Hc + *S. aureus*
- Prélevée <72h
- Patient OK



Patient recruitment: Registry and Platform entry

SNAP
Staphylococcus aureus
Network Adaptive Platform

SNAP
Staphylococcus aureus
Network Adaptive Platform

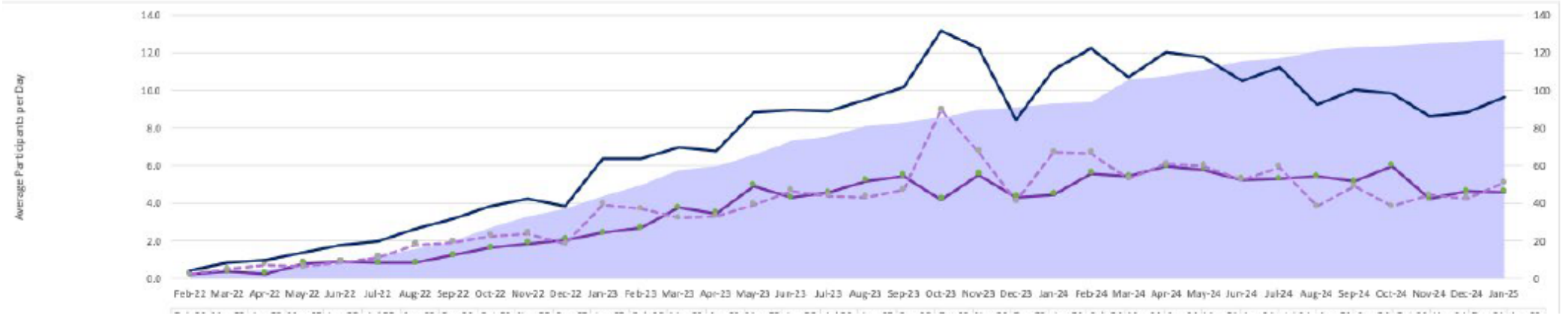


SNAP worldwide

SNAP Global – recruitment

- At the moment, **126 hospitals** are activated for the SNAP trial across **8 regions**.
- Global Platform: **3984** participants
- Global Registry: **4247** participants

Data cut-off 5-Feb-2025



National Coordinating Team France

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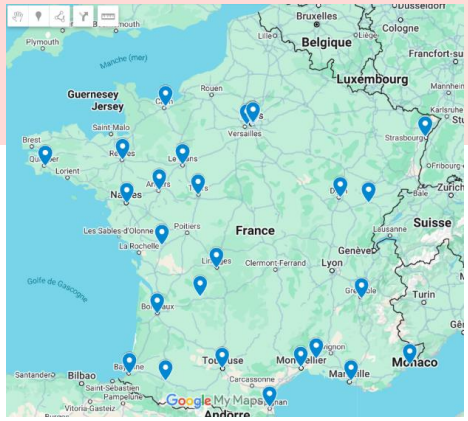
Project manager, Rennes University

Local changes to the SNAP protocol

- Country-specific pharmaco-economic analyses

National Coordinating Team France



- 32 sites, target enrolment 1000 patients
- Funding: National Research Agency for Aids & Emerging Infectious Diseases
- National Network for Clinical Research in IDs
- Pending CTIS authorization
- Expected enrolment start: November 2025
- First RCT: IV phages for persistent bacteremia ?

ecraid

Messages : Bactériémies à *S. aureus*

- **Une vraie maladie infectieuse émergente**
- **80% mortalité spontanée**
- **Possibilité de sauver 80% des patients si:**
  - **ATB bien choisis et rapides**
  - **Éradication foyer(s) infectieux & matériel**
  - **Monitoring durée bactériémie (hémoc contrôle 48 h)**
- **Sauvetages pour bactériémies réfractaires**
  - **Céfazoline + ertapénème pour SAMS ?**
  - **Daptomycine + bêtalactamine pour SARM**