Infection, Antimicrobien
Modelisation Evolution

Endocardite infectieuse
Prise en charge thérapeutique

Pr. Xavier Duval

Hôpital Bichat Claude Bernard, Université Paris cité

Fiche de synthèse RCP Bichat Endocardite Paris

Monsieur D. Christian, 53 ans

Poids : 90 kg Taille 170 cm	Clairance: 60 ml/min Créatinine : 117 µmol/L	Allergies : IODE ➢ choc anaphylactique

Histoire de la maladie :

. 2011:
Remplacement valvulaire aortique par valve mécanique + mise en place d'un tube de DACRON de 30 mm pour sténose de l'aorte. Anticoagulation efficace dès lors par AVK (Préviscan).

. Le 05 septembre 2019 :
Malaise avec score de Glasgow à 13. Au scanner cérébral non injecté il existe une **hémorragie sous arachnoïdienne** fronto-pariéto-temporale gauche Fisher 3 et des hypodensités temporo-pariéto-occipitales bilatérales séquellaires. Absence de cause sous-jacente retrouvée à l'hématome sur les IRM cérébrale du 10 juillet 2019.
Le 08 septembre: mise en évidence d'anévrysme mycotique à l'artériographie.

Hospitalisation en Réanimation en à la Fondation Rothschild du 09 au 15/10/2019 :
Bactériémie à ***Streptococcus lutetiensis*** sur les hémocultures périphériques du 08/10 et du 09/10/2019 qui dans le

contexte d'hémorragies cérébrales **sur anévrysme mycotique** font suspecter fortement une endocardite.

Le bilan initial retrouve:
. A l'ETT + ETO du 08/10: absence de végétation.
. TDM TAP le 11/10 qui montre: adénomégalie médiastinale et iliaque externe droite. Foie: hypodensité de 7 mm. Stigmates de chirurgie colique.

Début d'une antibiothérapie par **AMOXICILLINE 12 g/j + GENTAMICINE (3 jours) + RIFAMPICINE le 09/10/2019.**
Traitement de l'anévrysme mycotique pariétal gauche par artério-embolisation le 09/10/2019 (Dr CICIO).

Hospitalisé en maladies infectieuse à l'hôpital Bichat le 15/10/2019.

Localisations infectieuses : Endocardite sur prothèse à *Streptococcus lutetiensis* compliquée d'anévrysmes mycotiques cérébraux et hépatique	**Porte d'entrée :** **-** Coloscopie + FOGD : Ulcère pré pylorique et bulbite érosive. - Iléocoloscopie normale - En cours : Pano dentaire + consultation stomato + cs procto.

Imagerie médicale	
ETT – ETO 16/10 : - FEVG normale - Prothèse mécanique aortique de fonctionnement normal sans image d'addition. - **On retrouve l'image vide d'écho de 5x9 mm non circulante non pulsatile décrite dans le CR ETO d'il y a 7 jours semblant tout à fait stable**, un peu à distance du trigone mitro-aortique non typique d'abcès, pouvant correspondre au Valsalva, à confronter à l'imagerie nucléaire et si possible aux autres compte rendu post opératoires - Epaississement de la paroi postérieure de l'aorte ascendante de 1 cm non circulant non pulsatile. - Absence d'image d'addition sur les autres valves natives.	

TDM TAP 11/10 : adénomégalie médiastinale et iliaque externe droite. Foie: hypodensité de 7 mm. Stigmates de chirurgie colique.

Angioscanner abdominale 26/10 : Trois faux anévrismes intra hépatiques distaux : Deux de l'artère hépatique gauche à destinée du segment II de respectivement 12 et 4 mm. 1 millimétrique du segment VII.

IRM cérébrale : séquelles hémorragiques bi-occipitales, ainsi qu'un stigmate d'hémorragie méningée de la convexité gauche. Pas de lésion aiguë.

Imagerie nucléaire 17/10 :

- TEP-TDM : Valves non examinable. Hyperfixation de l'anastomose proximale du tube aortique. Intense hypermétabolisme recto-anale et de l'angle colique droit
- Scintigraphie aux leucoytes marquée : Foyer de recrutement leucocytaire de la partie proximale du tube aortique sus coronaire ave aspect de double contour (abcès ?) + Foyer de recrutement leucocytaire de la valve aortique

➔ Infection de la valve aortique et du tube aortique sus coronaire.

Monsieur D. Christian, 53 ans

- Est-ce une endocardite ? Diagnostic
- Faut-il faire un bilan d'extension ?
- Quelle prise en charge immédiate ?
  - Antibiotique
    - Initiation de l'antibiothérapie ?
      - Urgente / différée
  - Chirurgicale
- Quelle prise en charge ultérieure ?
- Comment éviter les récidives ?

Epidémiologie endocardite

Epidémiologie

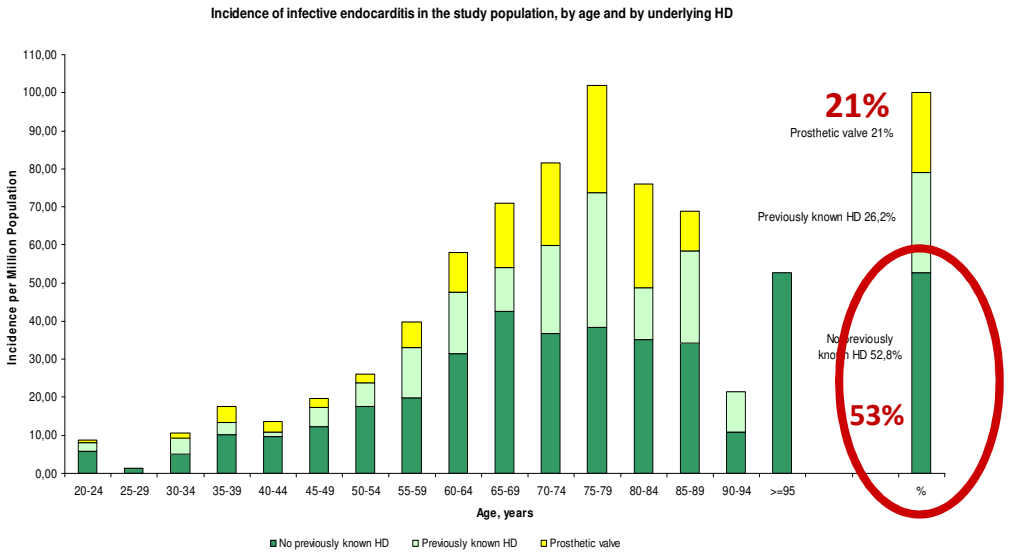
- **Incidence stable:** $30/10^6$/an soit 1400 cas /an

MAJOR ARTICLE

Incidence of infective endocarditis by age and by underlying HD

Preeminence of *Staphylococcus aureus* in Infective Endocarditis: A 1-Year Population-Based Survey

Christine Selton-Suty,[1] Marie Célard,[2] Vincent Le Moing,[3,4] Thanh Doco-Lecompte,[5] Catherine Chirouze,[6] Bernard Iung,[7,8] Christophe Strady,[9] Matthieu Revest,[10] François Vandenesch,[2] Anne Bouvet,[11] François Delahaye,[12,13] François Alla,[14] Xavier Duval,[8,15,16] Bruno Hoen,[6,17] and on behalf of the AEPEI Study Group[a]



Healthcare related IE: 25%

Selton Suty C, CID 2012; 54:1230-1239; Duval X, JACC 2012 ;59:1968-76

Clinical presentation, aetiology and outcome of infective endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) registry: a prospective cohort study

Gilbert Habib [1,2]*, Paola Anna Erba [3,4], Bernard Iung [5], Erwan Donal[6],

Table I Patient demographics and clinical characteristics

	Total ($n = 3116$)	Prosthesis+Repair ($n = 939$)	Native ($n = 1764$)	PM/ICD ($n = 308$)	*P*-value
Demography		**30%**	**57%**	**10%**	
Age (years)					
N	3116	939	1764	308	
Mean ± SD	59.25 ± 18.03	63.36 ± 16.81	55.61 ± 18.45	66.77 ± 14.11	<0.0001
Median (IQR)	63.0 (46.0–73.0)	67.0 (54.0–75.0)	58.0 (41.0–70.0)	69.0 (60.0–76.0)	<0.0001
Age ≥ 65 years	1443/3116 (46.3%)	538/939 (57.3%)	662/1764 (37.5%)	194/308 (63.0%)	<0.0001
Age ≥ 80 years	375/3116 (12.0%)	141/939 (15.0%)	163/1764 (9.2%)	56/308 (18.2%)	<0.0001
Females (%)	969/3116 (31.1%)	292/939 (31.1%)	553/1764 (31.3%)	86/308 (27.9%)	0.4901

ESC European Society of Cardiology
European Heart Journal (2019) **0**, 1–11
doi:10.1093/eurheartj/ehz620

JAMA | Original Investigation

Trends in Infective Endocarditis in California and New York State, 1998-2013

Nana Toyoda, MD; Joanna Chikwe, MD; Shinobu Itagaki, MD, MS; Annetine C. Gelijns, PhD; David H. Adams, MD; Natalia N. Egorova, PhD

Characteristic	2010-2013 (n = 20 820)	Annual Percentage Change, % (95% CI)
Disease type		
Native-valve endocarditis	14 248 (68.4)	−0.7 (−0.9 to −0.5)
Prosthetic-valve endocarditis	2875 (13.8)	1.3 (0.8 to 1.7)
Cardiac device-related endocarditis	848 (4.1)	8.8 (7.8 to 9.9)
Drug abuse-related endocarditis	2849 (13.7)	0.9 (0.4 to 1.3)
Mode of acquisition		
Community-acquired	10 159 (48.8)	−0.2 (−0.4 to 0.03)
Health care-associated	10 661 (51.2)	0.2 (−0.04 to 0.4)
Nosocomial	3185 (15.3)	−1.0 (−1.4 to −0.7)
Nonnosocomial	7476 (35.9)	0.8 (0.5 to 1.1)

Toyoda N, JAMA 2017

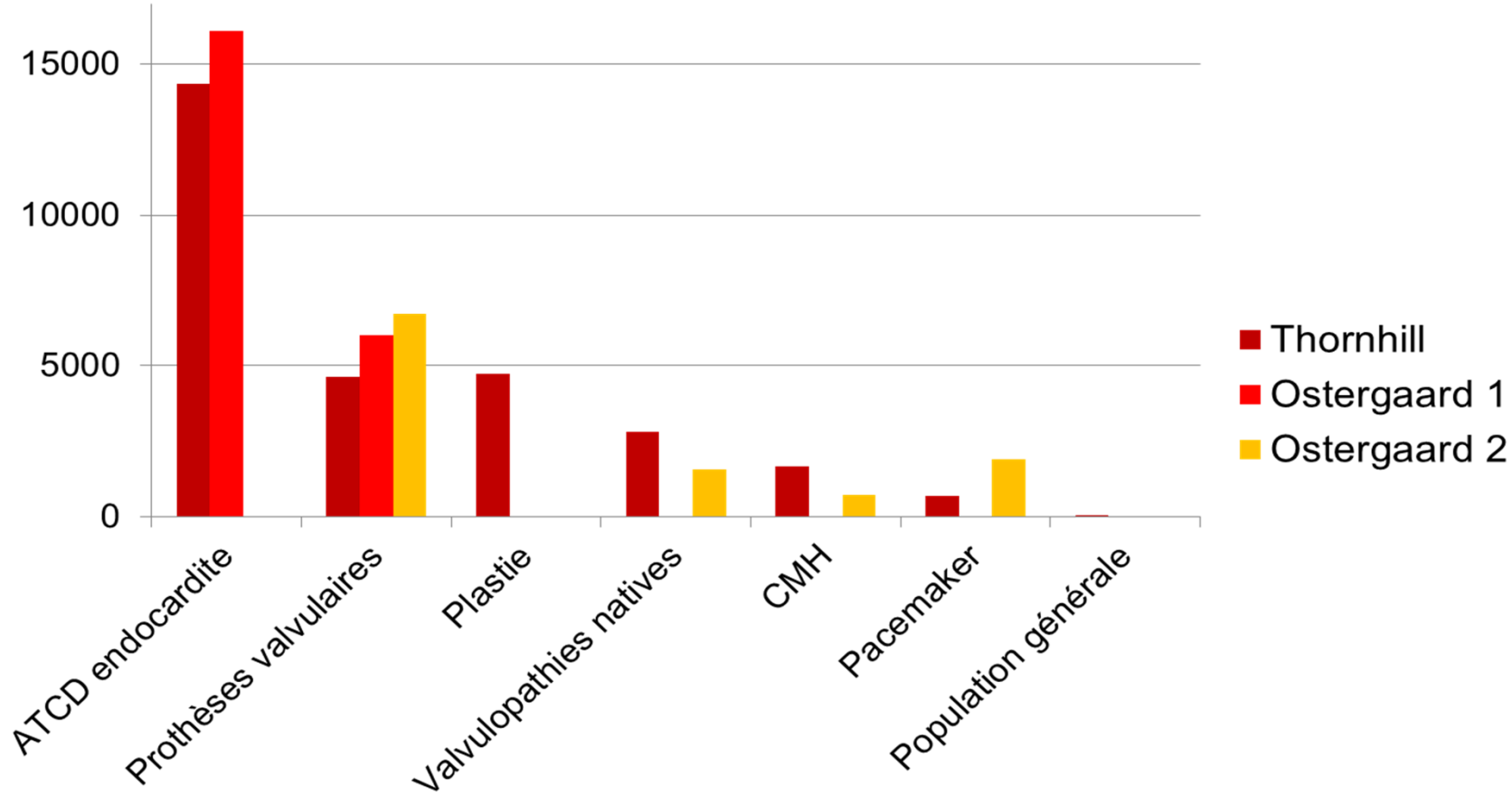
IE incidence

/ 100 000	Ostergaard L (Eur H J 2018) Ostergaard L (Eur H J 2019)	Thornhill (Eur H J 2018)
IE history	1 610	1 436
Prosthetic valve	670	453
Congenital heart valve	79	
CIED	189	68
Valve disorder	156	280
Hypertrophic cardiomyopathy	71	167
General population	16	3.62

Ostergaard L , Eur Heart J 2018
Thornhill MH, Eur Heart J. 2017
Ostergaard L , Eur Heart J 2019

Incidence de l'Endocardite selon la Cardiopathie

Incidence annuelle par **million**



Ostergaard L , Eur Heart J 2018
Thornhill MH, Eur Heart J. 2017
Ostergaard L , Eur Heart J 2019

Epidémiologie

- **Stabilité incidence:** 30/10^6/an soit 1400 cas /an
- 3ème causes d'infection mortelle (après sepsis, pneumonie)
- Rencontre **lésion valvulaire** / **bactériémie**

Mais modifications des caractéristiques de l'EI :

- Modification de l'hôte (valvulopathies/comorbidités)
- Modification des bactériémies

Location of IE

Location	Native valves	Prosthetic V.	Total n (%)
Aortic valve	55 (16%)	31(32%)	**86 (20%)**
Mitral valve	102 (30%)	18 (19%)	**120 (28%)**
Aortic + mitral valves	97 (29%)	25 (26%)	**122(28%)**
Tricuspid valve	31(9%)	2(2%)	33 (8%)
Pulmonic valve	0 (0.0%)	1(1.0%)	1 (0.2%)
Bilateral IE	36 (11%)	14 (14%)	50 (12%)
Pacemaker	10 (3%)	3 (3%)	**13 (3%)**
Undetermined	8 (2%)	3 (3%)	11 (2.5%)

Selton Suty C, CID 2012; 54:1230-1239; Duval X, JACC 2012 ;59:1968-76

Epidémiologie

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Mais modifications des caractéristiques de l'EI :

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- **Mortalité stable** : 15-20 %
- **Chirurgie valvulaire** **50 %**

TAVI

- 36% ⇨ 67% (2 ans)
- 15%

A Regueiro JAMA. 2016;316(10):1083-1092.

IE Micro organisms

Microorganism profile according to regions

Table 4. Microbiologic Etiology by Region in 2781 Patients With Definite Endocarditis

Cause of Endocarditis	No. (%) of Patients[a] Total Cohort (N=2781)	Patients Admitted Directly to Study Sites Only[b] (n=1558)	Region: North America (n=597)	South America (n=254)	Europe (n=1213)	Other (n=717)	*P* Value for the Difference Between Regions
Staphylococcus aureus	**869** (31)	487 (31)	256 (43)	43 (17)	339 (28)	231 (32)	<.001
Coagulase-negative staphylococcus	**304** (11)	161 (10)	69 (12)	18 (7)	156 (13)	61 (9)	.005
Viridans group streptococci	**483** (17)	288 (19)	54 (9)	66 (26)	198 (16)	165 (23)	<.001
Streptococcus bovis	**165** (6)	101 (7)	9 (2)	17 (7)	116 (10)	23 (3)	<.001
Other streptococci	**162** (6)	101 (7)	38 (6)	16 (6)	66 (5)	42 (6)	.86
Enterococcus species	**283** (10)	158 (10)	78 (13)	21 (8)	111 (9)	73 (10)	.05
HACEK	**44** (2)	26 (2)	2 (0.3)	6 (2)	19 (2)	17 (2)	.02
Fungi/yeast	**45** (2)	25 (2)	20 (3)	3 (1)	13 (1)	9 (1)	.002
Polymicrobial	**28** (1)	23 (2)	8 (1)	1 (0.4)	13 (1)	6 (0.8)	.60
Negative culture findings	**277** (10)	122 (8)	41 (7)	51 (20)	123 (10)	62 (9)	<.001
Other	**121** (4)	66 (4)	22 (4)	12 (5)	59 (5)	28 (4)	.61

43% 24% 28%

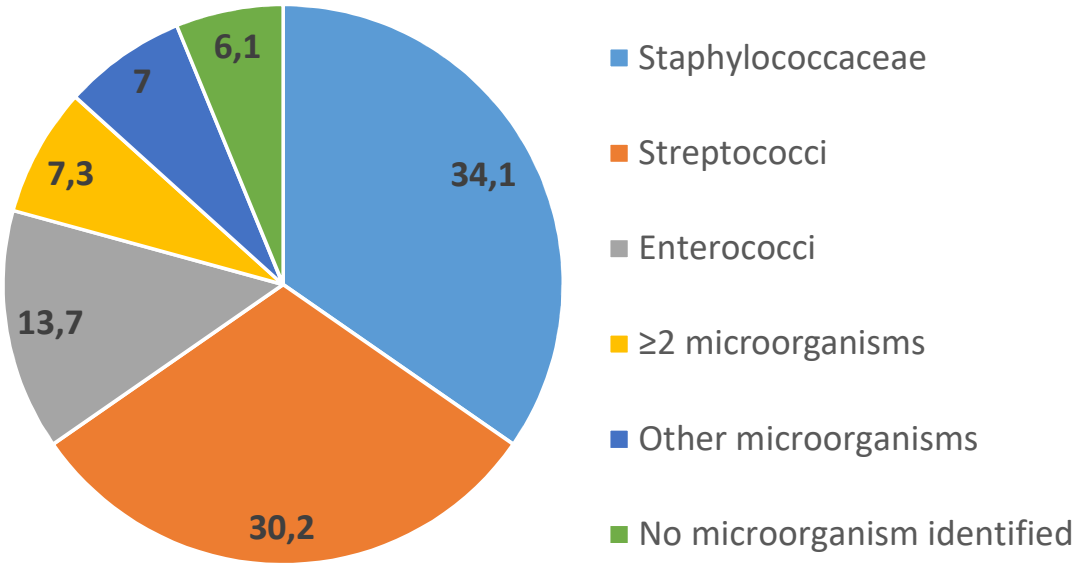
30% 47% 40%

Murdoch Arch Intern Med 2009

Endocarditis responsible microorganisms

1194 IE since January 1st 2017 (French AEPEI IE registry)

Microorganisms	
Streptococcaceae	544 (45.6)
Streptococci	361 (30.2)
Oral streptococci	198 (16.6)
Group D streptococci	121 (10.1)
Enterococci	164 (13.7)
Community-acquired enterococci	118 (9.9)
Enterococcus faecalis	154 (12.9)
Staphylococcaceae	407 (34.1)
Staphylococcus aureus	319 (26.7)
Coagulase-negative Staphylococci	88 (7.4)
Other microorganisms	83 (7.0)
≥2 microorganisms	87 (7.3)
No microorganism identified	73 (6.1)



Goehringer F. Clin Infect Dis 2024

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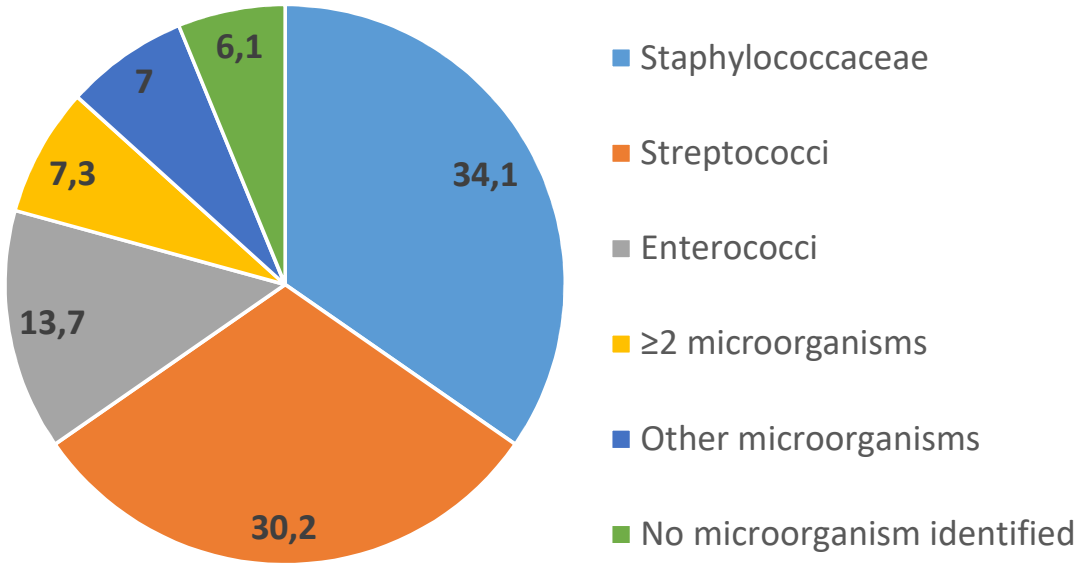

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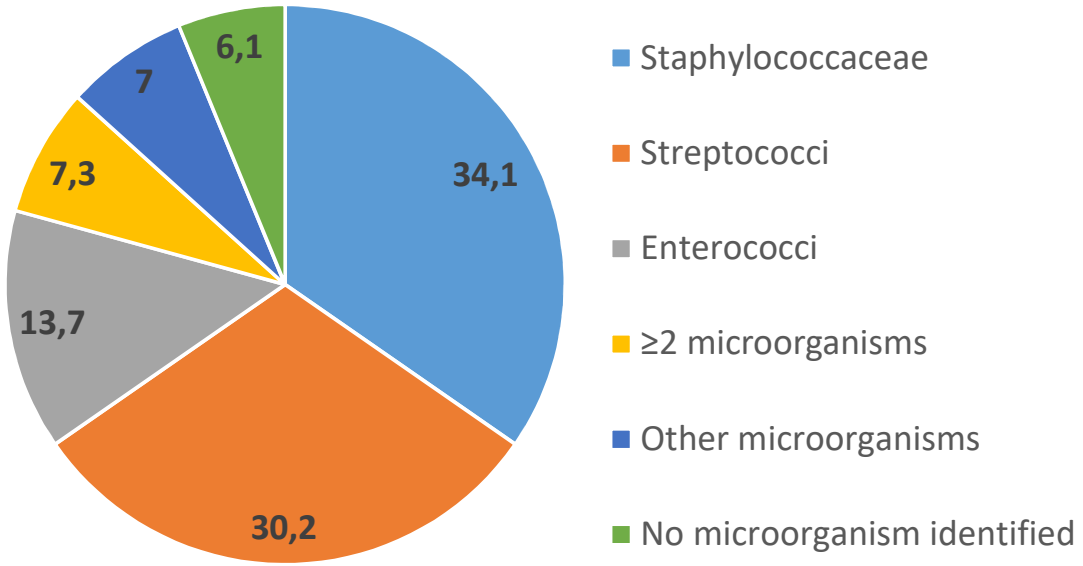
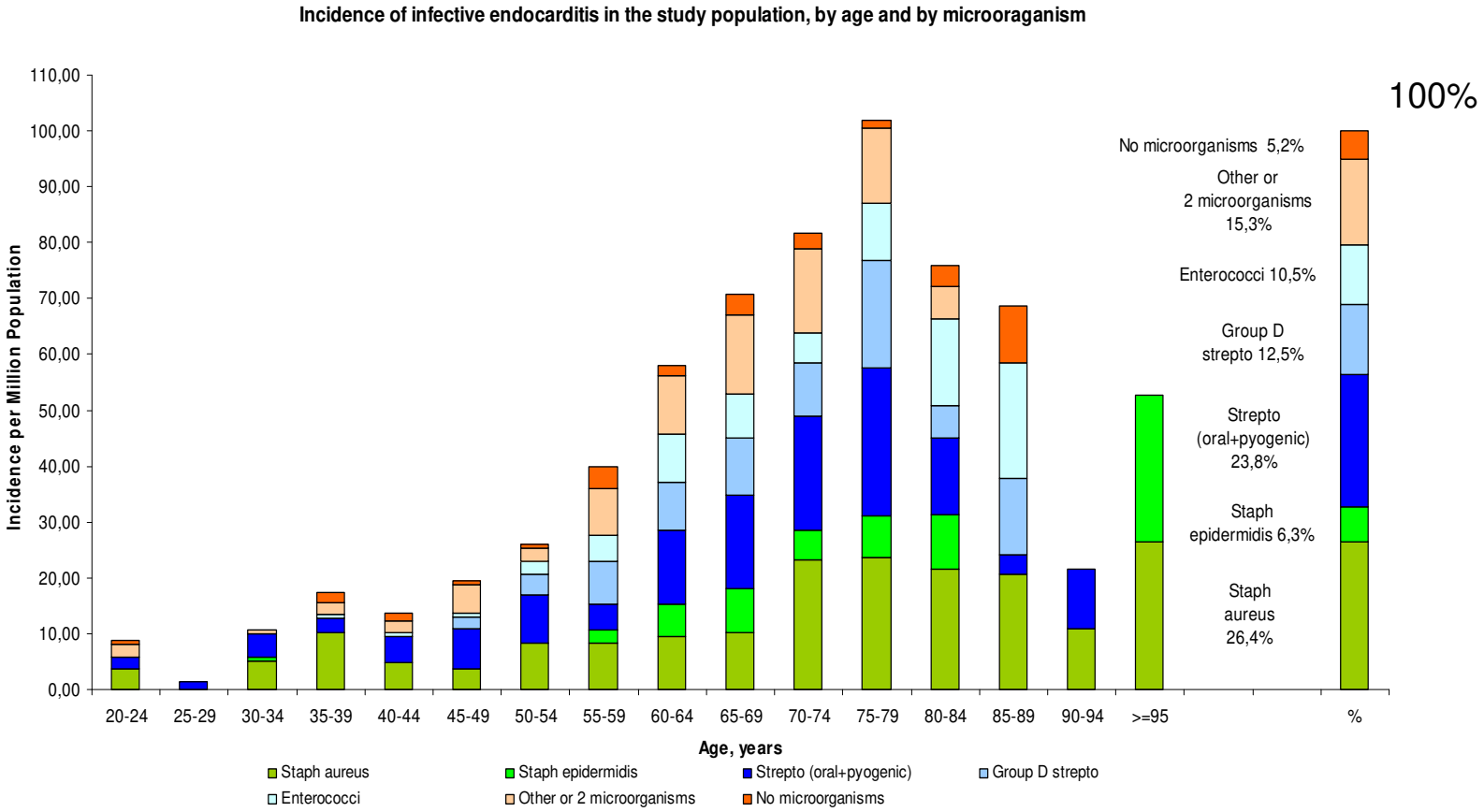


Goehringer F. Clin Infect Dis 2024

Infective Endocarditis

- Which microorganisms ?
  - Identified in 80-90% of definite IE
  - Gram positive cocci in 80% of IE
  - Distribution varies according to
    - Age
    - Cardiac valve
    - Mode of acquisition
    - Source of infection

Endocarditis responsible microorganisms and age



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Endocarditis responsible microorganisms and valve

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3116 IE: positives blood cultures

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3116 IE: positives blood cultures

	Native valve	Prosthesis	CIED
S. aureus (%)	33	23	46.5
Coag Neg Staph	9	18.5	19
Strepto *viridans*	15	10	3
Enterococci	13	22	13
S. gallolyticus	8	6	4
Gram Neg Bacilli	4	2.5	6

Endocarditis responsible microorganisms and valve

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Endocarditis responsible microorganisms and valve / acquisition modes

	Native valve endocarditis (78%)			
	Community-acquired IE	Health care-associated 18%		Drug abusers
Pathogens	55%	Nosocomial 15%	Non-nosocomial 3%	5%
Staphylococcus aureus	20/20 %	44/47%	25/42%	68/81%
CN Staphylococci	4/6%	12/15%	15/25%	0/3%
Oral streptococci*	26/28%	7/11%	0/6%	4/10%
Streptococcus bovis **	10/18%	3 %	3/8%	0/1%
Enterococcus	9%	6/14%	17/42%	4/5%
Pyogenic streptococci	8%	0%	0%	4%
Others	6%	14%	0%	0/3%
Negative-blood culture	9.5/11%	9/9 %	0/6%	0/5%
Microorganism not identified	5%	4.5%	0%	0%

Hoen B, Duval X, N Eng J Med 2013;368:1425-33

Endocarditis responsible microorganisms and valve

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	Prosthesis
S. aureus (%)	23
Coag Neg Staph	18.5
Strepto *viridans*	10
Enterococci	22
S. gallolyticus	6
Gram Neg Bacilli	2.5

Endocarditis responsible microorganisms and valve / acquisition modes

TAVI:

Microorganisms:

Enterococci species	25%
Staphylococcus aureus	23%
Coag Neg Staphylococci	17%

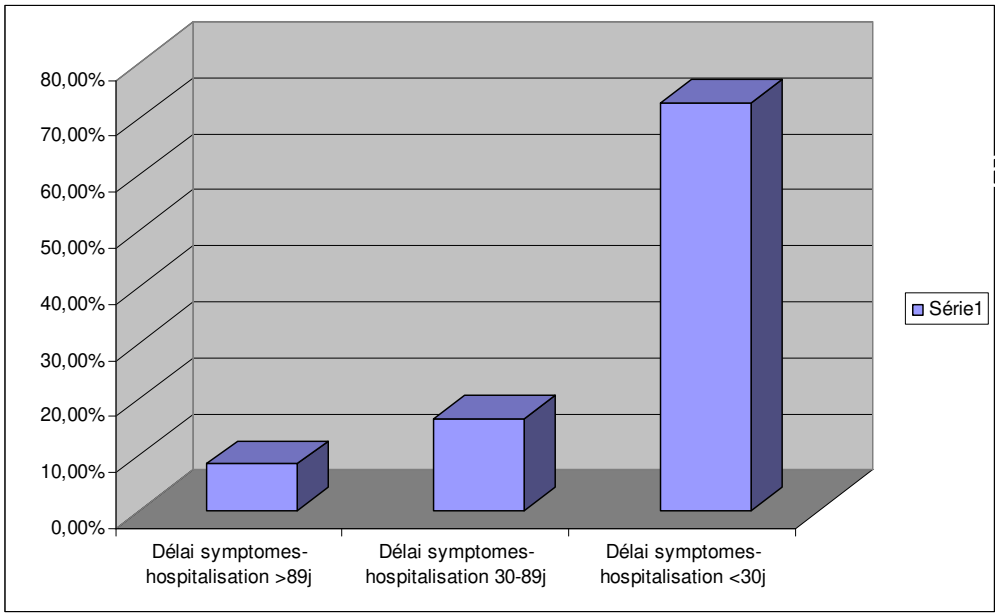
Prosthetic valve (17 %)			TOTAL
Early (< 2 mths) 1.0%	Mid term (2 – 12mths) 3.0%	Late (> 12 mths) 13%	
36/0%	7%	25%	26 %
0/17%	27%	9%	10 %
0/2%	7%	11%	18 %
0/2%	7%	9%	13 %
7.5/20%	7%	20%	10 %
0%	0%	3%	5 %
0%	33%	12%	8 %
17/40%	13%	12%	9%
40%	13%	8%	5%

Hoen B, Duval X, N Eng J Med 2013;368:1425-33

Endocarditis responsible microorganisms and Time interval First Symptom / IE Diagnosis

N'Guyen Y. Ann Med 2017

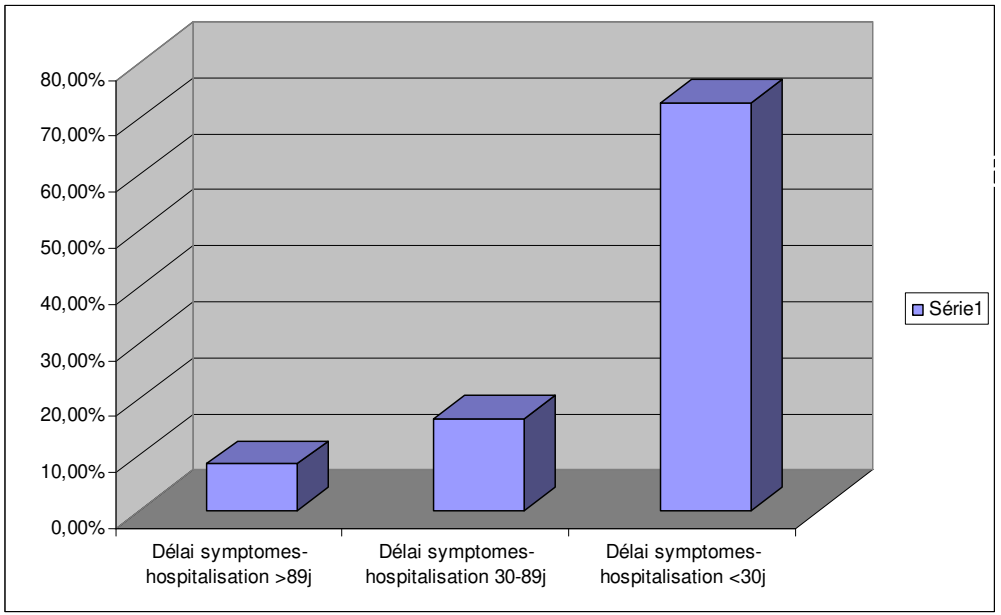
Endocarditis responsible microorganisms and Time interval First Symptom / IE Diagnosis



		< 1 month
Staph. aureus	**31%**	**91%**
Staph. epi	**11%**	73%
Strepto viridans	**22%**	39%
Strep bovis	**10%**	56%
Enterococci	**12%**	60%
Strept B or A	**4%**	**94%**
Strep pneumoniae	**2 %**	**100%**

N'Guyen Y. Ann Med 2017

Endocarditis responsible microorganisms and Time interval First Symptom / IE Diagnosis



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Staph. aureus	**31%**	**91%**	9 %
Staph. epi	**11%**	73%	27%
Strepto viridans	**22%**	39%	61%
Strep bovis	**10%**	56%	44%
Enterococci	**12%**	60%	40%
Strept B or A	**4%**	**94%**	6%
Strep pneumoniae	**2 %**	**100%**	0%

N'Guyen Y. Ann Med 2017

Endocarditis responsible microorganisms and source of infection

Endocarditis responsible microorganisms and source of infection

• **Oro-dental**	Oral streptococci and HACEK
• **Skin / KT**	Staphylococci
• **Digestive tract**	Gallolyticus streptococci, Enterococci
• **Urinary tract**	Enterococci
• **PET**	Rochalimea
• **Cow**	Q Fever

Endocardite infectieuse
Diagnostic

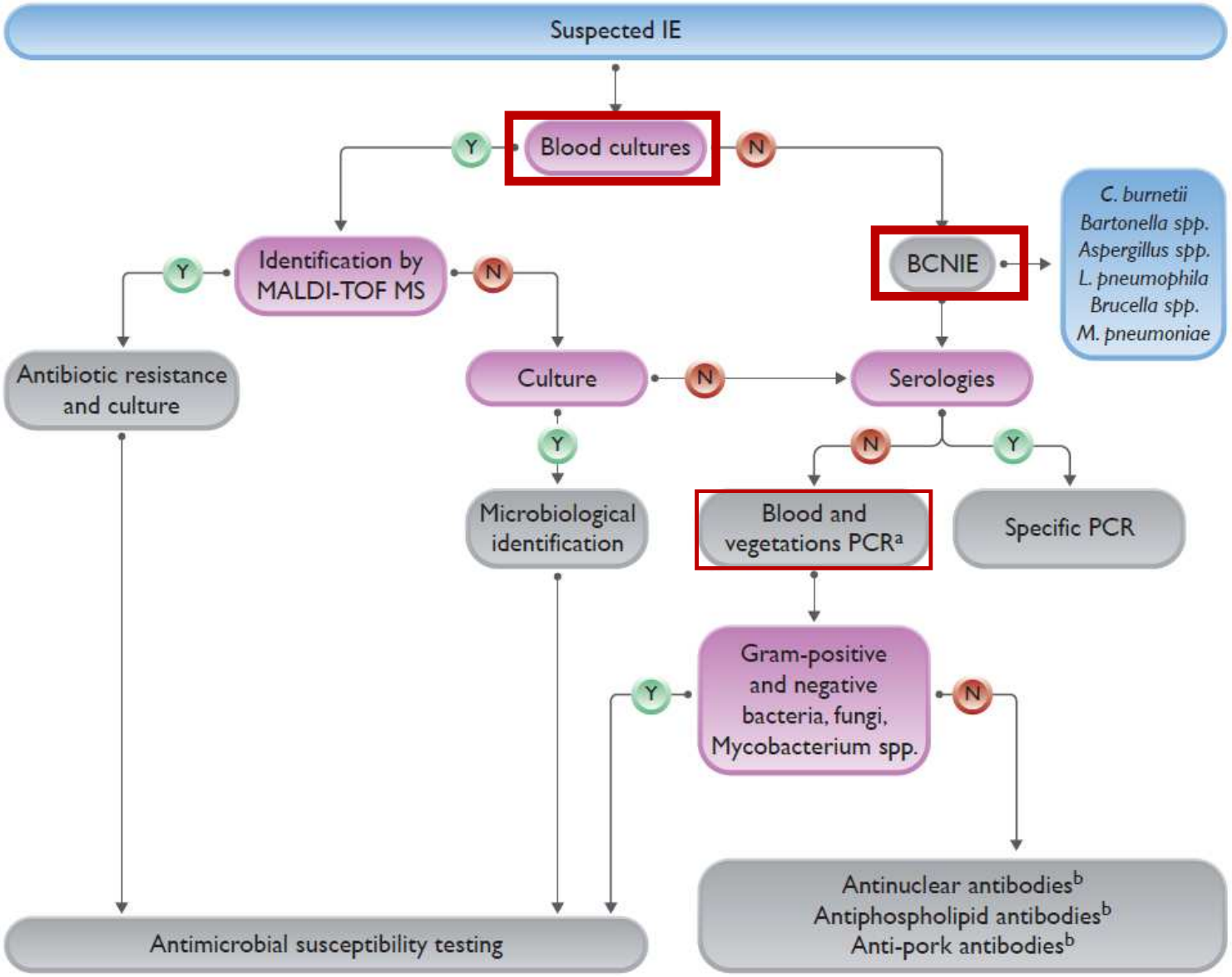
Endocardite infectieuse
Diagnostic

Critères majeurs:

- Présence prolongée de microorganismes dans le sang
- Atteinte valvulaire cardiaque (Prolifération / Destruction)

Classification Duke-Li 2009 → Duke- ISCVID 2023 / ESC 2023

2023



Cell free DNA

Clinical Infectious Diseases

VIEWPOINTS

The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis: Updating the Modified Duke Criteria

Vance G. Fowler, Jr.,[1,2] David T. Durack,[1] Christine Selton-Suty,[3] Eugene Athan,[4] Arnold S. Bayer,[5,6] Anna Lisa Chamis,[1] Anders Dahl,[7] Louis DiBernardo,[1] Emanuele Durante-Mangoni,[8] Xavier Duval,[9] Claudio Querido Fortes,[10] Emil Fosbøl,[11] Margaret M. Hannan,[12] Barbara Hasse,[13] Bruno Hoen,[14] Adolf W. Karchmer,[15] Carlos A. Mestres,[16] Cathy A. Petti,[1,17] María Nazarena Pizzi,[18] Stephen D. Preston,[19] Albert Roque,[20] Francois Vandenesch,[21,22] Jan T. M. van der Meer,[23] Thomas W. van der Vaart,[23] and Jose M. Miro[24,25]

I. MAJOR CRITERIA

A. Microbiologic Major Criteria

(1) Positive blood cultures

i. Microorganisms that commonly cause IE[a] isolated from 2 or more separate blood culture sets (Typical)[b]

or

ii. **Microorganisms that occasionally or rarely cause IE isolated from 3 or more separate blood culture sets (Nontypical)[b]**

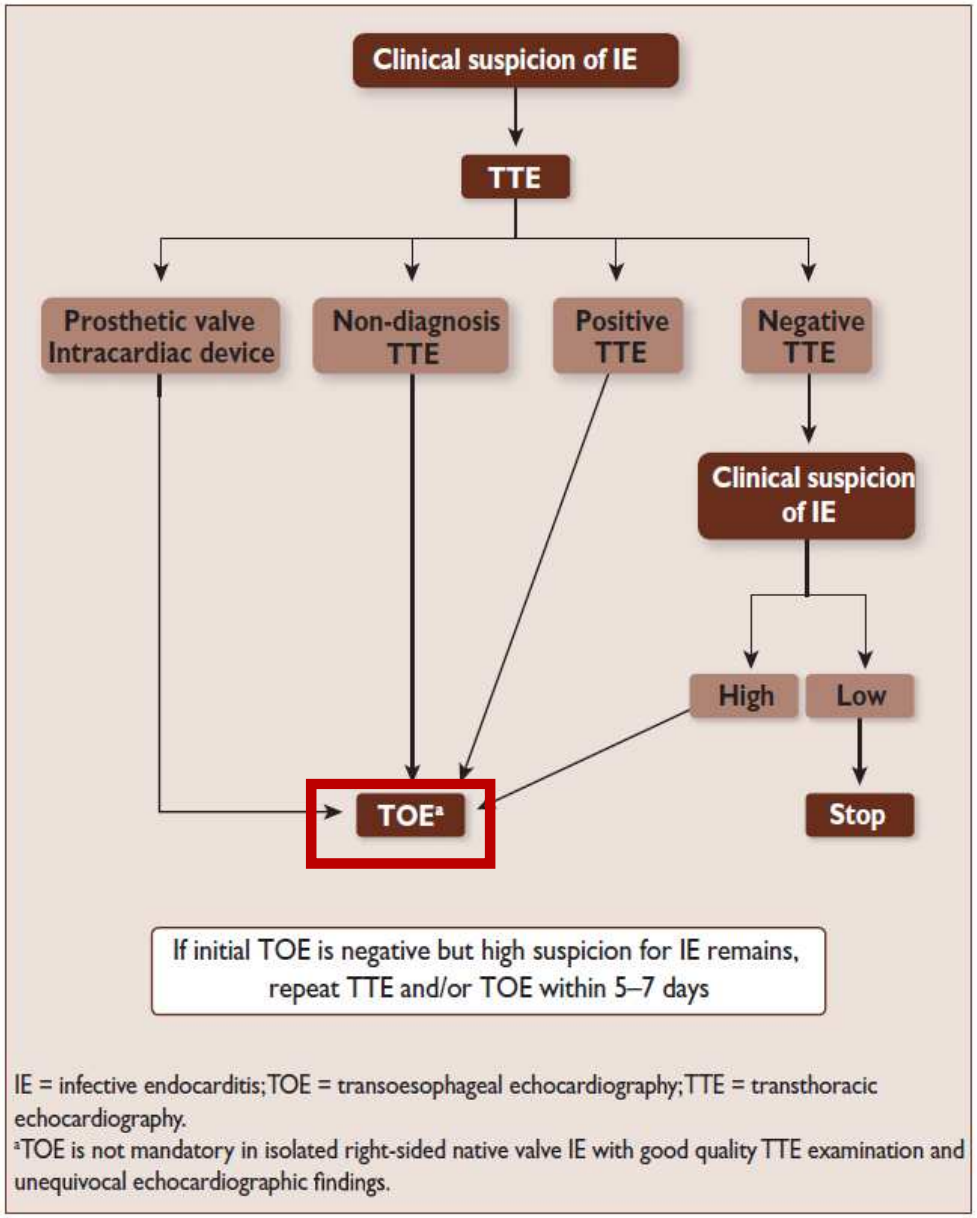
[b]"Blood culture set" is defined as a simultaneously drawn pair of 1 aerobic and 1 anaerobic bottle. "Positive" blood culture set is defined as microbial growth from at least 1 of the bottles. Blood cultures from separate venipuncture sites are strongly recommended whenever possible for evaluating suspected IE.

UNI_ENDO

Hémocultures uniques versus multiples dans le diagnostic de l'endocardite infectieuse

Investigateur coordonnateur: **Dr François Goerhinger**
Maladies infectieuses Nancy

Responsable scientifique : **Pr Xavier Duval**

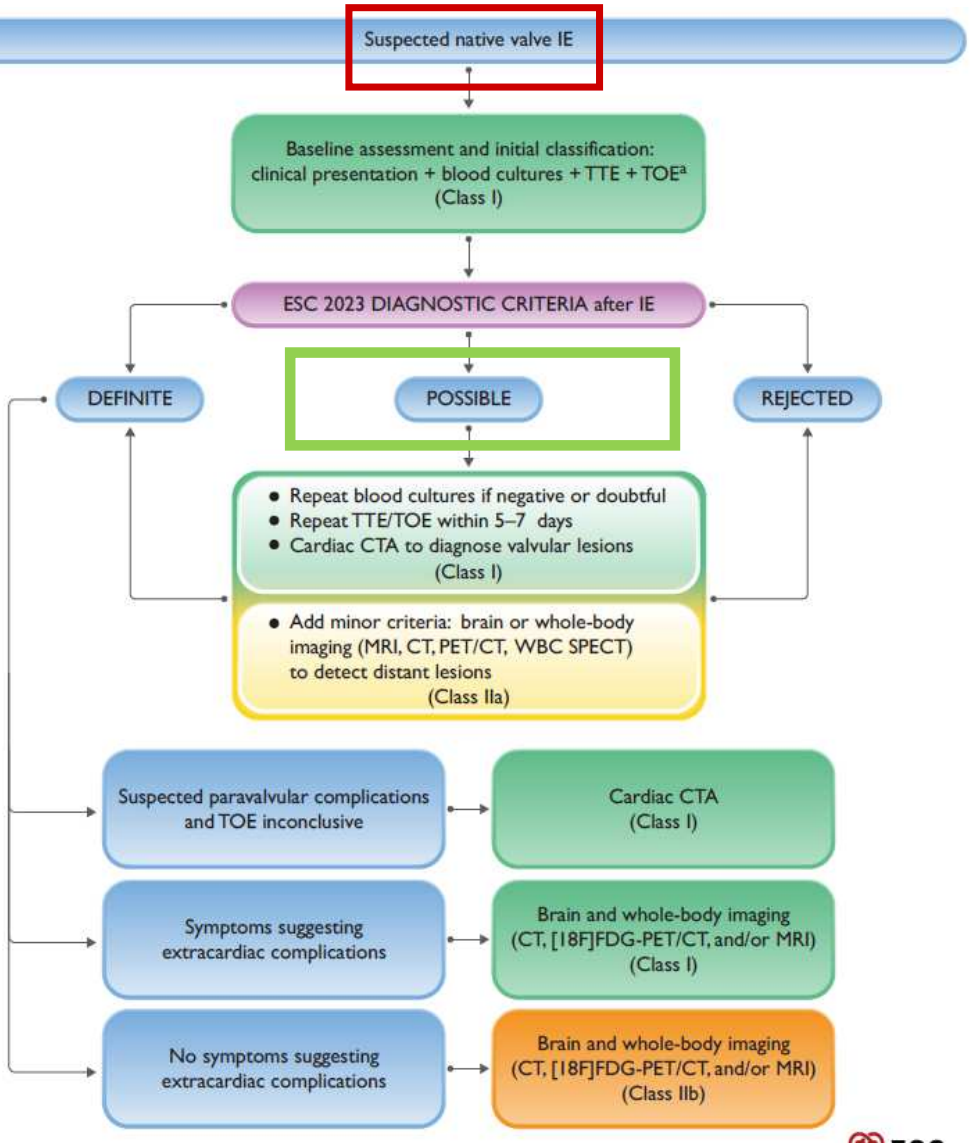


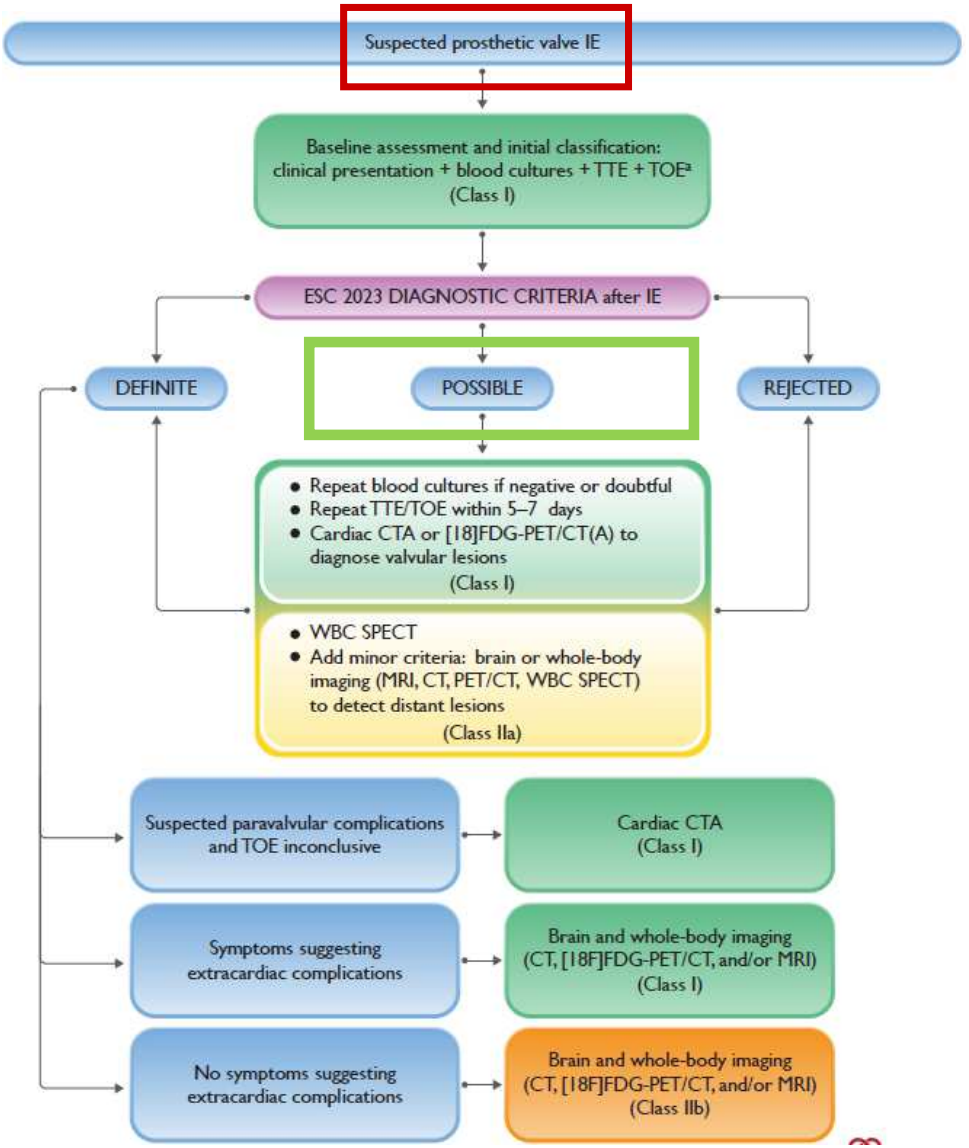
Sensibilité ETT + ETO:

- 86% (77-92) PVE
- 68% (62-74) TAVI IE

Stortecky J Am Coll Cardiol 2020;75:3020-30

2023


Suspected native valve IE
Baseline assessment and initial classification: clinical presentation + blood cultures + TTE + TOE[a] (Class I)
ESC 2023 DIAGNOSTIC CRITERIA after IE
DEFINITE
POSSIBLE
REJECTED
Repeat blood cultures if negative or doubtful
Repeat TTE/TOE within 5–7 days
Cardiac CTA to diagnose valvular lesions (Class I)
Add minor criteria: brain or whole-body imaging (MRI, CT, PET/CT, WBC SPECT) to detect distant lesions (Class IIa)
Suspected paravalvular complications and TOE inconclusive
Cardiac CTA (Class I)
Symptoms suggesting extracardiac complications
Brain and whole-body imaging (CT, [18F]FDG-PET/CT, and/or MRI) (Class I)
No symptoms suggesting extracardiac complications
Brain and whole-body imaging (CT, [18F]FDG-PET/CT, and/or MRI) (Class IIb)


Suspected prosthetic valve IE
Baseline assessment and initial classification: clinical presentation + blood cultures + TTE + TOE[a] (Class I)
ESC 2023 DIAGNOSTIC CRITERIA after IE
DEFINITE
POSSIBLE
REJECTED
Repeat blood cultures if negative or doubtful
Repeat TTE/TOE within 5–7 days
Cardiac CTA or [18]FDG-PET/CT(A) to diagnose valvular lesions (Class I)
WBC SPECT
Add minor criteria: brain or whole-body imaging (MRI, CT, PET/CT, WBC SPECT) to detect distant lesions (Class IIa)
Suspected paravalvular complications and TOE inconclusive
Cardiac CTA (Class I)
Symptoms suggesting extracardiac complications
Brain and whole-body imaging (CT, [18F]FDG-PET/CT, and/or MRI) (Class I)
No symptoms suggesting extracardiac complications
Brain and whole-body imaging (CT, [18F]FDG-PET/CT, and/or MRI) (Class IIb)

2023

2023 ESC modified diagnostic criteria

Major criteria

(i) Blood cultures positive for IE

(a) Typical microorganisms consistent with IE from two separate blood cultures:

Oral streptococci, *Streptococcus gallolyticus* (formerly *S. bovis*), HACEK group, *S. aureus*, *E. faecalis*

(b) Microorganisms consistent with IE from continuously positive blood cultures:

- ≥2 positive blood cultures of blood samples drawn >12 h apart.
- All of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart).

(c) Single positive blood culture for *C. burnetii* or phase I IgG antibody titre >1:800.

(ii) Imaging positive for IE:

Valvular, perivalvular/periprosthetic and foreign material anatomic and metabolic lesions characteristic of IE detected by any of the following imaging techniques:

- Echocardiography (TTE and TOE).
- Cardiac CT.
- [18F]-FDG-PET/CT(A).
- WBC SPECT/CT.

Quel que soit le type de valve

Characterization of ^{18}F-Fluorodeoxyglucose Uptake Pattern in Noninfected Prosthetic Heart Valves

Cédric Mathieu, MD; Nidaa Mikaïl, MD; Khadija Benali, MD; Bernard Iung, MD; Xavier Duval, MD, PhD; Patrick Nataf, MD; Guillaume Jondeau, MD, PhD; Fabien Hyafil, MD, PhD; Dominique Le Guludec, MD, PhD; François Rouzet, MD, PhD

Circ Cardiovasc Imaging. 2017

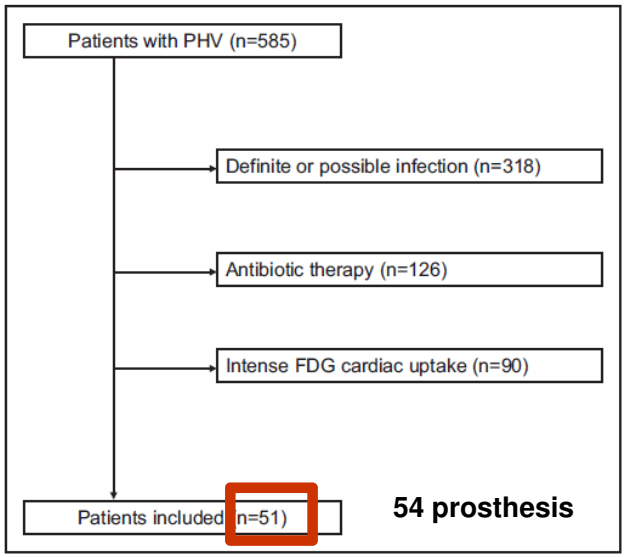


Figure 1. Study flow chart. PHV indicates prosthetic heart valve.

biological (n=**32**) – mechanical (n=**22**) prosthesis

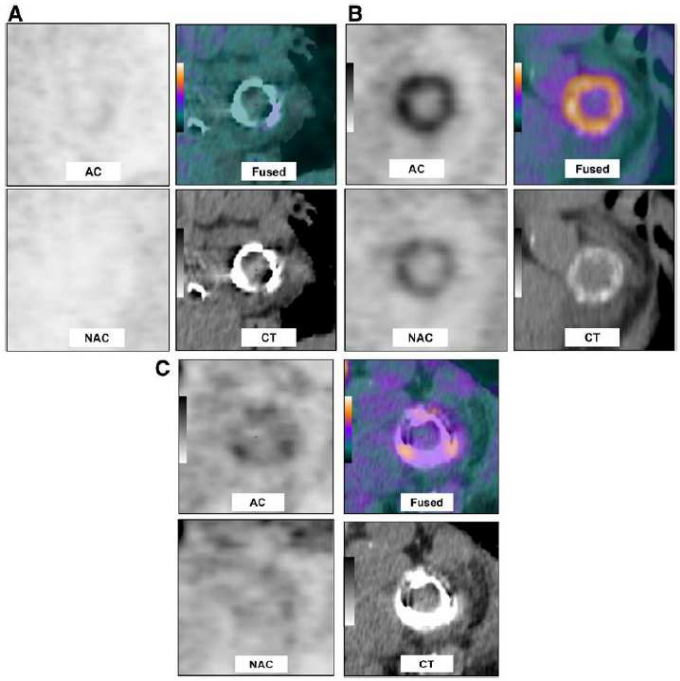
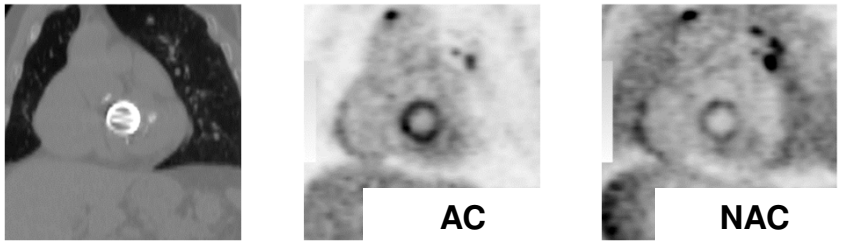


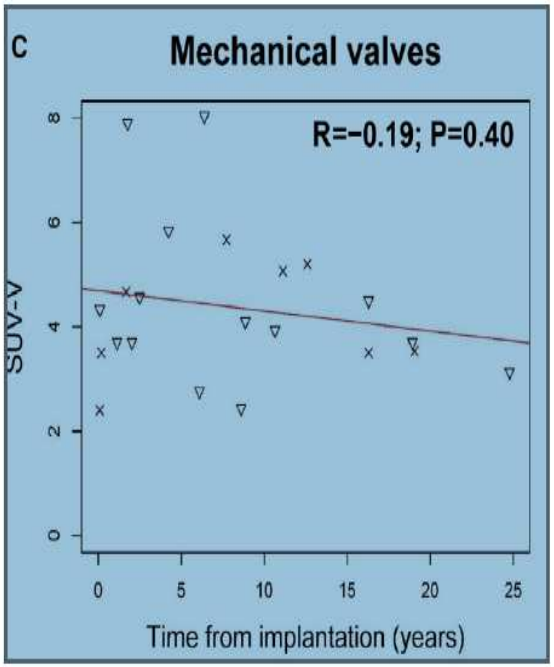
Figure 2. Examples of ^{18}F-FDG perivalvular uptake in noninfected patients.

PET Interpretation: specific cautions



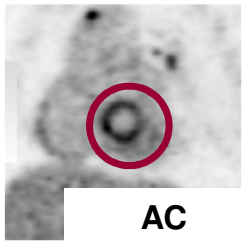
Intense / Homogeneous uptake on the PV

- **Visual analysis of perivalvular uptake**
  - Uptake: **n=50 /54 all** **93%** **Homogeneous in**
- **Quantitative analysis (SUV-V)**
  - Mechanical: 4.4±1.5
  - Biological: 3.4±0.9 (p=0.01)

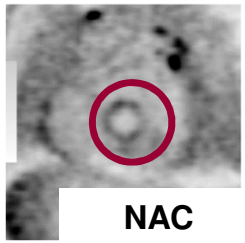


Mathieu C et al. Circ Cardiovasc Imaging 2017

PET Interpretation: specific cautions



AC

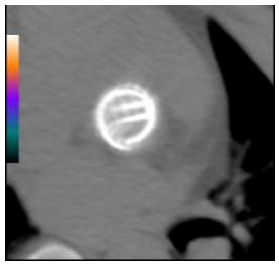


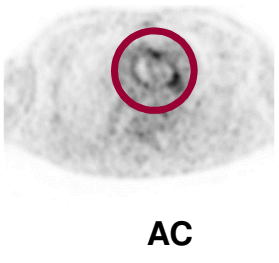
NAC

Non infected prosthesis

Intense / Homogeneous uptake on the PV

Intense / Heterogeneous uptake on the PV in IE pts





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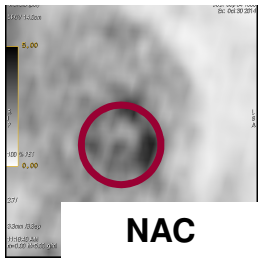


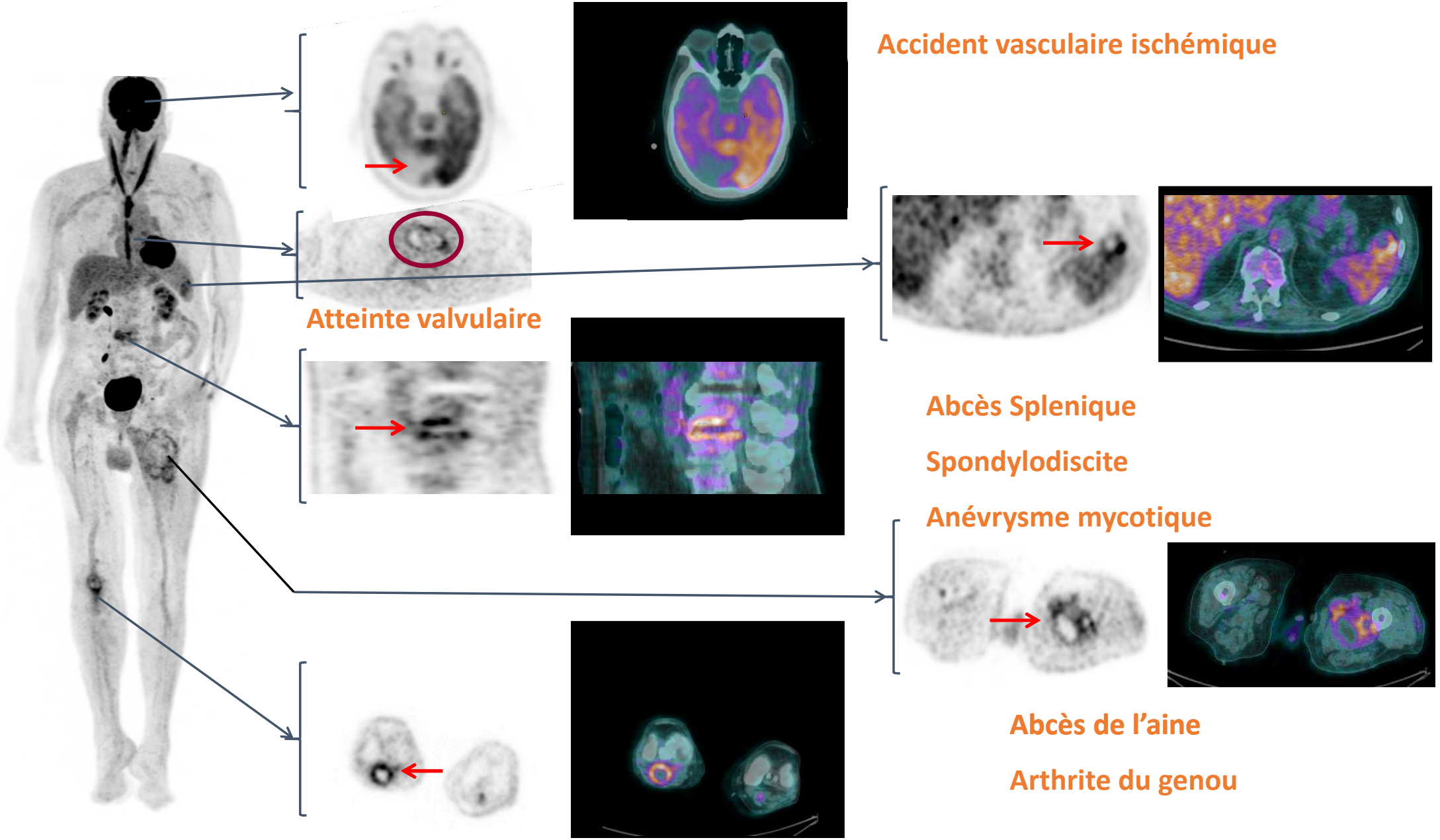
NAC

Heterogeneity or

Extension beyond the prosthetic ring

rather than intensity of the uptake to distinguish infected from non-infected prosthesis

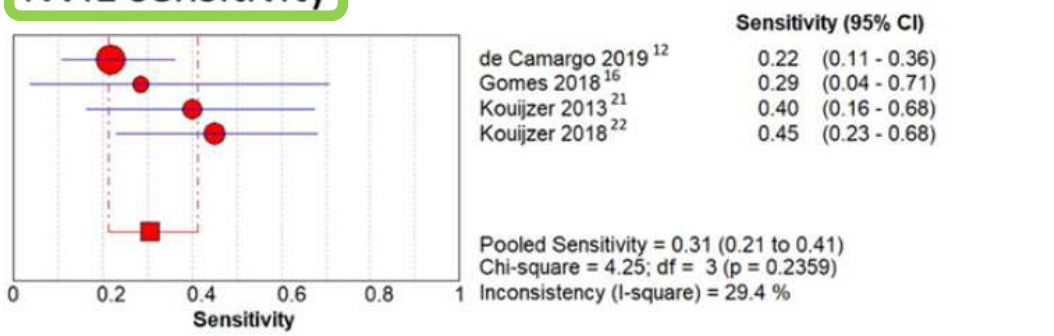
Mathieu C et al. Circ Cardiovasc Imaging 2017

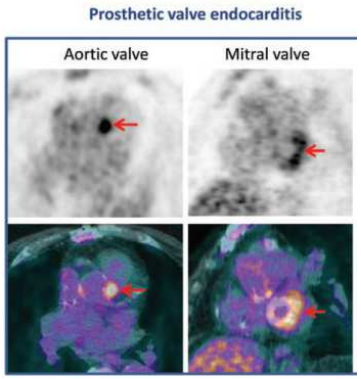

Accident vasculaire ischémique
Atteinte valvulaire
Abcès Splenique
Spondylodiscite
Anévrysme mycotique
Abcès de l'aine
Arthrite du genou

FDG-PET/CT in infective endocarditis

- **Performances in diagnosing (peri)valvular infection**

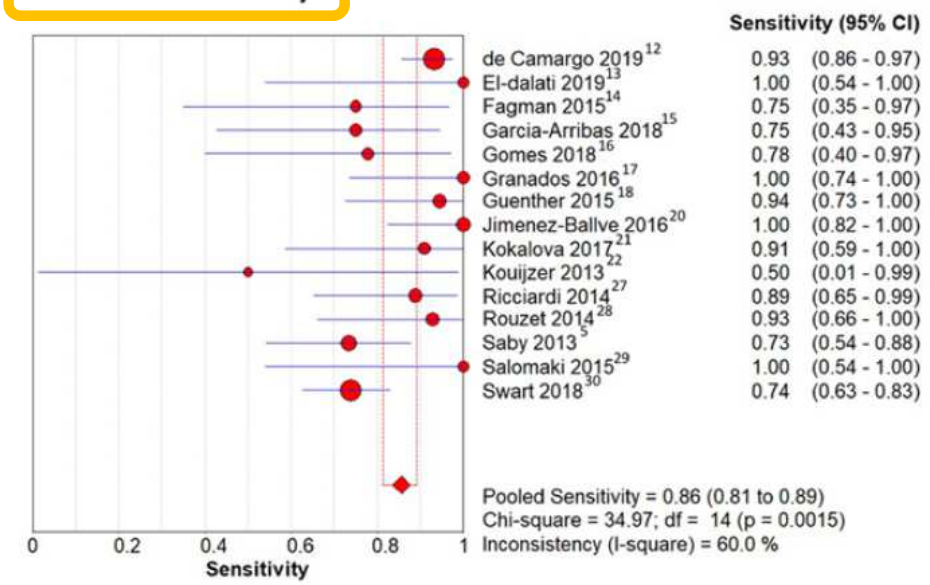
NVIE sensitivity





NV sensitivity **0.31 (0.21-0.41)**
NV specificity 0.98 (0.95-0.99)

PVIE sensitivity

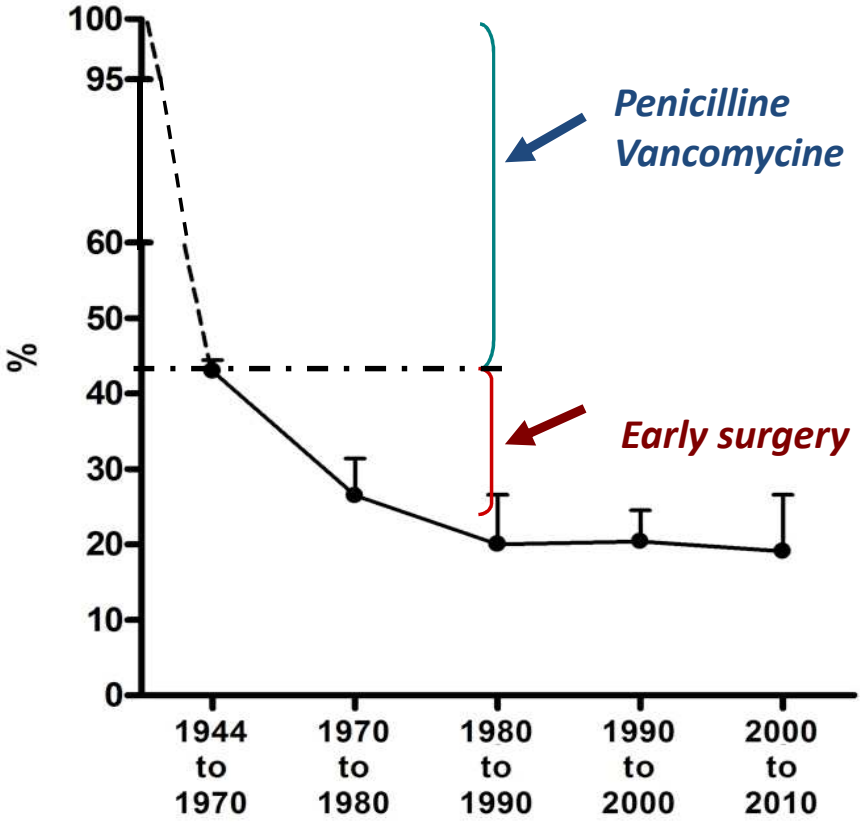


PV sensitivity **0.80 (0.81-0.89)**
PV specificity 0.84 (0.79-0.88)

Endocardite infectieuse
Traitement

Endocardite infectieuse

Influence of therapy



24 largest series (8589 cases)

In-hospital mortality

Antibiothérapie

Chirurgie

Thuny F. Lancet 2012;10;379:965-75;

The 'Endocarditis

The 'Endocarditis Reference Centre'

Characteristics of the reference centre

1. Immediate access to diagnostic procedures should be possible, including TTE, TOE, multislice CT, MRI, and nuclear imaging.
2. Immediate access to cardiac surgery should be possible during the early stage of the disease, particularly in case of complicated IE (HF, abscess, large vegetation, neurological, and embolic complications).
3. Several specialists should be present on site (the 'Endocarditis Team'), including at least cardiac surgeons, cardiologists, anaesthesiologists, ID specialists, microbiologists and, when available, specialists in valve diseases, CHD, pacemaker extraction, echocardiography and other cardiac imaging techniques, neurologists, and facilities for neurosurgery and interventional neuroradiology .

The 'Endocarditis Team'

When to refer a patient with IE to an 'Endocarditis Team' in a reference centre

1. Patients with complicated IE (i.e. endocarditis with HF, abscess, or embolic or neurological complication or CHD), should be referred early and managed in a reference centre with immediate surgical facilities.
2. Patients with non-complicated IE can be initially managed in a non-reference centre, but with regular communication with the reference centre, consultations with the multidisciplinary 'Endocarditis Team', and, when needed, with external visit to the reference centre.

Traitement

Faut-il opérer le patient ?

Quelle antibiothérapie ?

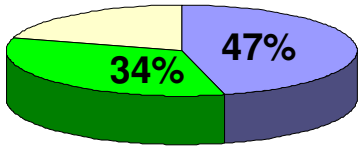
Quels traitements associés ?

Traitement

Faut-il opérer le patient ?

- **Chirurgie de remplacement valvulaire**

  - Indiquée dans **70%** des patients
  - Pratiquée chez 50%
    - Indication cardiaque: **47%**
    - Indication infectieuse: **34%**
    - Indication embolique: 21%



B. Iung Eur Heart J

Traitement

Faut-il opérer le patient ?

- **Chirurgie de remplacement valvulaire**

  - Indiquée dans **70%** des patients
  - Pratiquée chez 50%
    - Indication cardiaque: **47%**
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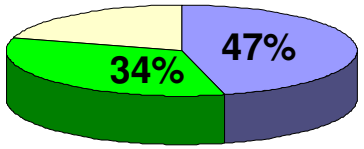


TAVI: 15%

A Regueiro JAMA. 2016;316(10):1083-1092.

Fiche de synthèse RCP Bichat Endocardite Paris

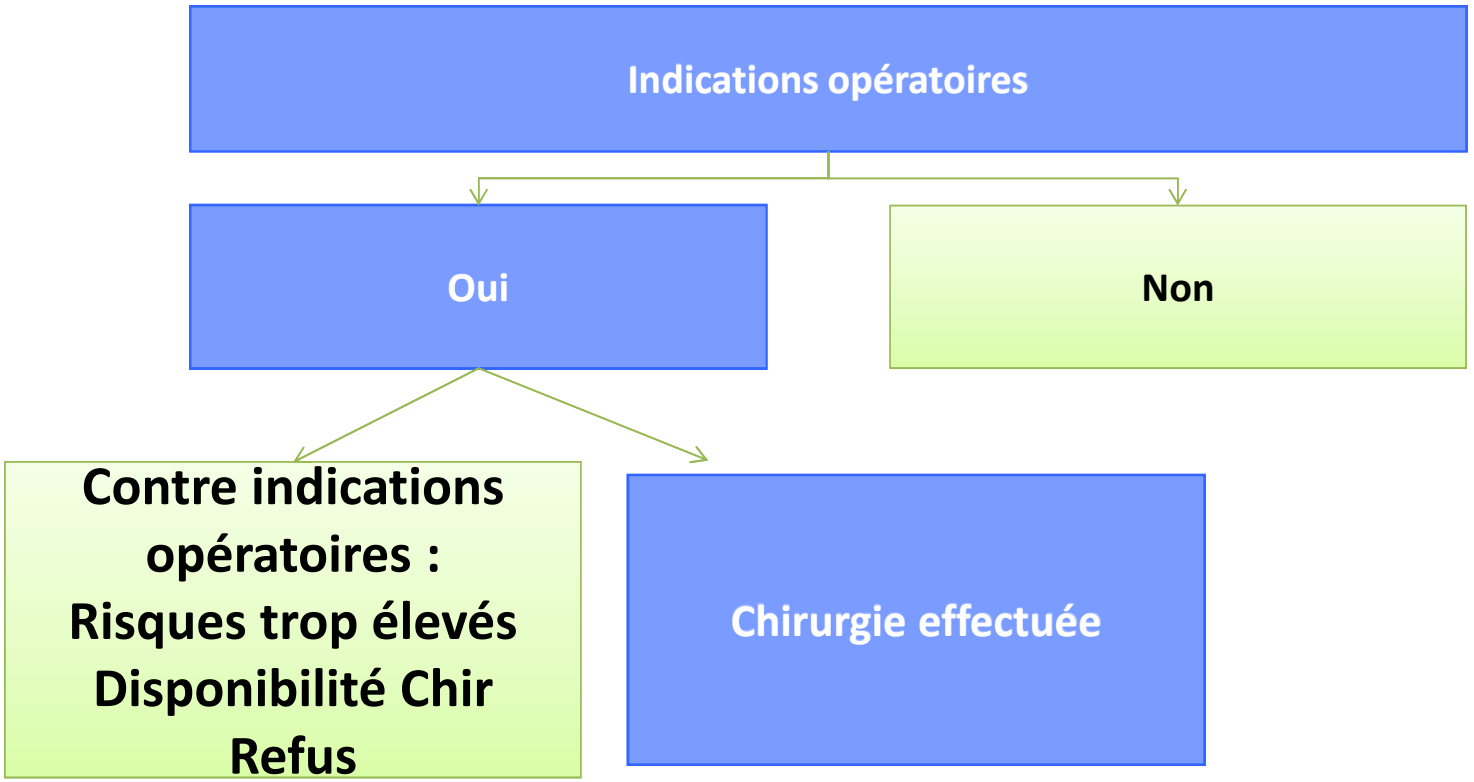
Monsieur D. Christian, 53 ans

Valve aortique mécanique et tube dacron
Hémoculture ***Streptococcus lutetiensis***
Image vide d'écho à l'ETO
Scintigraphie leucocytes marqués fixe

Quelles questions ?

- **Chirurgie**
  - Qui ?
  - Quand ?
  - Comment ?

Indications opératoires



2023

Chirurgie valvulaire _ Indications 2023

Recommendations	Class[b]	Level[c]
(i) Heart failure		
Emergency[d] surgery is recommended in aortic or mitral NVE or PVE with severe acute regurgitation, obstruction, or fistula causing refractory pulmonary oedema or cardiogenic shock.[420,423,424,429,476,477]	I	B
Urgent[d] surgery is recommended in aortic or mitral NVE or PVE with severe acute regurgitation or obstruction causing symptoms of HF or echocardiographic signs of poor haemodynamic tolerance.[5,420–422,429]	I	B

2023

Chirurgie valvulaire _ Indications 2023

(ii) Uncontrolled infection		
Urgent[d] surgery is recommended in locally uncontrolled infection (abscess, false aneurysm, fistula, enlarging vegetation, prosthetic dehiscence, new AVB).[5,420,421,429,445]	I	B
Urgent[d] or non-urgent surgery is recommended in IE caused by fungi or multiresistant organisms according to the haemodynamic condition of the patient.[420]	I	C
Urgent[d] surgery should be considered in IE with persistently positive blood cultures >1 week or persistent sepsis despite appropriate antibiotic therapy and adequate control of metastatic foci.[436,437]	IIa	B
Urgent[d] surgery should be considered in PVE caused by *S. aureus* or non-HACEK Gram-negative bacteria[5,385,449]	IIa	C

Prosthetic valve *Staphylococcus aureus* IE // Cardiac surgery

Clinical Infectious Diseases
MAJOR ARTICLE

Impact of Early Valve Surgery on Outcome of *Staphylococcus aureus* Prosthetic Valve Infective Endocarditis: Analysis in the International Collaboration of Endocarditis–Prospective Cohort Study

Catherine Chirouze,[1,2] François Alla,[3,4,5] Vance G. Fowler Jr,[6] Daniel J. Sexton,[6] G. Ralph Corey,[6] Vivian H. Chu,[6] Andrew Wang,[6] Marie-Line Erpelding,[4,5] Emanuele Durante-Mangoni,[7] Nuria Fernández-Hidalgo,[8] Efthymia Giannitsioti,[9] Margaret M. Hannan,[10] Tatjana Lejko-Zupanc,[11] José M. Miró,[12] Patricia Muñoz,[13] David R. Murdoch,[14] Pierre Tattevin,[15] Christophe Tribouilloy,[16] and Bruno Hoen[1,2,17,18]; on behalf of the ICE Prospective Investigators[a]

Mortality was significantly lower in patients treated both with surgery and antibiotics compared with those treated only medically (33.7% vs. 59%; $P = 0.001$).
However, a propensity score analysis, adjusted for survival bias, failed to demonstrate an overall significant survival benefit at 1 year of EVS in *S. aureus* PVE

C Chirouze Clin Infect Dis 2015

Valvular surgery_ 2015 ESC indications

3. Prevention of embolism				
Aortic or mitral NVE or PVE with persistent vegetations >10 mm after one or more embolic episode despite appropriate antibiotic therapy	Urgent	I	B	9,58,72, 113,222
Aortic or mitral NVE with vegetations >10 mm, associated with severe valve stenosis or regurgitation, and low operative risk	Urgent	IIa	B	9
Aortic or mitral NVE or PVE with isolated very large vegetations (>30 mm)	Urgent	IIa	B	113
Aortic or mitral NVE or PVE with isolated large vegetations (>15 mm) and no other indication for surgery[e]	Urgent	IIb	C	

AEPEI score

https://www.endocardite.org

2023

Chirurgie valvulaire _ Indications 2023

(iii) Prevention of embolism		
Urgent[d] surgery is recommended in aortic or mitral NVE or PVE with persistent vegetations ≥10 mm after one or more embolic episodes despite appropriate antibiotic therapy.[451,455,457,471,478]	I	B
Urgent[d] surgery is recommended in IE with vegetation ≥10 mm and other indications for surgery.[5,460,465,466,471,478]	I	C
Urgent[d] surgery may be considered in aortic or mitral IE with vegetation ≥10 mm and without severe valve dysfunction or without clinical evidence of embolism and low surgical risk.[460,463,465,473,478]	IIb	B

Quelles questions ?

- **Chirurgie**
  - OUI
    - Image vide d'écho
    - Infection de tube
  - Quand ?
    - Discussion
  - Comment

CHIRURGENDO

Chirurgie valvulaire très précoce versus traitement conventionnel dans la prévention du risque embolique chez les patients présentant une endocardite à haut risque embolique : un essai randomisé

Conseil scientifique n°2 du 19/12/2019

Investigateur coordonnateur: **Pr Xavier DUVAL**
Centre d'investigations cliniques/Service des Maladies infectieuses et tropicales
Hôpital Bichat Claude Bernard, Paris

Responsable scientifique : **Pr. Jean-François OBADIA**
Service de chirurgie cardiovasculaire Hôpital Louis Pradel, Lyon

Antibiothérapie ?

Antibiothérapie

- Quel(s) antibiotique(s)
- Quelle dose ?
- Quelle durée ?

Quelles questions ?

- Quelle est la sensibilité du microorganisme ?

  (impacte choix et dose)

  CMI (strepto et enterocoque)

Antibiothérapie

- **Quel(s) antibiotique(s)**
- **Quelle dose ?**
- **Quelle durée ?**

Quelles questions ?

- Quelle est la sensibilité du microorganisme ?

  (impacte choix et dose)
- S'agit-il d'une EI sur Valve native/prothèse ?

  (bi/trithérapie; durée)

  4 semaines versus ≥ 6 semaines

Antibiothérapie

- **Quel(s) antibiotique(s)**
- **Quelle dose ?**
- **Quelle durée ?**

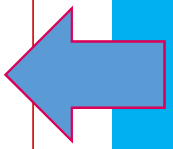
Quelles questions ?

- Quelle est la sensibilité du microorganisme ?

  (impacte choix et dose)
- S'agit-il d'une EI sur Valve native/prothèse ?

  (bi/trithérapie; durée)
- Existe-t-il des complications ? (abcès cardiaque ou à distance; embolie, anévrysmes)

  (bi/trithérapie; durée)



Antibiothérapie

- **Quel(s) antibiotique(s)**
- **Quelle dose ?**
- **Quelle durée ?**

Quelles questions ?

- Quelle est la sensibilité du microorganisme ?

  (impacte choix et dose)
- S'agit-il d'une EI sur Valve native/prothèse ?

  (bi/trithérapie; durée)
- Existe-t-il des complications ? (abcès cardiaque ou à distance; embolie, anévrysmes)

  (bi/trithérapie; durée)
- Allergie à certains AB/ fonction rénale ?

Antibiothérapie

- **Quel(s) antibiotique(s)**
- **Quelle dose ?**
- **Quelle durée ?**

- Traitement antibiotique dans l'attente des résultats des hémocultures
  - Chez qui ?
  - Quel traitement antibiotique ?
- Traitement des endocardites à streptococoques oraux et digestifs
- Traitement des endocardites à enterocoque
- Traitement des endocardites à Staphylocoque
- Autres microorganismes

- Prophylaxie

Traitement

Quelle antibiothérapie ?

INFECTION AND IMMUNITY, Dec. 1974, p. 1433–1438

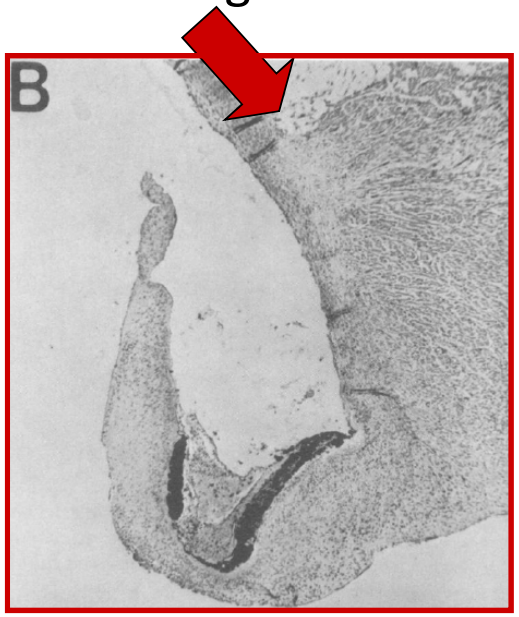
Vol. 10, No. 6
Printed in U.S.A.

Role of the Vegetation in Experimental *Streptococcus viridans* Endocarditis

EDWARD W. HOOK III AND MERLE A. SANDE

Modèle EI du lapin

Pré-traitement par AVK => EI **sans** végétation



EI 'habituelle'

*Pré-traitement AVK => EI **sans** végétation*

Le traitement court est efficace en l'absence de végétation

TABLE 1. *Rate of killing of S. viridans in control (with vegetations) and anticoagulated rabbits (without vegetations) treated with penicillin*

Days of therapy	Log viable bacteria/g of tissue	
	Rabbits with vegetations	Rabbits without vegetations
0	9.5	9.3
1	8.8	<2
2	7.2	3.1
3	5.4	<2
4	4.4	<2

Hook III EW, Sande MA. Infection Immunity 1974

Le traitement court est efficace en l'absence de végétation

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1	8.8	<2
2	7.2	3.1
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4	4.4	<2

Hook III EW, Sande MA. Infection Immunity 1974

Traitement : informations microbiologiques nécessaires

- **Streptocoques oraux et *S. bovis*** (S. *gallolyticus*):
  - CMI de l'amoxicilline et cefotaxime

- **Entérocoques:**
  - CMI de la pénicilline et de l'amoxicilline,
  - Recherche haut niveau de résistance à la gentamicine,
  - Sensibilité aux glycopeptides

- **Staphylocoques:**
  - Sensibilité à l'oxacilline et autres AB (gentamicine pour SARM)

- **HACCEK:**
  - Recherche de bêta-lactamase et CMI de l'amoxicilline

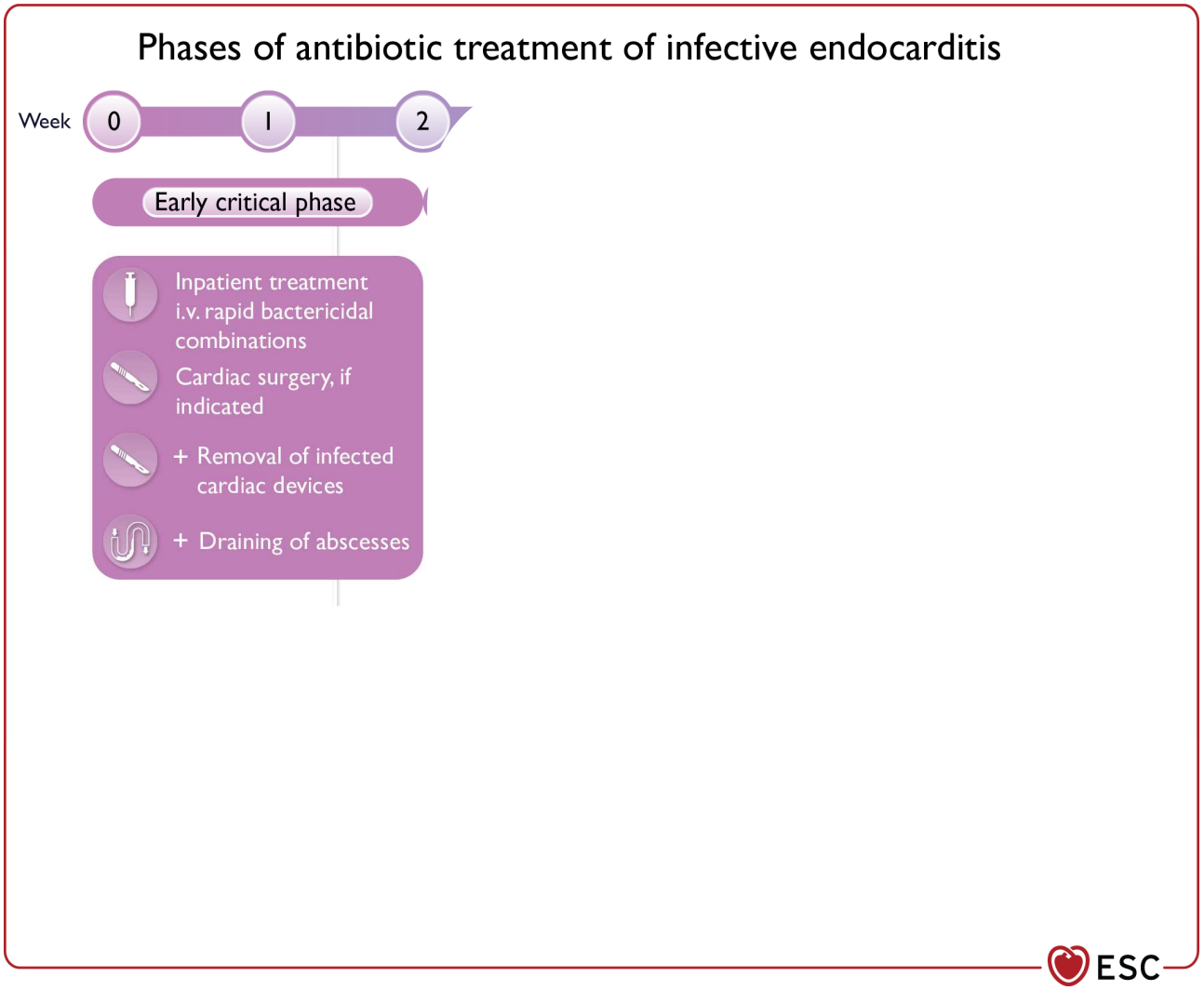
Recommandations thérapeutiques : références

- Baddour L, et al. **Circulation (2015)**

- Guidelines on the prevention, diagnosis,and treatment of infective endocarditis.The Task Force on the Prevention, Diagnosis, and Treatment of Infective Endocarditis of the European Society of Cardiology (ESC) Delgado et al. **European Heart Journal (2023)**

- HAS Prophylxie endocardite (Mars 2024)
- French position paper (Dec 2024)

Phases of antibiotic treatment for infective endocarditis in relation to outpatient parenteral antibiotic therapy and partial oral endocarditis treatment



2023 ESC Guidelines for the management of endocarditis
(European Heart Journal; 2023 – doi: 10.1093/eurheartj/ehad193)

2023

Antibiotic pending for microbiological identification Recommendations 2023

2023

Antibiotic pending for microbiological identification Recommendations 2023

Recommendation Table 10 — Recommendations for antibiotic regimens for initial empirical treatment of infective endocarditis (before pathogen identification)[a]

Recommendations		Class[b]	Level[c]
In patients with community-acquired NVE or late PVE (≥12 months post-surgery), ampicillin in combination with ceftriaxone or with (flu)cloxacillin and gentamicin should be considered using the following doses:[255]		IIa	C
Adult antibiotic dosage and route			
Ampicillin	12 g/day i.v. in 4–6 doses		
Ceftriaxone	4 g/day i.v. or i.m. in 2 doses		
(Flu)cloxacillin	12 g/day i.v. in 4–6 doses		
Gentamicin[d]	3 mg/kg/day i.v. or i.m. in 1 dose		

Contents lists available at ScienceDirect

Infectious Diseases Now

journal homepage: www.sciencedirect.com/journal/infectious-diseases-now

Guidelines

Antibiotic therapy and prophylaxis of infective endocarditis – A SPILF-AEPEI position statement on the ESC 2023 guidelines

Empirical antimicrobial treatment of suspected IE is recommended in each of the following situations:

- Acute onset with rapid progression of symptoms over the last week
- Large vegetation (>10 mm)
- Sepsis
- Before surgery when emergency valve surgery is indicated.

In all other situations, antibiotic treatment may be deferred until the results of blood cultures are available.

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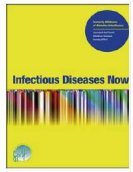

Guidelines

Antibiotic therapy and prophylaxis of infective endocarditis – A SPILF-AEPEI position statement on the ESC 2023 guidelines

Empirical Treatment

For native valve IE and **late-onset prosthetic valve IE** (ie, symptoms onset > 1 year post-valve implantation), preferred empirical treatment may be

- **amoxicillin (200 mg/kg/day) + cefazolin (100 mg/kg/day)**
- combined with gentamicin (5 mg/kg/day) only in patients with sepsis

or (if allergy to β-lactams) vancomycin (30 mg/kg/day, continuous infusion after a loading dose).

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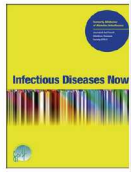

Guidelines

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Empirical Treatment

For native valve IE and **late-onset prosthetic valve IE** (ie, symptoms onset > 1 year post-valve implantation), preferred empirical treatment may be

- **amoxicillin (200 mg/kg/day) + cefazolin (100 mg/kg/day)**
- combined with gentamicin (5 mg/kg/day) only in patients with sepsis

or (if allergy to β-lactams) vancomycin (30 mg/kg/day, continuous infusion after a loading dose).

For **early-onset prosthetic valve IE** (ie, symptoms onset < 1 year post-valve implantation), preferred empirical treatment may be

- **daptomycin (12 mg/kg/day),** or vancomycin (30 mg/kg/day, continuous infusion after a loading dose)
- combined with **cefepime** (2 g IV/8h)
- combined with **gentamicin** (5 mg/kg/day) **only in patients with sepsis**

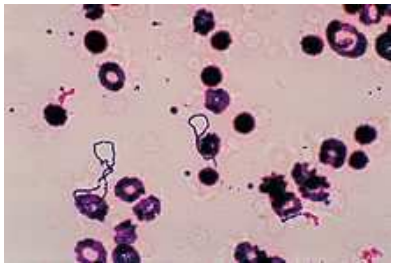
Monsieur D. Christian, 53 ans

Valve aortique mécanique et tube dacron
Hémoculture ***Streptococcus lutetiensis***
Image vide d'écho à l'ETO
Scintigraphie leucocytes marqués fixe

Quels traitements proposez-vous ?

1. Chirurgie de remplacement valvulaire
2. Amoxicilline 200 mg/kg pdt 2 S
3. Amoxicilline 100 mg/kg pdt 2 S et gentamicine pdt 2 S
4. Amoxicilline 100 mg/kg pdt 4 S
5. Vancomycine 30 mg/kg pdt 6 S
6. Vous n'êtes pas en mesure de déterminer la durée du traitement à ce stade

Endocardites à Streptocoque

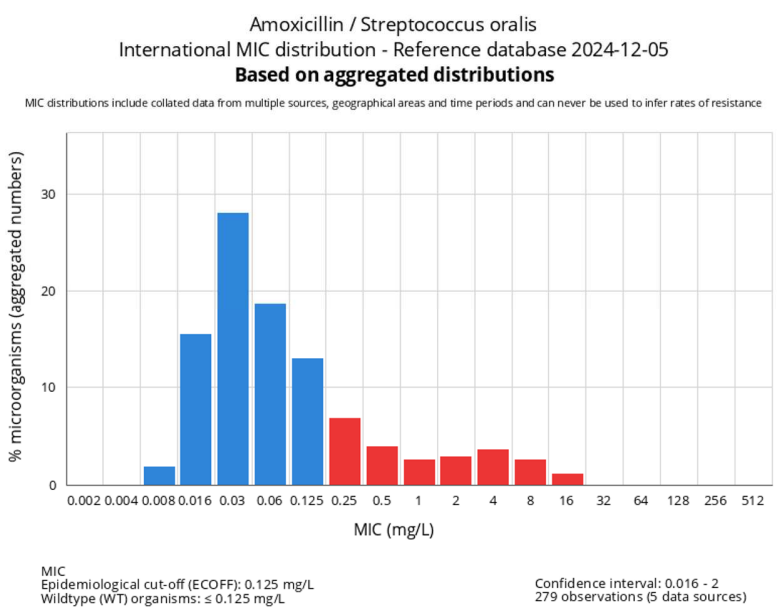


≈ 30%

Comparaison des CMI streptocoque Penicilline/amoxicilline/ceftriaxone

→ Pourquoi mesurer la CMI de l'antibiotique pour les EI à streptocoques**?**

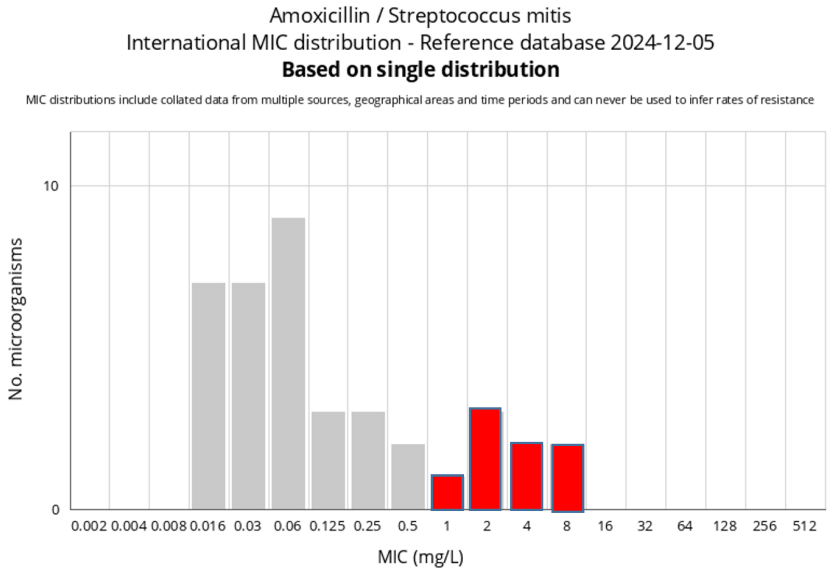
MIC distribution Amoxicillin *Streptococcus oralis*



MIC
Epidemiological cut-off (ECOFF): 0.125 mg/L
Wildtype (WT) organisms: ≤ 0.125 mg/L

Confidence interval: 0.016 - 2
279 observations (5 data sources)

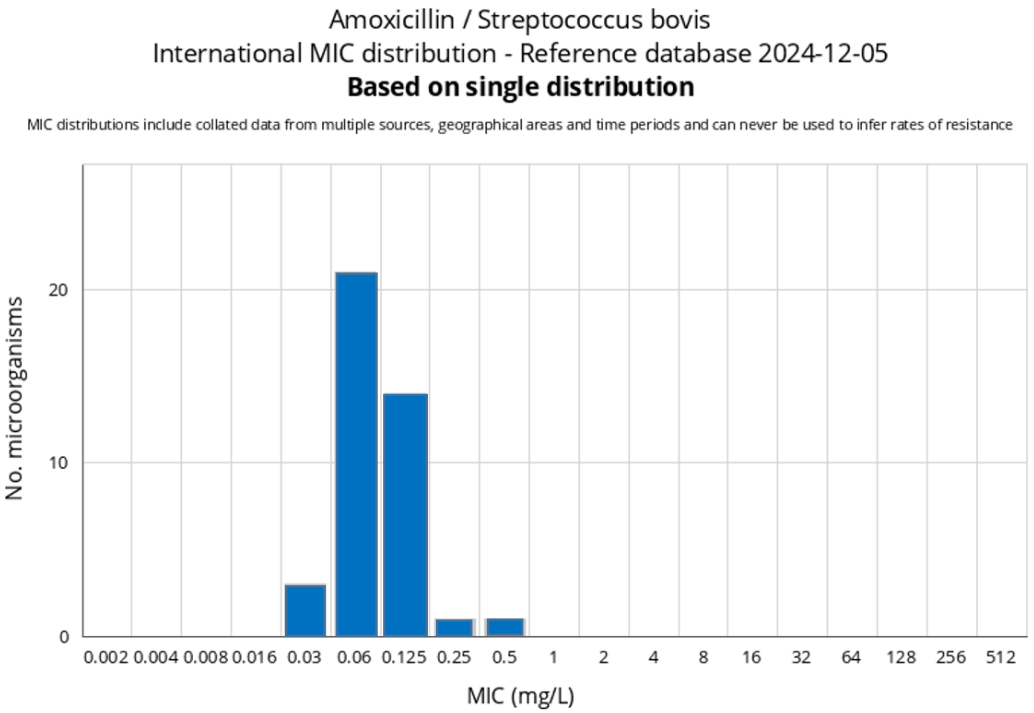
MIC distribution Amoxicillin *Streptococcus mitis*



MIC
Epidemiological cut-off (ECOFF): -
Wildtype (WT) organisms: -

Confidence interval: -
39 observations

MIC distribution Amoxicillin *Streptococcus bovis*



MIC
Epidemiological cut-off (ECOFF): ID
Wildtype (WT) organisms: -

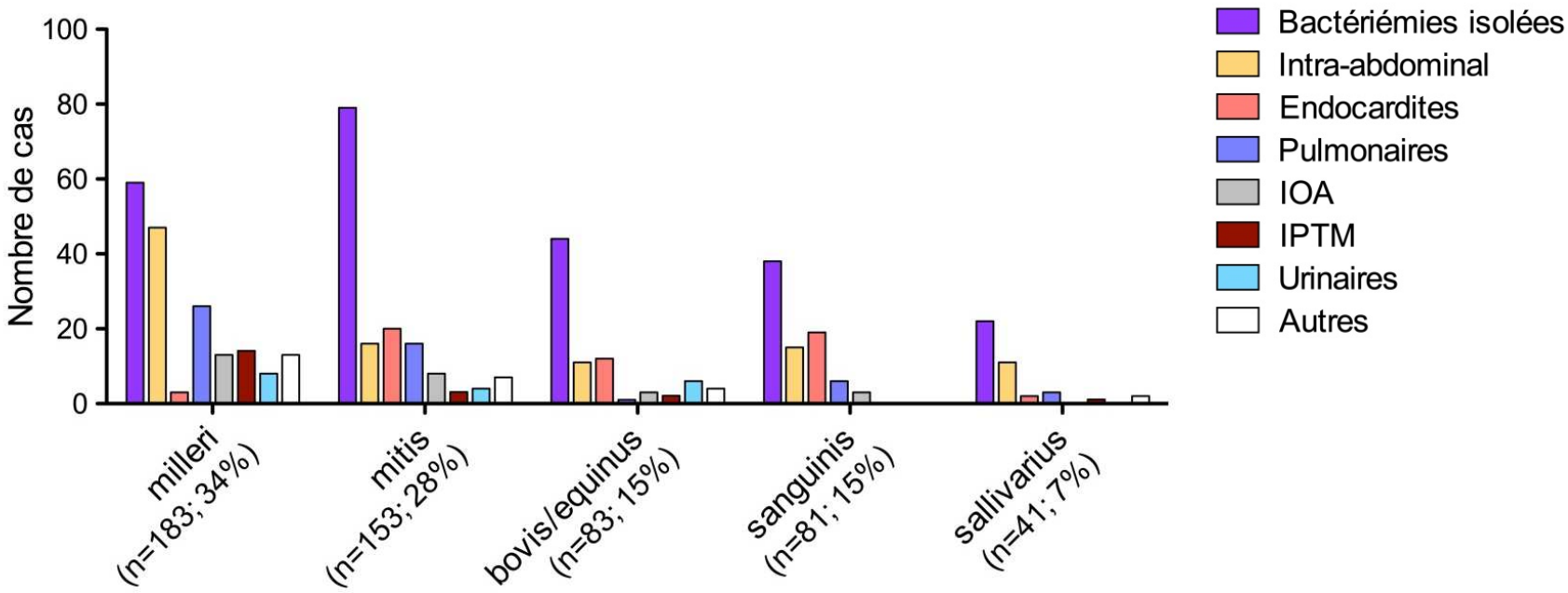
Confidence interval: -
40 observations

Comparaison des CMI streptocoque Penicilline/amoxicilline/ceftriaxone

→ Pourquoi mesurer la CMI à **l'antibiotique que l'on va utiliser ?**

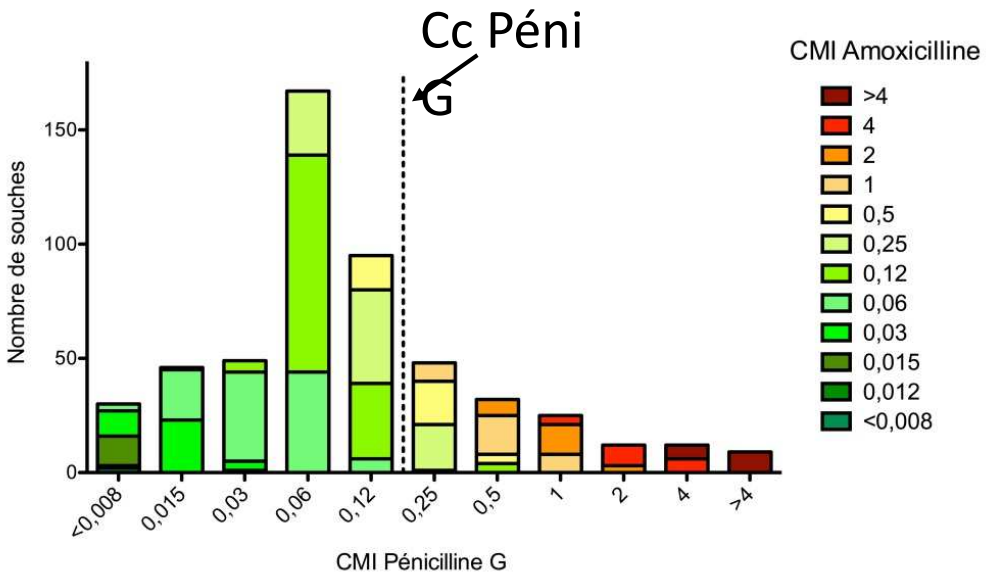
Comparaison des CMI streptocoque Penicilline/amoxicilline/ceftriaxone

- 547 cas d'infections invasives à Streptocoques « *viridans* »



→ Antibiogramme en diffusion + E-tests + CMI Sensititre™ pour 514 souches

Sensibilité à la Pénicilline G vs. Amoxicilline (Sensititre™)



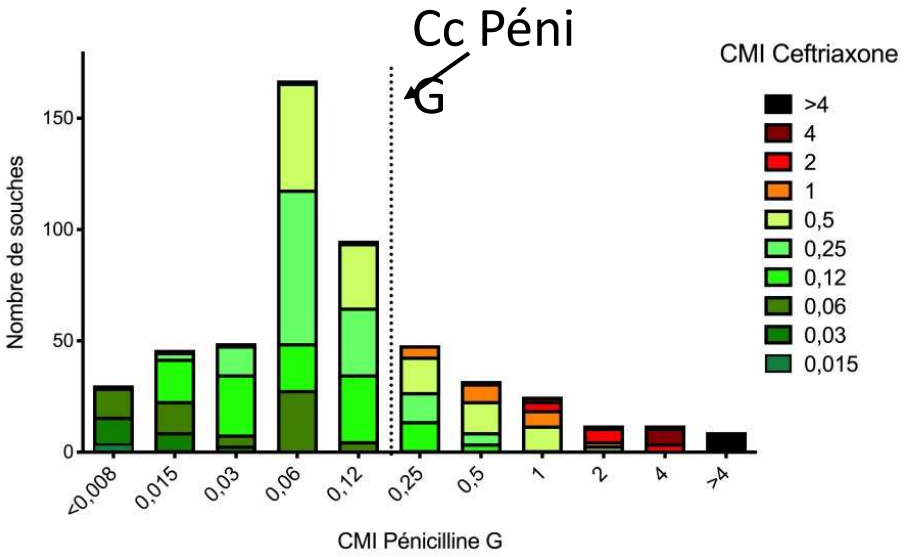
Conc. critiques AMX : 0.5 – 2 mg/L

		Pénicilline G			
		≤ 0.125	0.25 – 2	> 2	Total
AMX	≤ 0.125	309 (60.1%)	7 (1.4%)	0	316 (61.5%)
	0.25	60 (11.7%)	23 (4.5%)	0	83 (16.1%)
	0.5	12 (2.3%)	19 (3.7%)	0	31 (6.0%)
	1	0	34 (6.6%)	0	34 (6.6%)
	2	0	24 (4.7%)	0	24 (4.7%)
	> 2	0	5 (1.0%)	21 (4.1%)	26 (5.1%)
	Total	381 (74.1%)	112 (21.8%)	21 (4.1%)	514 (100%)

59% *sanguinis*

- Toutes les souches sensibles à la Péni G sont bien sensibles à l'AMX
- Certaines souches de sensibilité diminuée à la Péni G sont I voire R à l'AMX (12 % du total, 56 % des souches I à la Péni G)

Sensibilité à la Pénicilline G vs. Ceftriaxone (Sensititre™)



Conc. critique CRO : 0.5 mg/L

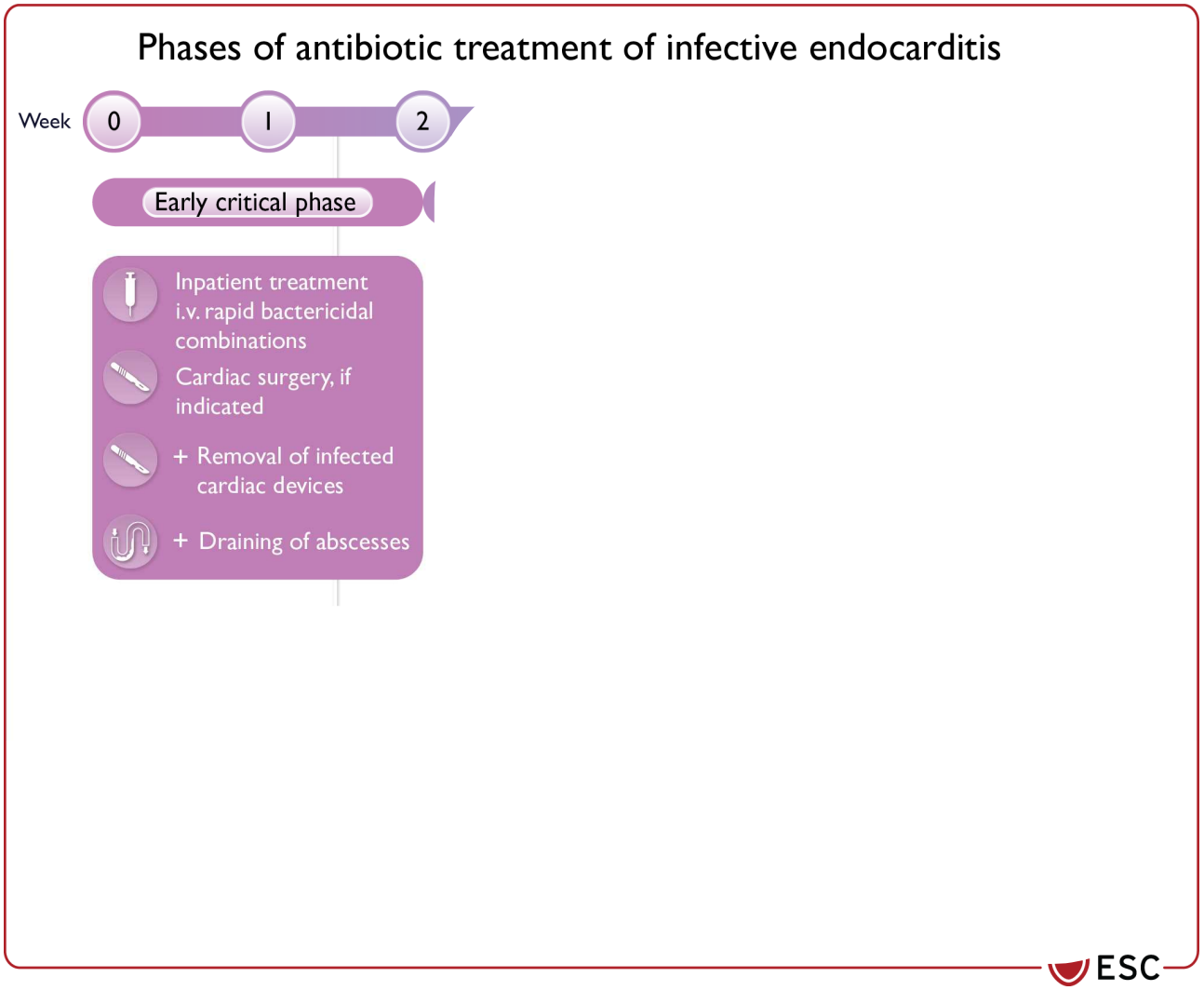
		Pénicilline G			
		≤ 0.125	0.25 – 2	> 2	Total
CRO	≤ 0.125	186 (36.2%)	13 (2.5%)	0	199 (38.7%)
	0.25	114 (22.2%)	20 (3.9%)	0	134 (26.1%)
	0.5	79 (15.4%)	43 (8.4%)	0	122 (23.7%)
	1	2* (0.4%)	22 (4.3%)	0	24 (4.7%)
	> 1	0	14 (2.7%)	21 (4.1%)	35 (6.8%)
	Total	381 (74.1%)	112 (21.8%)	21 (4.1%)	514 (100%)

* Discordance avec E-test

50% *mitis*
39% *sanguinis*

- Toutes les souches sensibles à la Péni G sont bien sensibles à la Ceftriaxone (sauf 2 ?)
- Certaines souches de sensibilité diminuée à la Péni G sont R à la Ceftriaxone (7 % du total, 32 % des souches I à la Péni G)

Phases of antibiotic treatment for infective endocarditis in relation to outpatient parenteral antibiotic therapy and partial oral endocarditis treatment



2023 ESC Guidelines for the management of endocarditis
(European Heart Journal; 2023 – doi: 10.1093/eurheartj/ehad193)

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oral streptococci and *Streptococcus gallolyticus* group

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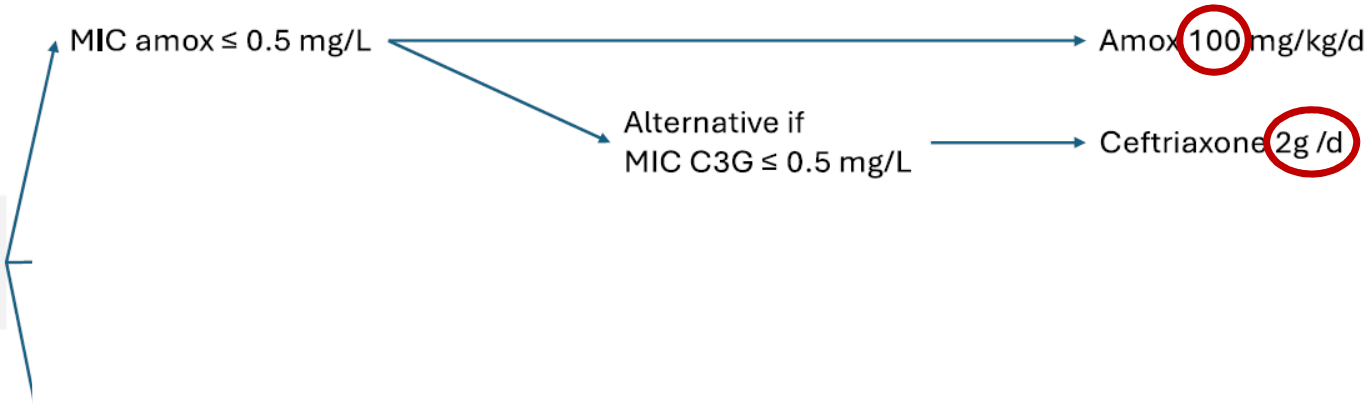

Fig. 1. Algorithm for the choice of antibiotic in streptococcal IE according to the MICs of amoxicillin and ceftriaxone. Abbreviations: MIC: minimal inhibitory concentration, C3G: ceftriaxone, amox: amoxicillin.

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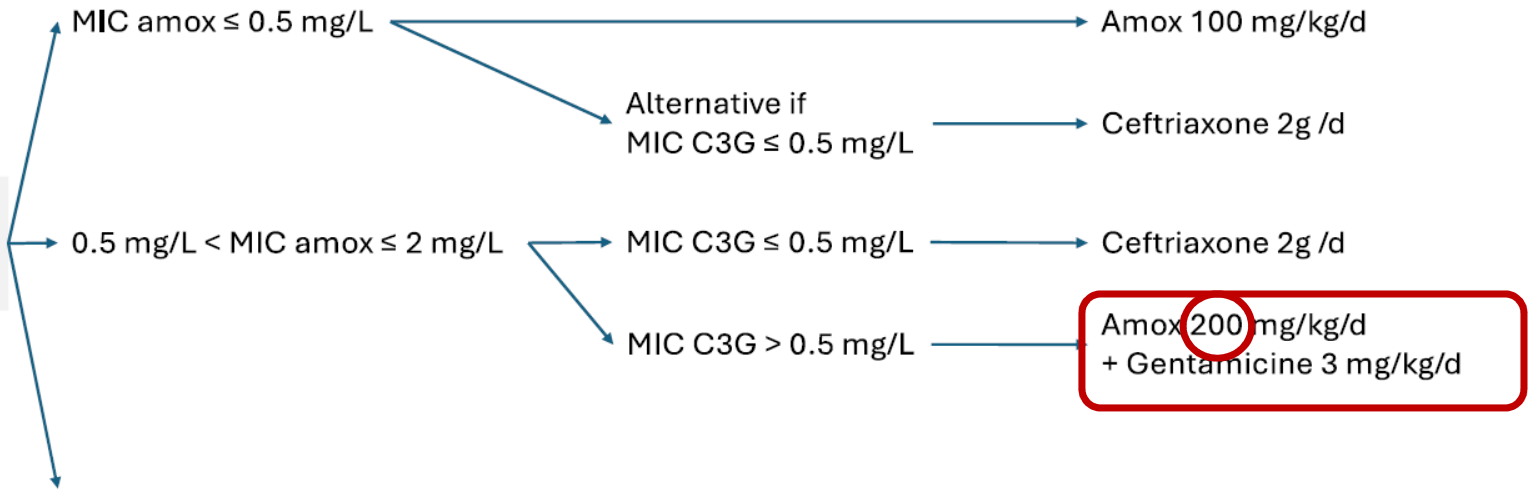
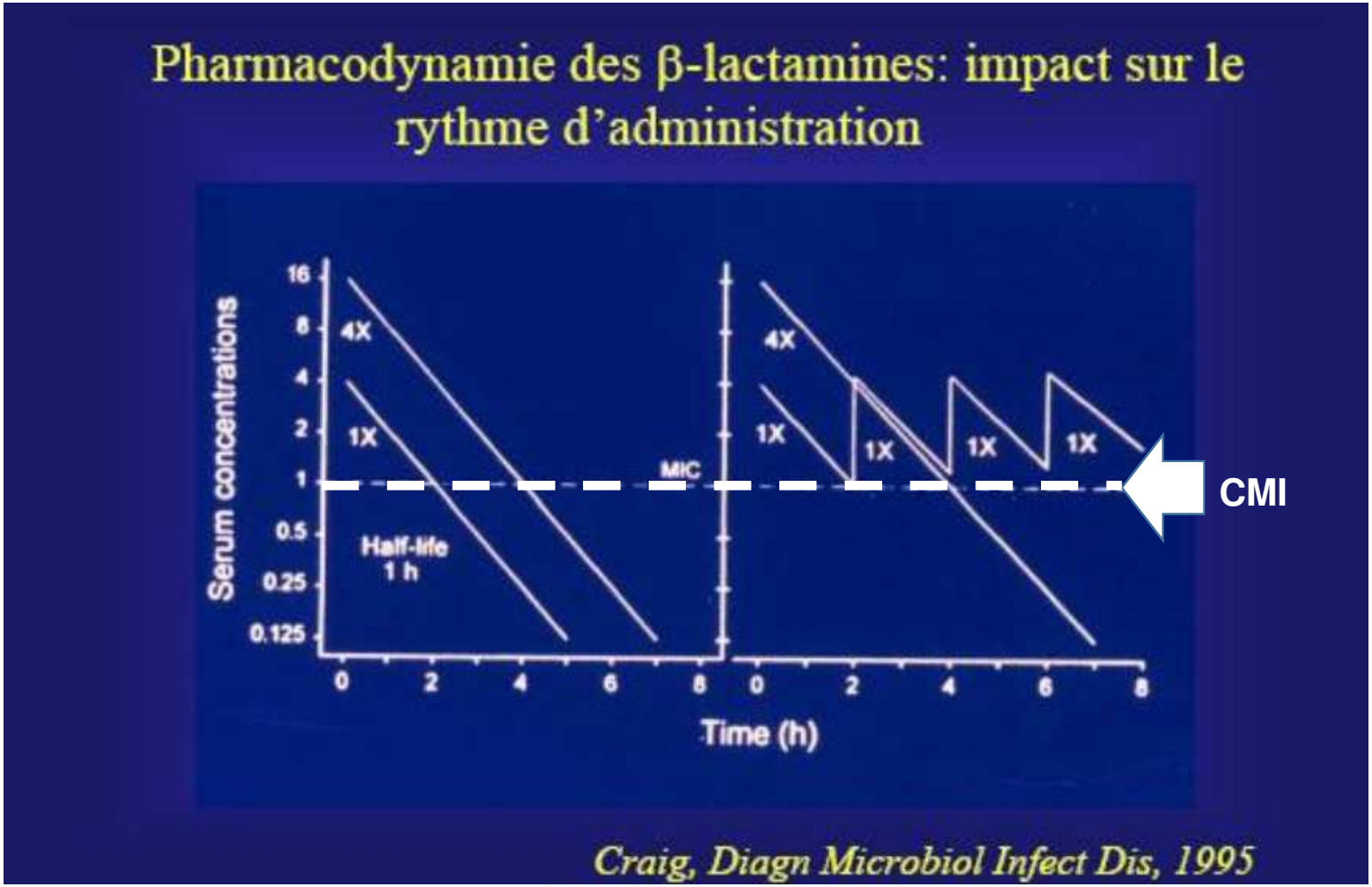


Fig. 1. Algorithm for the choice of antibiotic in streptococcal IE according to the MICs of amoxicillin and ceftriaxone. Abbreviations: MIC: minimal inhibitory concentration, C3G: ceftriaxone, amox: amoxicillin.

Pharmacodynamie des β-lactamines: impact sur le rythme d'administration



Craig, Diagn Microbiol Infect Dis, 1995

Solutions:

Augmenter le nombre de perfusions (4 à 6 par jour)

Ou faire de la perfusion continue

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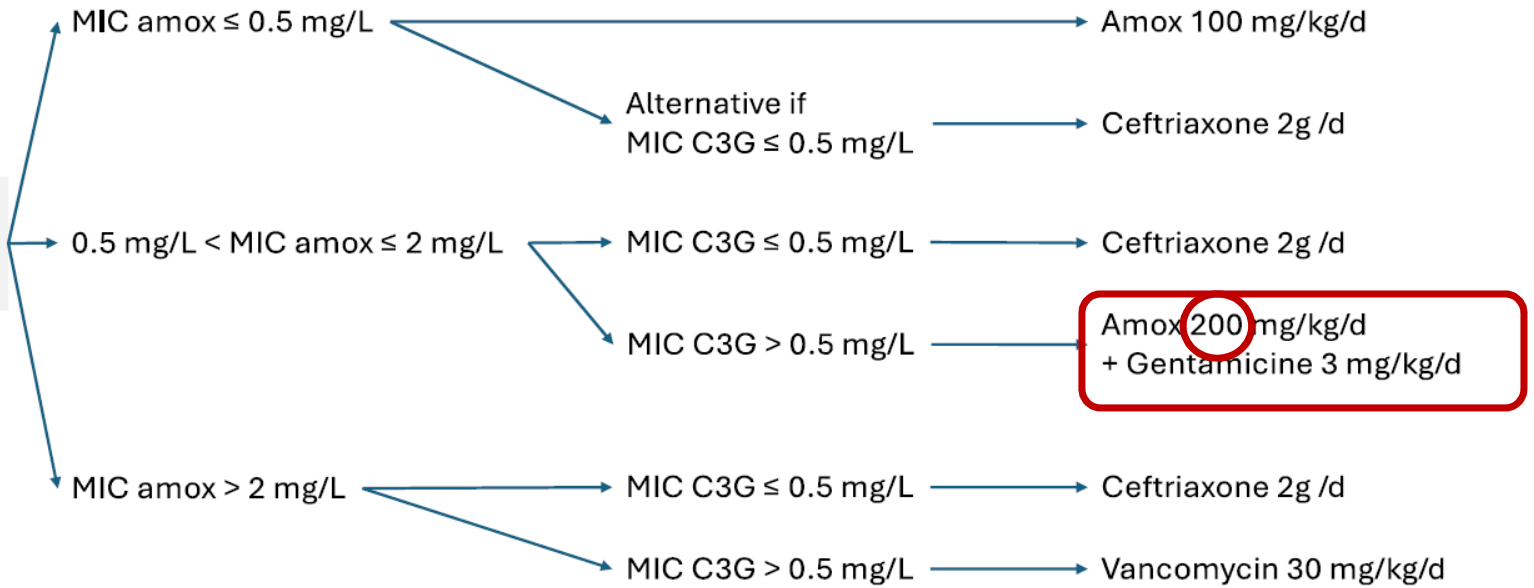


Fig. 1. Algorithm for the choice of antibiotic in streptococcal IE according to the MICs of amoxicillin and ceftriaxone. Abbreviations: MIC: minimal inhibitory concentration, C3G: ceftriaxone, amox: amoxicillin.

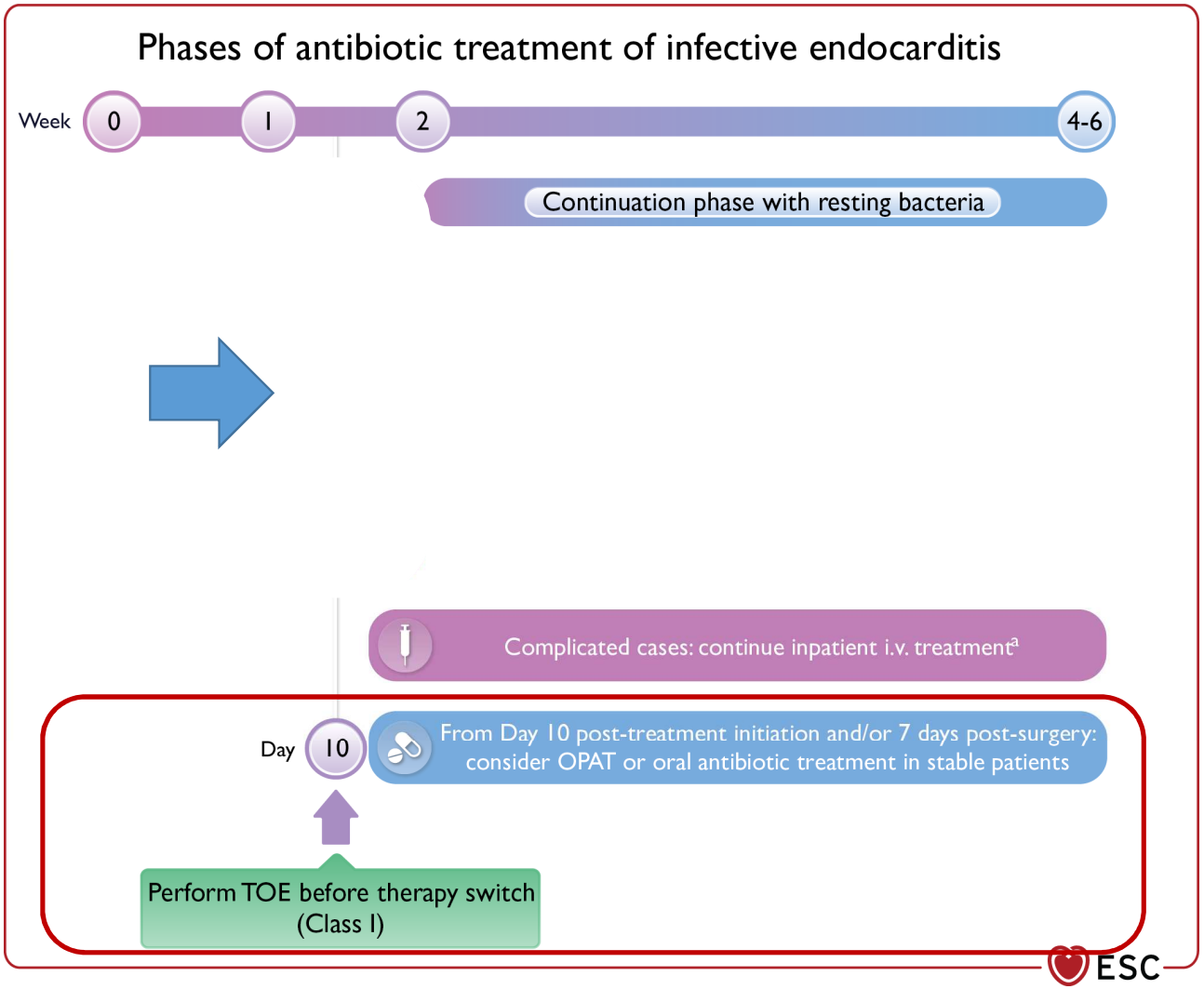
Traitement antibiotique ambulatoire (OPAT) ?

- Traitement parentéral ambulatoire
- Traitement (relai) oral ambulatoire

Table 21 **Criteria that determine suitability of outpatient parenteral antibiotic therapy for infective endocarditis (adapted from Andrews *et al.*[205])**

Phase of treatment	Guidelines for use
Critical phase (weeks 0–2)	• Complications occur during this phase • Preferred inpatient treatment during this phase • Consider OPAT if: oral streptococci or *Streptococcus bovis*,[a] native valve,[b] patient stable, no complications
Continuation phase (beyond week 2)	• Consider OPAT if medically stable • Do not consider OPAT if: HF, concerning echocardiographic features, neurological signs, or renal impairment
Essential for OPAT	• Educate patient and staff • Regular post-discharge evaluation (nurses 1/day, physician[c] in charge 1 or 2/week)[d] • Prefer physician-directed programme, not home-infusion model

Phases of antibiotic treatment for infective endocarditis in relation to outpatient parenteral antibiotic therapy and partial oral endocarditis treatment



2023 ESC Guidelines for the management of endocarditis
(European Heart Journal; 2023 – doi: 10.1093/eurheartj/ehad193)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

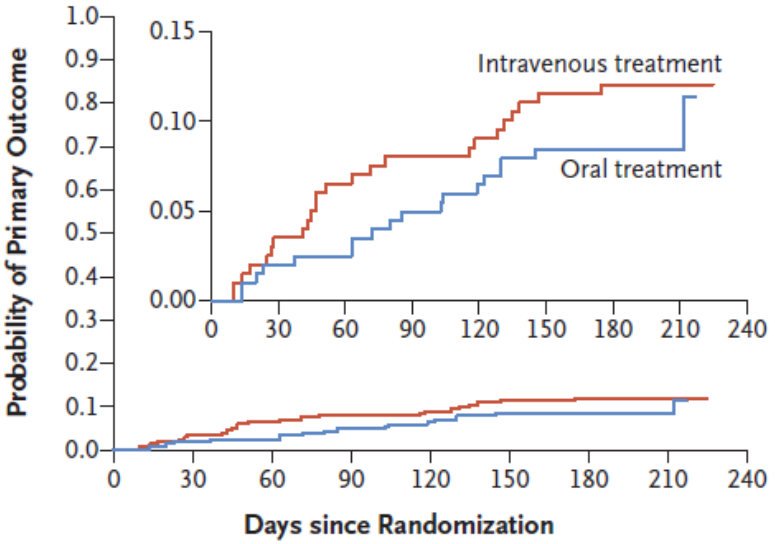
Kasper Iversen, M.D., D.M.Sc., Nikolaj Ihlemann, M.D., Ph.D., Sabine U. Gill, M.D., Ph.D., Trine Madsen, M.D., Ph.D., Hanne Elming, M.D., Ph.D., Kaare T. Jensen, M.D., Ph.D., Niels E. Bruun, M.D., D.M.Sc., Dan E. Høfsten, M.D., Ph.D., Kurt Fursted, M.D., D.M.Sc., Jens J. Christensen, M.D., D.M.Sc., Martin Schultz, M.D., Christine F. Klein, M.D., Emil L. Fosbøll, M.D., Ph.D., Flemming Rosenvinge, M.D., Henrik C. Schønheyder, M.D., D.M.Sc., Lars Køber, M.D., D.M.Sc., Christian Torp-Pedersen, M.D., D.M.Sc., Jannik Helweg-Larsen, M.D., D.M.Sc., Niels Tønder, M.D., D.M.Sc., Claus Moser, M.D., Ph.D., and Henning Bundgaard, M.D., D.M.Sc.

Inclusion and exclusion criteria

Inclusion criteria

- Left-sided endocarditis based on the Duke criteria
- Infected with one of the following microorganisms:
    - ⇒ Streptococci
    - ⇒ *Enterococcus faecalis*
    - ⇒ *Staphylococcus aureus*
    - ⇒ Coagulase-negative staphylococci
- ≥ 18 years
- ≥ 10 days of appropriate parenteral antibiotic treatment overall, and at least 1 week of appropriate parenteral treatment after valve surgery
- T < 38.0 °C > 2 days
- C-reactive protein dropped to less than 25% of peak value or < 20 mg/L, and white blood cell count < 15 x 10^9/L during antibiotic treatment
- No sign of abscess formation revealed by echocardiography
- Transthoracic and transesophageal echocardiography performed within 48 hours of randomization

Iversen K, NEJM 2018



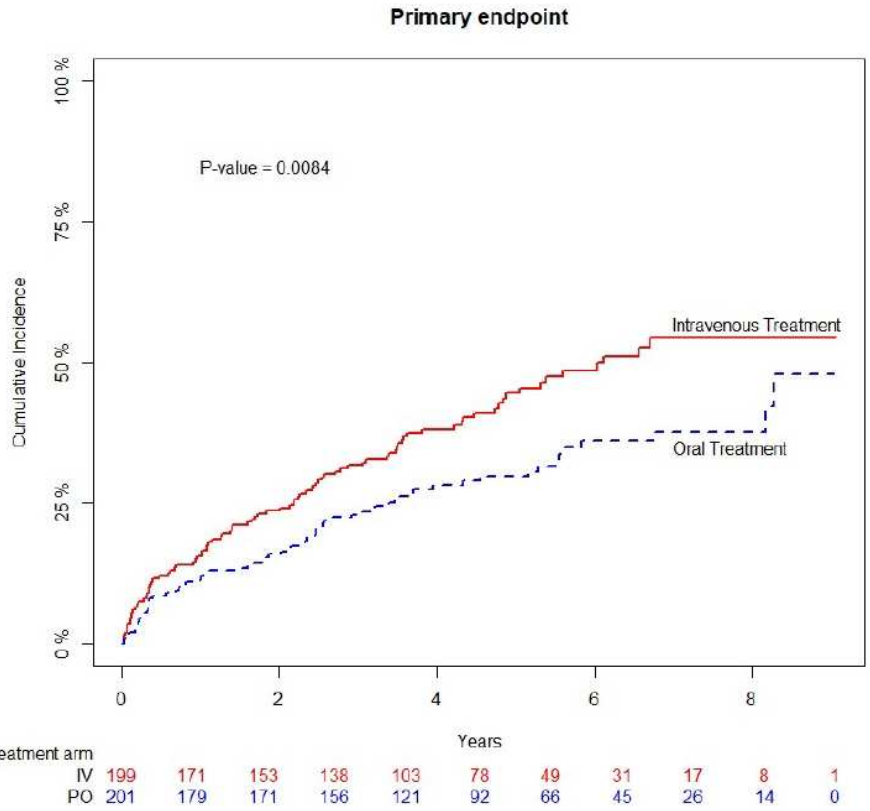
No. at Risk

Intravenous treatment	199	192	186	183	181	176	174	28	0
Oral treatment	201	197	196	191	188	184	183	36	0

Figure 2. Kaplan–Meier Plot of the Probability of the Primary Composite Outcome.

The primary composite outcome was all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with the primary pathogen, from randomization until 6 months after antibiotic treatment was completed. The oral treatment group shifted from intravenously administered antibiotics to orally administered antibiotics at a median of 17 days after the start of treatment. The inset shows the same data on an enlarged y axis.

Iversen K, NEJM 2018



Iversen K, NEJM 2022

Recommendations for outpatient antibiotic treatment of infective endocarditis

Recommendations	Class	Level
Outpatient parenteral or oral antibiotic treatment should be considered in patients with left-sided IE caused by *Streptococcus* spp., *E. faecalis*, *S. aureus*, or CoNS who were receiving appropriate i.v. antibiotic treatment for at least 10 days (or at least 7 days after cardiac surgery), are clinically stable, and who do not show signs of abscess formation or valve abnormalities requiring surgery on TOE.	IIa	A
Outpatient parenteral antibiotic treatment is not recommended in patients with IE caused by highly difficult-to-treat microorganisms, liver cirrhosis (Child-Pugh B or C), severe cerebral nervous system emboli, untreated large extracardiac abscesses, heart valve complications, or other severe conditions requiring surgery, severe post-surgical complications, and PWID-related IE.	III	C

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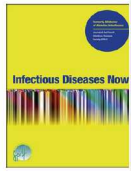


Guidelines

Antibiotic therapy and prophylaxis of infective endocarditis – A SPILF-AEPEI position statement on the ESC 2023 guidelines

Outpatient oral endocarditis treatment

	First line oral antibiotic regimen	Alternative oral antibiotic regimen
Streptococcus spp.	Amoxicillin + rifampicin *or* Amoxicillin + moxifloxacin	*Awaiting results of the RODEO trial* Amoxicillin

Oral antibiotic	Dosage if patient ≤ 70kg	Dosage if patient > 70kg
Amoxicillin	1.5g tid	2g tid
Rifampicin	600mg qd	900mg qd
Moxifloxacin	400mg qd	400mg qd
Levofloxacin	500mg qd	750mg qd
Cotrimoxazole	320/1600 mg tid	320/1600 mg tid
Ciprofloxacin	750 mg bid	750 mg bid

Quel traitement proposez-vous ?

1. **Chirurgie de remplacement valvulaire**
2. Amoxicilline 200 mg/kg pdt 2 S
3. Amoxicilline 100 mg/kg pdt 2 S et gentamicine pdt 2 S
4. **Amoxicilline 100 mg/kg pdt 4 S**
5. Vancomycine 30 mg/kg pdt 6 S
6. **Vous n'êtes pas en mesure de déterminer la durée du traitement à ce stade**

Quelle surveillance ?

Surveillance du traitement de l'EI
Efficacité

- **Critères cliniques:**
  - Courbe de température +++
  - ECG
  - Disparition des signes emboliques
- **Critères biologiques:**
  - Négativation des hémocultures ++++
  - Normalisation du bilan inflammatoire
  - Dosages sériques des antibiotiques
- **Critères échographiques:**
  - Végétation/ Abcès
  - Régurgitation/tolérance

Guérison = absence de rechute à l'arrêt du tt.

Causes de persistance de la fièvre au cours d'une EI sous traitement

- Antibiothérapie inadaptée ou insuffisante.
- Intolérance médicamenteuse.
- Dilution insuffisante de la péni G dans les perfusions.
- Phlébite au point d'injection.
- Accident thrombo-embolique.
- Foyer infectieux persistant au niveau de la porte d'entrée.
- Foyer infectieux secondaire (métastase septique).
- Foyer infectieux persistant au niveau de l'endocarde valvulaire (abcès septal ou paravalvulaire).

Un homme de 53 ans avec valve aortique mécanique et tube valvé

Vous avez opéré le patient à J7 de l'antibiothérapie

La culture de la valve revient positive

Les hémocultures se négativent à J10

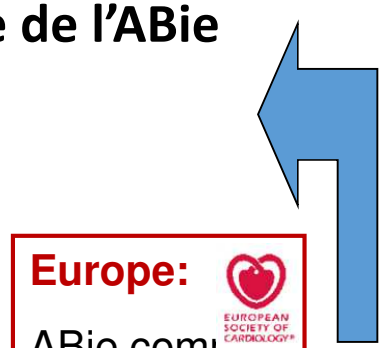
Quelle durée de traitement antibiotique proposez-vous ?

- Celle d'une EI sur prothèse
- Celle d'une EI sur valve native
- J0 ABie = J0 traitement
- J0 ABie = J7 (date de chirurgie)
- J0 ABie = J10 (date de négativation des hémocultures)

Durée ABie

American Heart Association®
ACC/AHA 2015

- **T0: jour avec hémoc négative**
- **Si culture valve positive/** abcès à chir **: reprendre AB à J0**
- **Si mise en place d'une valve au cours de la phase aigue, durée de l'ABie**
  - **Si culture de valve positive ou Abcès: comme EI sur prothèse**
  - **Dans le cas contraire: comme valve native (?)**
- **Si complication: spondylodiscite…**
  - **ABie IV pdt durée traitement EI**
  - **AB per os jusqu'à la durée cumulée complète**



Europe:
ABie comme valve native

El Enterocoque

El Enterocoque

	Native valve endocarditis (78%)				PM and Def IE (5%)	Prosthetic valve IE (17%)			TOTAL
	Community-acquired IE 55%	Health care-associated 18%		Drug abusers 5%		Early (< 2 mths) 1.0%	Mid term (2 – 12mths) 3.0%	Late (> 12 mths) 13%	
Pathogens		Nosocomial 15%	Non-nosocomial 3%						
Staphylococcus aureus	20/20 %	44/47%	25/42%	68/81%	23%	36/0%	7%	25%	26 %
CN Staphylococci	4/6%	12/15%	15/25%	0/3%	54%	0/17%	27%	9%	10 %
Oral streptococci*	26/28%	7/11%	0/6%	4/10%	0%	0/2%	7%	11%	18 %
Streptococcus bovis **	10/18%	3 %	3/8%	0/1%	4%	0/2%	7%	9%	12 %
Enterococcus	9%	6/14%	17/42%	4/5%	0%	7.5/20%	7%	20%	10 %
Pyogenic streptococci	8%	0%	0%	4%	0%	0%	0%	3%	5 %
Others	6%	14%	0%	0/3%	16%	0%	33%	12%	8 %
Negative-blood culture	9.5/11%	9/9 %	0/6%	0/5%	8%	17/40%	13%	12%	9%
Microorganism not identified	5%	4.5%	0%	0%	0%	40%	13%	8%	5%

≈ 10%

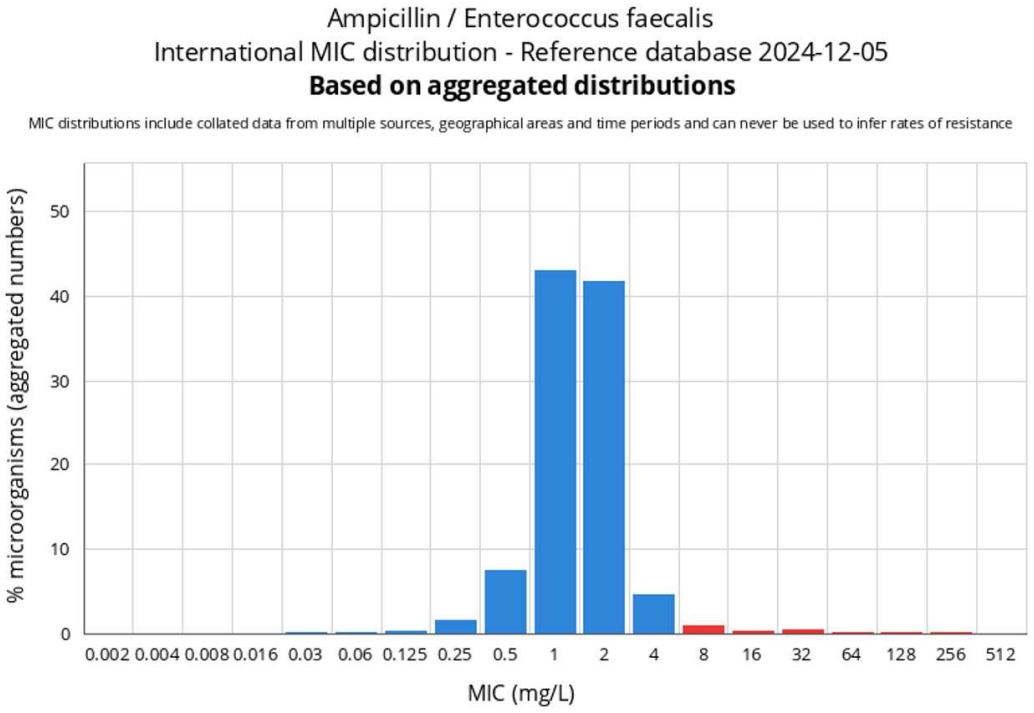
TAVI:

Microorganisms:

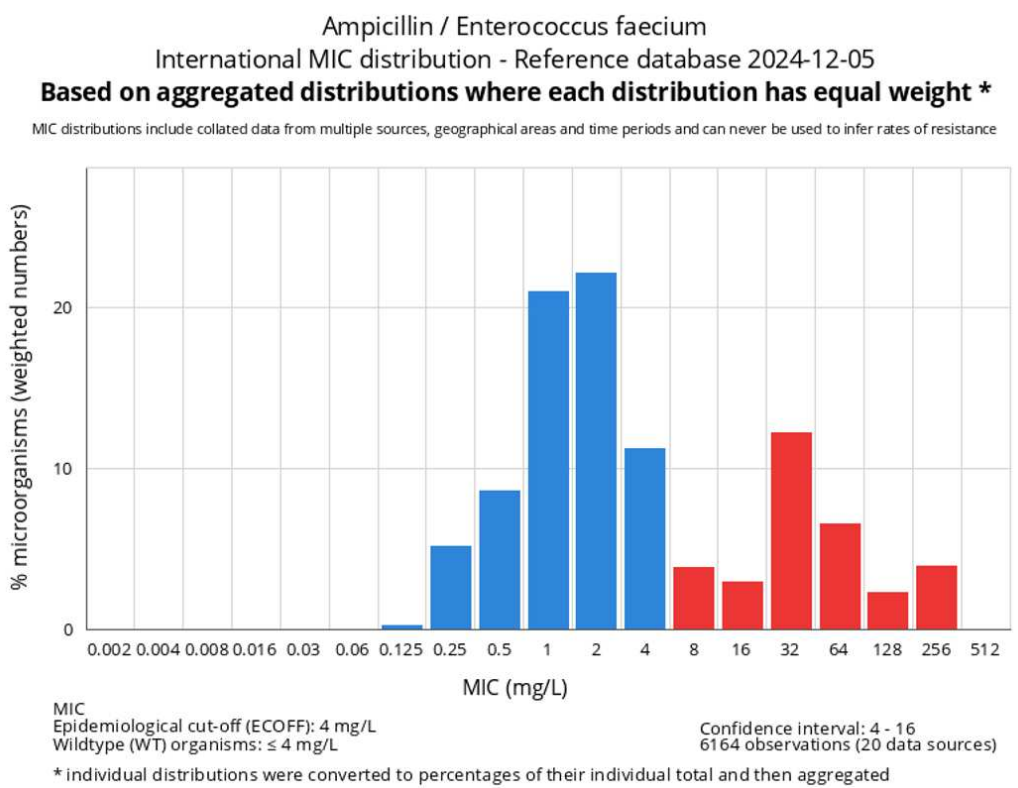
Enterococci species	25%
Staphylococcus aureus	23%
Coag Neg Staphylococci	17%

Hoen B, Duval X, N Eng J Med 2013;368:1425-33

MIC distribution Amoxicillin *Enterococcus faecalis*



MIC distribution Amoxicillin *Enterococcus faecium*



Synergie
betalactamines
Aminosides

Entérocoque

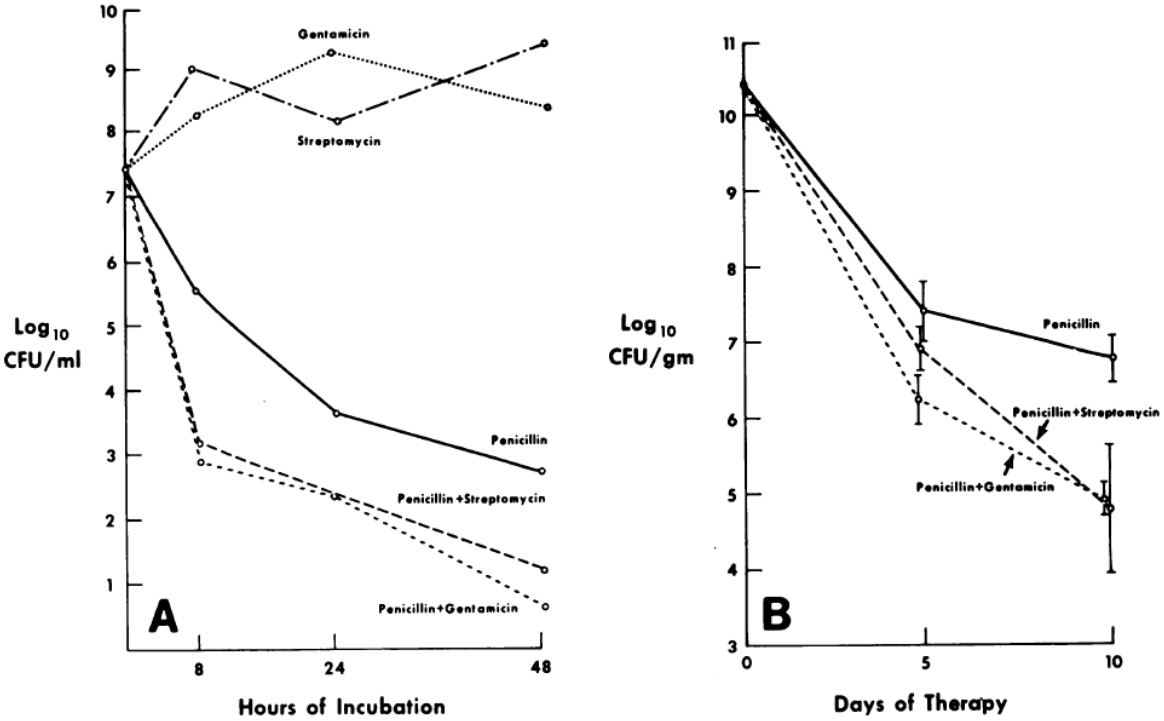


FIG. 1. (A) *Rate of killing of streptomycin-susceptible enterococci in broth by antibiotics. Concentration of antibiotics: penicillin, 10 μg/ml; gentamicin, 5 μg/ml; and streptomycin, 10 μg/ml.* (B) *Rate of eradication of streptomycin-susceptible enterococci from cardiac vegetations in experimental endocarditis after 5 and 10 days of antibiotic therapy* (Ⱦ *represents geometric mean with standard error*).

Hook III EW et al. Antimicrob Agents Chemother 1975

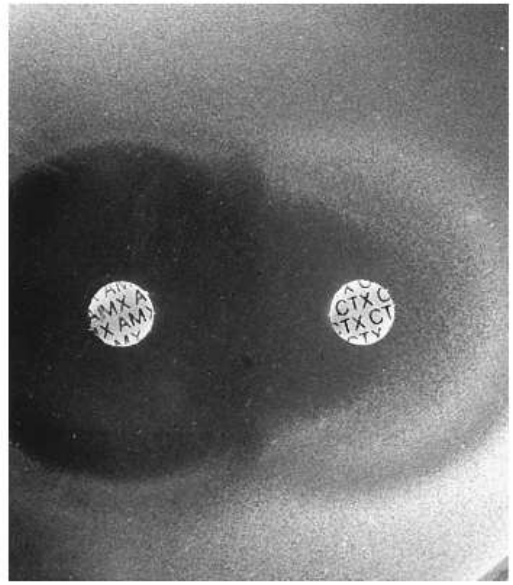


FIG. 1. Synergistic effect between amoxicillin and cefotaxime against JH2-2 on brain heart infusion agar. AMX, amoxicillin; CTX, cefotaxime.

Mainardi JL Antimicrob Agents Chemother 1995, p. 1984–1987

2023

EI Enterocoque

Recommendations for antibiotic treatment or infective endocarditis due to enterococcus spp

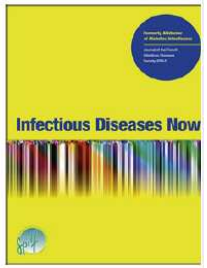
Situation	Antibiotique	Posologie	Durée
Souche sensible aux bêtalactamines et de bas niveau de résistance à la gentamicine			
EI VNative et EI VProthétique	Amoxicilline	200 mg/kg/j en 4–6 doses	6 semaines
	+ ou Ceftriaxone (pour E. faecalis)	4 g/j IV en 2 doses	6 semaines
	Ou Gentamicine	3 mg/kg/j IV en 1 dose	2 premières semaines

Concentration résiduelle de CTX 20-30 mg/L

Contents lists available at ScienceDirect

Infectious Diseases Now

journal homepage: www.sciencedirect.com/journal/infectious-diseases-now



Guidelines

Enterococcal IE

Antibiotic therapy and prophylaxis of infective endocarditis – A SPILF-AEPEI position statement on the ESC 2023 guidelines

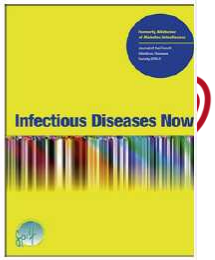
- For strains susceptible to amoxicillin and regardless the level of gentamicin resistance: amoxicillin + ceftriaxone for 6 weeks, **whether on native or prosthetic valves**. Particular attention should be paid to the nephrotoxicity and neurotoxicity of the combination.

Amoxicillin	**200 mg/kg/24h in 6 IV doses**
Ceftriaxone	4g/24h in 2 IV doses

Contents lists available at ScienceDirect

Infectious Diseases Now

journal homepage: www.sciencedirect.com/journal/infectious-diseases-now



ESC

Guidelines

Enterococcal IE

Antibiotic therapy and prophylaxis of infective endocarditis – A SPILF-AEPEI position statement on the ESC 2023 guidelines

Check for updates

Enterococcus faecalis

For amoxicillin-resistant strains or in patients unable to tolerate β-lactams

Daptomycin*: there are currently insufficient data to recommend a combination with a β-lactam antibiotic for *E. faecalis* strains susceptible to daptomycin and vancomycin. In case of a combination, ceftaroline appears to be the most suitable companion.

Vancomycin (6 weeks) + gentamicin (non HLAR strain) during the first 2 weeks of treatment. Particular attention should be paid to the nephrotoxicity of the combination.

www.escardio.org/guidelines

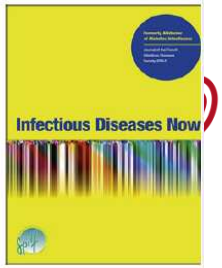
Gentamicin	3 mg/kg/24h in 1 IV dose
Vancomycin	24 hour-continuous infusion; serum drug level target around 20-25 mg/L
Daptomycin	12 mg/kg/24h in 1 IV dose

* Only if MIC ≤ 2 mg/L.

Contents lists available at ScienceDirect

Infectious Diseases Now

journal homepage: www.sciencedirect.com/journal/infectious-diseases-now



ESC

Guidelines

Enterococcal IE

Antibiotic therapy and prophylaxis of infective endocarditis – A SPILF-AEPEI position statement on the ESC 2023 guidelines

Check for updates

Enterococcus faecium (even in strain susceptible to amoxicillin) and for Non HLAR

Vancomycin (6 weeks) + gentamicin (non HLAR strain) during the first 2 weeks of treatment. Particular attention should be paid to the nephrotoxicity of the combination.

Contents lists available at ScienceDirect

Infectious Diseases Now

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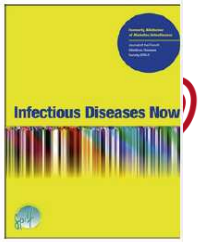


Guidelines

Antibiotic therapy and prophylaxis of infective endocarditis – A SPILF-AEPEI position statement on the ESC 2023 guidelines

How to prevent crystalluria due to amoxicillin in the treatment of IE?

When using high-dose amoxicillin in IE, it is essential to:

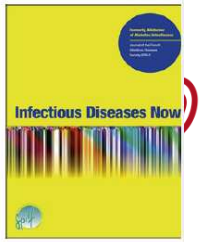
- comply with amoxicillin administration procedures: maximum dose of 200 mg/kg/day, not to exceed 12g/day, maximum of 2g per infusion in a volume of 100 mL, minimum infusion time of 20 min, ideally 1h or continuously with an infusion pump.

- keep the patient well hydrated,
- alkalinize urine (target urinary pH > 7 using dipsticks)
- monitor renal function and diuresis.

Contents lists available at ScienceDirect

Infectious Diseases Now

journal homepage: www.sciencedirect.com/journal/infectious-diseases-now



Guidelines

Antibiotic therapy and prophylaxis of infective endocarditis – A SPILF-AEPEI position statement on the ESC 2023 guidelines

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- keep the patient well hydrated,

- alkalinize urine (target urinary pH > 7 using dipsticks)

- monitor renal function and diuresis.

If available, monitoring of crystalluria may be useful; if it occurs, it predicts acute kidney injury and may necessitate change of therapy, i.e. change to a cephalosporin in streptococcal IE.

Occurrence of crystalluria does not contra-indicate the subsequent use of amoxicillin, particularly as antibiotic prophylaxis.

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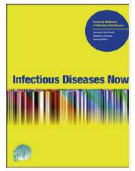


Guidelines

Antibiotic therapy and prophylaxis of infective endocarditis – A SPILF-AEPEI position statement on the ESC 2023 guidelines

Outpatient oral endocarditis treatment

	First line oral antibiotic regimen	Alternative oral antibiotic regimen
Enterococcus faecalis	Amoxicillin + moxifloxacin	*Awaiting results of the RODEO trial* Amoxicillin

Oral antibiotic	Dosage if patient ≤ 70kg	Dosage if patient > 70kg
Amoxicillin	1.5g tid	2g tid
Rifampicin	600mg qd	900mg qd
Moxifloxacin	400mg qd	400mg qd
Levofloxacin	500mg qd	750mg qd
Cotrimoxazole	320/1600 mg tid	320/1600 mg tid
Ciprofloxacin	750 mg bid	750 mg bid

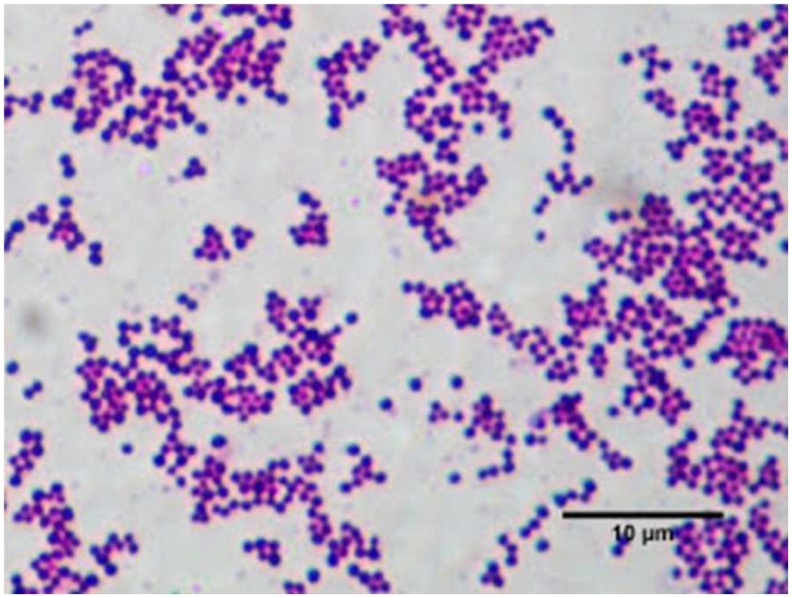
Cas clinique

Homme, 47 ans, bicuspidie aortique

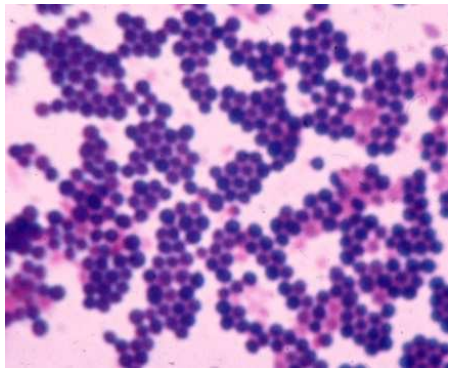
- Fièvre aiguë (72 h)
- Lésions hémorragiques plantaires
- Souffle diastolique aortique
- Patient prostré
- Hémocultures: cocci Gram+

Culture:

Staphylococcus aureus



Endocardites à Staphylocoque



Endocardites à Staphylocoque

	Native valve endocarditis (78%)				PM and Def IE (5%)	Prosthetic valve IE (17%)			TOTAL
	Community-acquired IE 55%	Health care-associated 18%		Drug abusers 5%		Early (< 2 mths) 1.0%	Mid term (2 – 12mths) 3.0%	Late (> 12 mths) 13%	
Pathogens		Nosocomial 15%	Non-nosocomial 3%						
Staphylococcus aureus	20/20 %	44/47%	25/42%	68/81%	23%	36/0%	7%	25%	26 %
CN Staphylococci	4/6%	12/15%	15/25%	0/3%	54%	0/17%	27%	9%	10 %
Oral streptococci*	26/28%	7/11%	0/6%	4/10%	0%	0/2%	7%	11%	18 %
Streptococcus bovis **	10/18%	3 %	3/8%	0/1%	4%	0/2%	7%	9%	13 %
Enterococcus	9%	6/14%	17/42%	4/5%	0%	7.5/20%	7%	20%	10 %
Pyogenic streptococci	8%	0%	0%	4%	0%	0%	0%	3%	5 %
Others	6%	14%	0%	0/3%	16%	0%	33%	12%	8 %
Negative-blood culture	9.5/11%	9/9 %	0/6%	0/5%	8%	17/40%	13%	12%	9%
Microorganism not identified	5%	4.5%	0%	0%	0%	40%	13%	8%	5%

≈ 36%

Hoen B, Duval X, N Eng J Med 2013;368:1425-33

Endocardite à SDMS

Valve Native

Recommendations for antibiotic treatment for staphylococcal NVE

Situation	Regimen	Comments	Duration
Methicillin-sensitive staphylococci			
Without allergy to β-lactams	**Cefazolin** **Or** **(Cl)oxacillin**	Preferred option in case of meningitis.	**Left-sided NVE** **4-week** treatment if i) apyrexia obtained in the first few days of treatment and ii) blood cultures negative by day 3 **6 weeks** in other cases **Right-sided NVE** **2-week** treatment if i) apyrexia obtained in the first few days of treatment and ii) blood cultures negative by day 3 **4 weeks** in other cases

Cefazoline dans EI Staphylocoque SDMS Valve native

Patient non allergique ?

CMI CLINICAL MICROBIOLOGY AND INFECTION
ESCMID

Comparative outcomes of cefazolin versus antistaphylococcal penicillins in methicillin-susceptible *Staphylococcus aureus* infective endocarditis: a *post hoc* analysis of a prospective multicentre French cohort study

Raphaël Lecomte [1, 3, *], Alexis Bourreau [1, 3], Colin Deschanvres [1, 3], Nahéma Issa [5], Paul Le Turnier [1, 3], Benjamin Gaborit [1, 3], Marie Chauveau [1, 3], Anne-Gaëlle Leroy [2], Thierry Le Tourneau [4], Jocelyne Caillon [2], Fabrice Camou [5], David Boutoille [1, 3]

The overall 90-day mortality rate was 27.6% (58/210 patients), 24.5% (13/53) in the cefazolin group vs. 28.7% (45/157) in the ASP group (p 0.561). Premature antimicrobial discontinuation due to adverse events occurred less frequently with cefazolin than with ASPs (0/53 vs. 13/157 patients; p 0.042). In

Conclusions: ***Cefazolin seems to be a possible alternative to ASPs in MSSA endocarditis****. More studies are needed to confirm these results and determine which treatment should be recommended as first-line therapy.*

Clin Microbiol Infect 2021

CLOCEBA

Etude randomisée multicentrique de non infériorité comparant l'efficacité de la Cloxacilline à la Céfazoline pour le traitement des bactériémies à *Staphylococcus aureus* sensible à la méticilline

PHRC National

Coordinating Investigator: F-Xavier LESCURE
Scientific director: Xavier Duval
Methodologist: Charles Burdet

Comment améliorer le pronostic des endocardites à Staphylocoque ?

- Optimisation antibiotique ?

Initial Low-Dose Gentamicin for *S. aureus* Bacteremia and Endocarditis is Nephrotoxic

Renal toxic effects, by original randomized treatment arms

Toxic effect	Daptomycin arm	Standard therapy arm			
		Overall	P^a	Vancomycin	ASP
Renal impairment adverse events					
Overall population	8/120 (7)	21/116 (18)	.01	10/53 (19)	11/63 (17)
Patients aged ≥65 years	2/30 (7)	12/38 (32)	.02	6/16 (38)	6/22 (27)
Patients with diabetes	3/44 (7)	12/42 (29)	.01	5/21 (24)	7/21 (33)
Clinically significant decrease in CrCl					
Overall population	9/113 (8)	26/109 (24)	.002	10/46 (22)	16/63 (25)
Patients aged ≥65 years	3/27 (11)	15/35 (43)	.01	5/13 (39)	10/22 (45)
Patients with diabetes	3/44 (7)	12/40 (30)	.01	5/19 (26)	7/21 (33)

Cosgrove SE, Clin Infect Dis 2009; 8:713-21

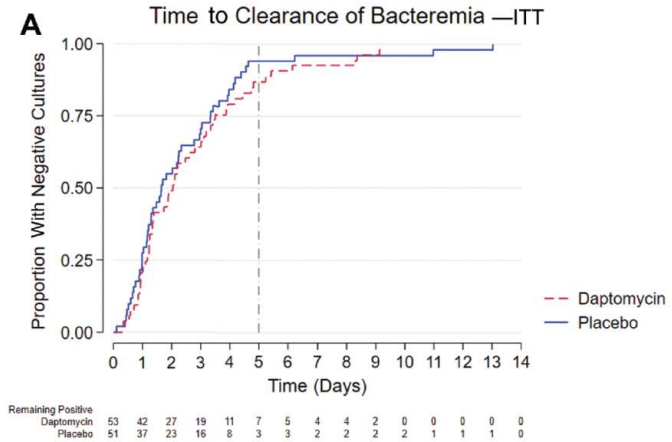
Clinical Infectious Diseases

MAJOR ARTICLE

Adjunctive Daptomycin in the Treatment of Methicillin-susceptible *Staphylococcus aureus* Bacteremia: A Randomized, Controlled Trial

Matthew P. Cheng,[1,a] Alexander Lawandi,[2,a] Guillaume Butler-Laporte,[2,a] Samuel De l'Étoile-Morel,[2] Katryn Paquette,[3] and Todd C. Lee[2,4,5]

[1]Division of Infectious Diseases, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA, [2]Division of Infectious Diseases, Department of Medicine, McGill University, Montreal, Quebec, Canada, [3]Division of Neonatology, Montreal Children's Hospital, McGill University, Montreal, Quebec, Canada, [4]Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada, and [5]Clinical Practice Assessment Unit, Department of Medicine, McGill University, Montreal, Quebec, Canada



SDMS

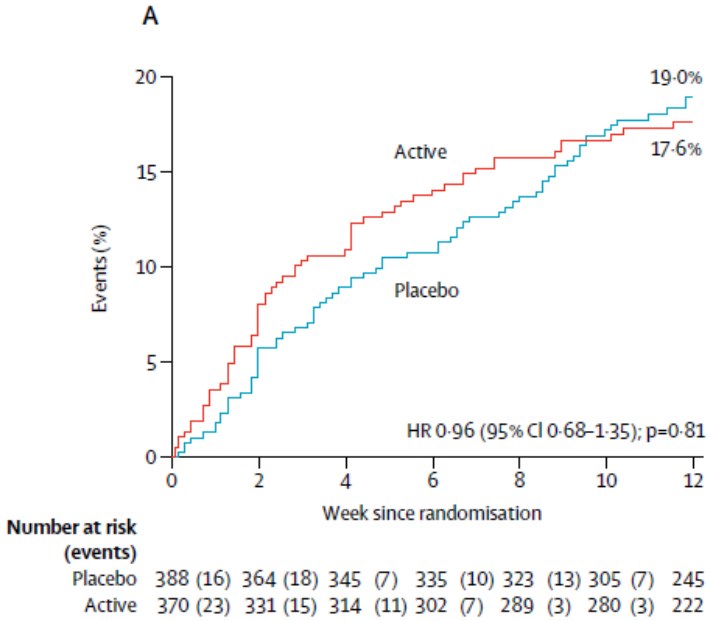
Peni M + Dapto VS Peni M:

Variable	No. (%) Placebo (n = 51)	Daptomycin (n = 53)	Total (n = 104)	*P* Value
All-cause mortality (30 days)	6 (11.8)	8 (15.1)	14 (13.5)	.62
All-cause mortality (90 days)	9 (17.7)	10 (18.9)	19 (18.3)	1

Cheng MP, Clin Infect Dis 2021

Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial

*Guy E Thwaites, Matthew Scarborough, Alexander Szubert, Emmanuel Nsutebu, Robert Tilley, Julia Greig, Sarah A Wyllie, Peter Wilson, Cressida Auckland, Janet Cairns, Denise Ward, Pankaj Lal, Achyut Guleri, Neil Jenkins, Julian Sutton, Martin Wiselka, Gonzalez-Ruiz Armando, Clive Graham, Paul R Chadwick, Gavin Barlow, N Claire Gordon, Bernadette Young, Sarah Meisner, Paul McWhinney, David A Price, David Harvey, Deepa Nayar, Dakshika Jeyaratnam, Tim Planche, Jane Minton, Fleur Hudson, Susan Hopkins, John Williams, M Estee Török, Martin J Llewelyn, Jonathan D Edgeworth, A Sarah Walker, on behalf of the United Kingdom Clinical Infection Research Group (UKCIRG)**



SDMS

Peni M + Rifam VS Peni M:

Thwaites GE, Lancet 2018

Rifampin for the treatment of NV SA IE

- **Etude C/T rétrospective (EI à SA sur VN - SAMS/R**
  - 42 cas d'EI ayant reçu au moins une dose de RIF (méd 20j)
  - 42 témoins appariés sur la date du diagnostic (2004 – 2005)

	cas	témoins	p
Sélection d'isolats RIF-R	**9 (21%)**	**0**	**<0,001**
Temps médian à RIF-R (n=9, jours, moy (range)	**16 (11 – 26)**	**-**	**-**
ALT > 5 x baseline	**9 (21%)**	**1 (2%)**	**0,01**
Interactions médicamenteuses	**22 (52%)**	**0**	**<0,001**

- **Résultats complémentaires**
  - Les **résistances sont survenues lorsque la RIF a été introduite chez des patients encore bactériémiques**
  - Mortalité plus élevée chez les cas (mais gravité possiblement plus élevée également : plus de localisations SNC, plus d'AG)

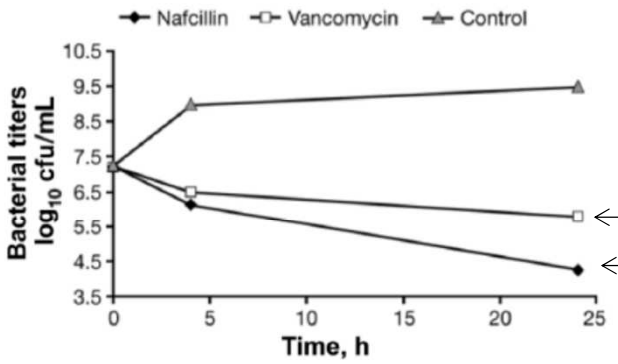
Riedel DJ, AAC 2008;52:2463-7

Vancomycine – les 'faits'

- ***In vitro*: bactéricidie lente**

- **Etudes cliniques**
  - **Vanco < β-lactamines sur SAMS**
  - **Durée médiane bactériémies**
    - **2 j si SAMS/oxacilline**
    - **5 j si SAMS/vanco, 7 j si SARM/vanco**

Stryjewski et al. Clin Infect Dis 2007; Chang et al. Medicine 2003



← Vanco
← Peni M

Figure 1. Time-kill curves for methicillin-susceptible *Staphylococcus aureus*, comparing nafcillin with vancomycin at 4 times the MIC. cfu, colony-forming units. Adapted from Small and Chambers [5].

Recommendations for antibiotic treatment for staphylococcal NVE

Situation	Regimen	Comments	Duration
Methicillin-sensitive staphylococci			
Without allergy to β-lactams	Cefazolin Or (Cl)oxacillin	Preferred option in case of meningitis.	**Left-sided NVE** **4-week** treatment if i) apyrexia obtained in the first few days of treatment and ii) blood cultures negative by day 3 **6 weeks** in other cases **Right-sided NVE** **2-week** treatment if i) apyrexia obtained in the first few days of treatment and ii) blood cultures negative by day 3 **4 weeks** in other cases
Early or non-severe late allergy to penicillin	**Cefazolin**		

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Situation	Regimen	Comments	Duration
Methicillin-sensitive staphylococci			
Without allergy to β-lactams	Cefazolin Or (Cl)oxacillin	Preferred option in case of meningitis.	<u>Left-sided NVE</u> 4-week treatment if i) apyrexia obtained in the first few days of treatment and ii) blood cultures negative by day 3 6 weeks in other cases <u>Right-sided NVE</u> 2-week treatment if i) apyrexia obtained in the first few days of treatment and ii) blood cultures negative by day 3 4 weeks in other cases
Early or non-severe late allergy to penicillin	Cefazolin		
Late severe allergy to penicillin	Daptomycin with fosfomycin		

Clinical Infectious Diseases

MAJOR ARTICLE

Daptomycin Plus Fosfomycin Versus Daptomycin Alone for Methicillin-resistant *Staphylococcus aureus* Bacteremia and Endocarditis: A Randomized Clinical Trial

Miquel Pujol,[1,a] José-María Miró,[2,a] Evelyn Shaw,[1] Jose-María Aguado,[3] Rafael San-Juan,[3] Mireia Puig-Asensio,[4] Carles Pigrau,[4] Esther Calbo,[5]

Background. We aimed to determine whether daptomycin plus fosfomycin provides higher treatment success than daptomycin alone for methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia and endocarditis.

Methods. A randomized (1:1) phase 3 superiority, open-label, and parallel group clinical trial of adult inpatients with MRSA bacteremia was conducted at 18 Spanish hospitals. Patients were randomly assigned to receive either 10 mg/kg of daptomycin intravenously daily plus 2 g of fosfomycin intravenously every 6 hours, or 10 mg/kg of daptomycin intravenously daily. Primary endpoint was treatment success 6 weeks after the end of therapy.

Results. Of 167 patients randomized, 155 completed the trial and were assessed for the primary endpoint. Treatment success at 6 weeks after the end of therapy was achieved in 40 of 74 patients who received daptomycin plus fosfomycin and in 34 of 81 patients who were given daptomycin alone (54.1% vs 42.0%; relative risk, 1.29 [95% confidence interval, .93–1.8]; $P = .135$). At 6 weeks, daptomycin plus fosfomycin was associated with lower microbiologic failure (0 vs 9 patients; $P = .003$) and lower complicated bacteremia (16.2% vs 32.1%; $P = .022$). Adverse events leading to treatment discontinuation occurred in 13 of 74 patients (17.6%) receiving daptomycin plus fosfomycin, and in 4 of 81 patients (4.9%) receiving daptomycin alone ($P = .018$).

Conclusions. Daptomycin plus fosfomycin provided 12% higher rate of treatment success than daptomycin alone, but this difference did not reach statistical significance. This antibiotic combination prevented microbiological failure and complicated bacteremia, but it was more often associated with adverse events.

Endocardite à SDMR

Valve Native

Recommendations for antibiotic treatment for staphylococcal NVE

Situation	Regimen	Comments	Duration
Methicillin-resistant staphylococcie			
Without allergy to β-lactams	**Daptomycin** With **ceftaroline** or **Daptomycin** With **fosfomycin**	**Duration of the combination therapy**: as long as the bacteremia lasts and for a maximum of 7 days from the 1st negative blood culture. If vancomycin MIC ≤ 1 mg/L.	**Left-sided NVE** **4-week** treatment if i) apyrexia obtained in the first few days of treatment and ii) blood cultures negative by day 3 **6 weeks** in other cases **Right-sided NVE** **2-week** treatment if i) apyrexia obtained in the first few days of treatment and ii) blood cultures negative by day 3 **4 weeks** in other cases

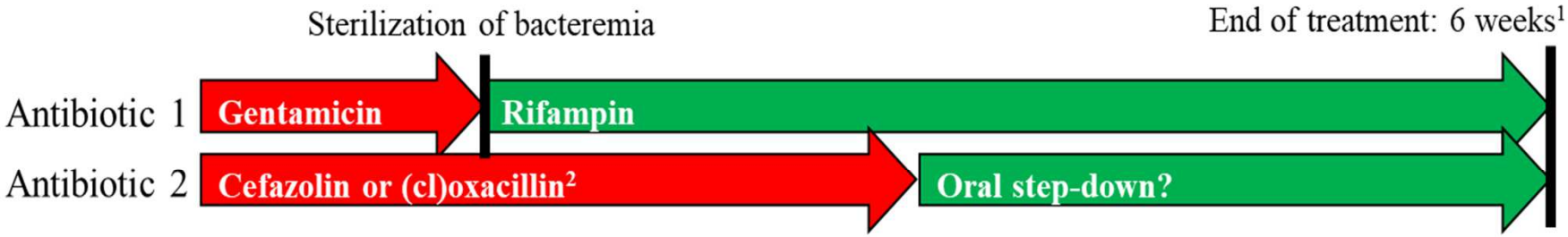
Recommendations for antibiotic treatment for staphylococcal NVE

Situation	Regimen	Comments	Duration
Methicillin-resistant staphylococcie			
		Duration of the combination therapy: as long as the bacteremia lasts and for a maximum of 7 days from the 1st negative blood culture.	Left-sided NVE **4-week** treatment if i) apyrexia obtained in the first few days of treatment and ii) blood cultures negative by day 3 **6 weeks** in other cases Right-sided NVE **2-week** treatment if i) apyrexia obtained in the first few days of treatment and ii) blood cultures negative by day 3 **4 weeks** in other cases
Late severe allergy to penicillin or allergy to cephalosporins	**Daptomycin** With **fosfomycin** or **Vancomycin**	If vancomycin MIC ≤ 1 mg/L.	

Endocardite à SDMS

Valve Prothètique

Treatment of methicillin-susceptible staphylococcal prosthetic valve endocarditis



[1]6 weeks after the first day of effective therapy: negative blood culture in the case of initial positive blood culture or day of surgery if valve cultures are positive.

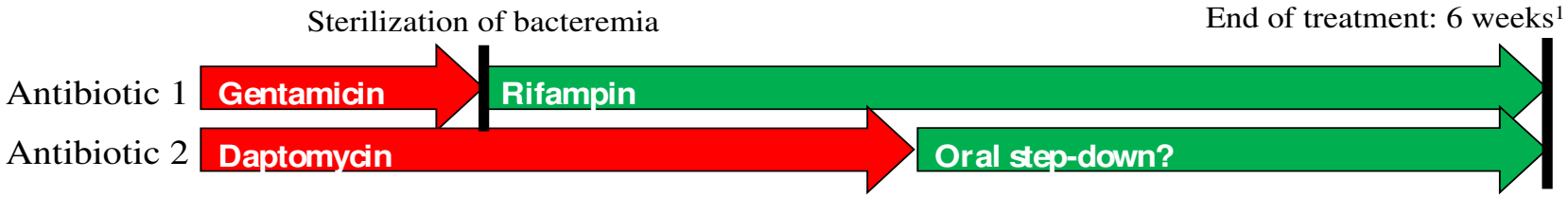
[2]The choice of cefazolin *vs* (cl)oxacillin should follow the same rules than for NVE

Endocardite à SDMR

Valve Prothètique

Treatment of methicillin-susceptible staphylococcal prosthetic valve endocarditis

Treatment of methicillin-resistant staphylococcal prosthetic valve endocarditis (or in case of allergy to betalactams)



[1]6 weeks after the first day of effective therapy: negative blood culture in the case of initial positive blood culture or day of surgery if valve cultures are positive.

Clinical Infectious Diseases

MAJOR ARTICLE

Is Rifampin Use Associated With Better Outcome in Staphylococcal Prosthetic Valve Endocarditis? A Multicenter Retrospective Study

Audrey Le Bot,[1] Raphaël Lecomte,[2] Pierre Gazeau,[3] François Benezit,[1] Cédric Arvieux,[1] Séverine Ansart,[3] David Boutoille,[2] Rozenn Le Berre,[4] Céline Chabanne,[5] Matthieu Lesouhaitier,[1] Loren Dejoies,[6,7] Erwan Flecher,[5] Jean-Marc Chapplain,[1] Pierre Tattevin,[1,7,8] and Matthieu Revest[1,7,8]; Pour le Groupe d'Epidémiologie et Recherche en Infectiologie Clinique du Centre et de l'Ouest (GERICCO)

Results. We enrolled 180 patients with PVE due to *Staphylococcus aureus* (n = 114, 63.3%), or coagulase-negative staphylococci (n = 66, 36.7%), on bioprosthesis (n = 111, 61.7%), mechanical valve (n = 67, 37.2%), or both (n = 2). There were 132 males (73.3%),

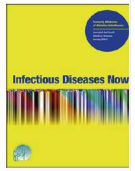
Conclusions. **A large proportion (43.9%) of staphylococcal PVE received no rifampin. One-year survival and relapse rates similar in patients treated with or without rifampin.**

Le Bot A, Clin Infect Dis 2021

Contents lists available at ScienceDirect

Infectious Diseases Now

journal homepage: www.sciencedirect.com/journal/infectious-diseases-now



Guidelines

Antibiotic therapy and prophylaxis of infective endocarditis – A SPILF-AEPEI position statement on the ESC 2023 guidelines

Outpatient oral endocarditis treatment

	First line oral antibiotic regimen	Alternative oral antibiotic regimen
Staphylococcus spp.	*Awaiting results of the RODEO trial* Rifampicin + levofloxacin	Cotrimoxazole

Oral antibiotic	Dosage if patient ≤ 70kg	Dosage if patient > 70kg
Amoxicillin	1.5g tid	2g tid
Rifampicin	600mg qd	900mg qd
Moxifloxacin	400mg qd	400mg qd
Levofloxacin	500mg qd	750mg qd
Cotrimoxazole	320/1600 mg tid	320/1600 mg tid
Ciprofloxacin	750 mg bid	750 mg bid

EI à staphylocoques - Pacemaker ou DEF

EI à staphylocoques - Pacemaker ou DEF

- **Même** schéma thérapeutique qu'une EI sur prothèse

ET

- Ablation systématique du PM (sonde et boîtier)

Endocardites à hémocultures négatives

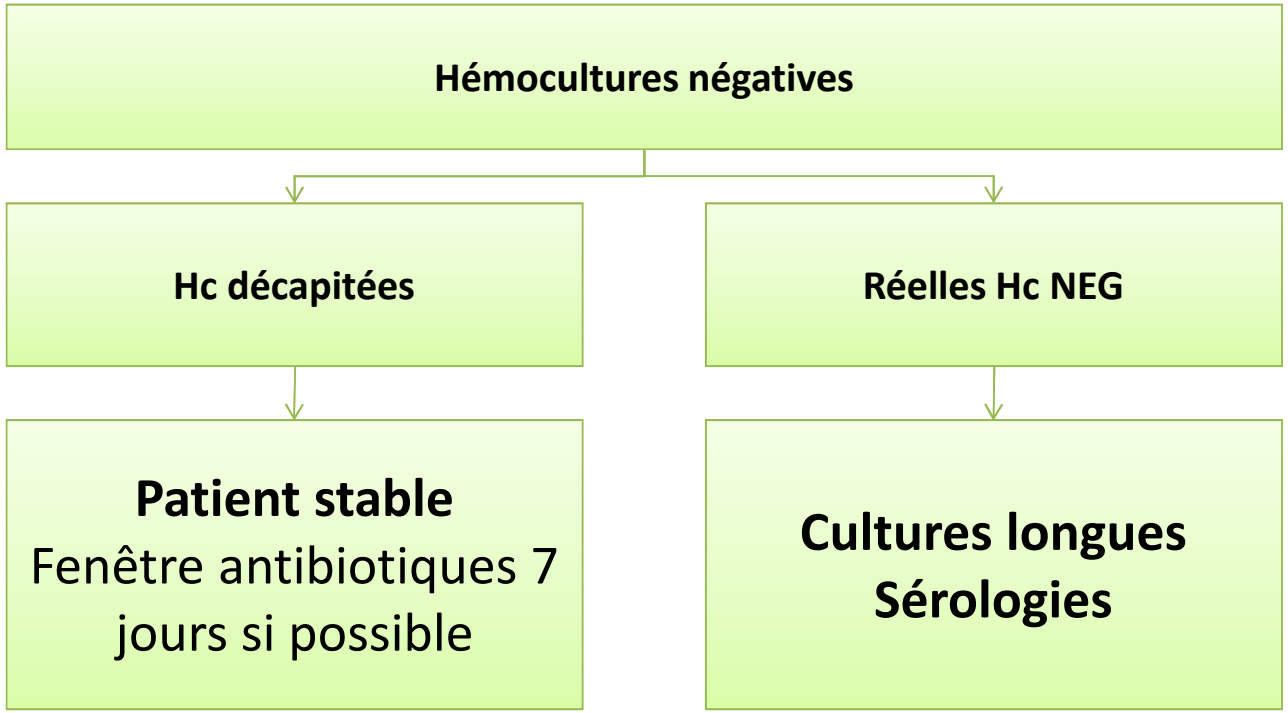
Endocardites à hémocultures négatives

	Native valve endocarditis (78%)				PM and Def IE (5%)	Prosthetic valve IE (17%)			TOTAL
	Community-acquired IE 55%	Health care-associated 18%		Drug abusers 5%		Early (< 2 mths) 1.0%	Mid term (2 – 12mths) 3.0%	Late (> 12 mths) 13%	
Pathogens		Nosocomial 15%	Non-nosocomial 3%						
Staphylococcus aureus	20/20 %	44/47%	25/42%	68/81%	23%	36/0%	7%	25%	26 %
CN Staphylococci	4/6%	12/15%	15/25%	0/3%	54%	0/17%	27%	9%	10 %
Oral streptococci*	26/28%	7/11%	0/6%	4/10%	0%	0/2%	7%	11%	18 %
Streptococcus bovis **	10/18%	3 %	3/8%	0/1%	4%	0/2%	7%	9%	13 %
Enterococcus	9%	6/14%	17/42%	4/5%	0%	7.5/20%	7%	20%	10 %
Pyogenic streptococci	8%	0%	0%	4%	0%	0%	0%	3%	5 %
Others	6%	14%	0%	0/3%	16%	0%	33%	12%	8 %
Negative-blood culture	9.5/11%	9/9 %	0/6%	0/5%	8%	17/40%	13%	12%	9%
Microorganism not identified	5%	4.5%	0%	0%	0%	40%	13%	8%	5%

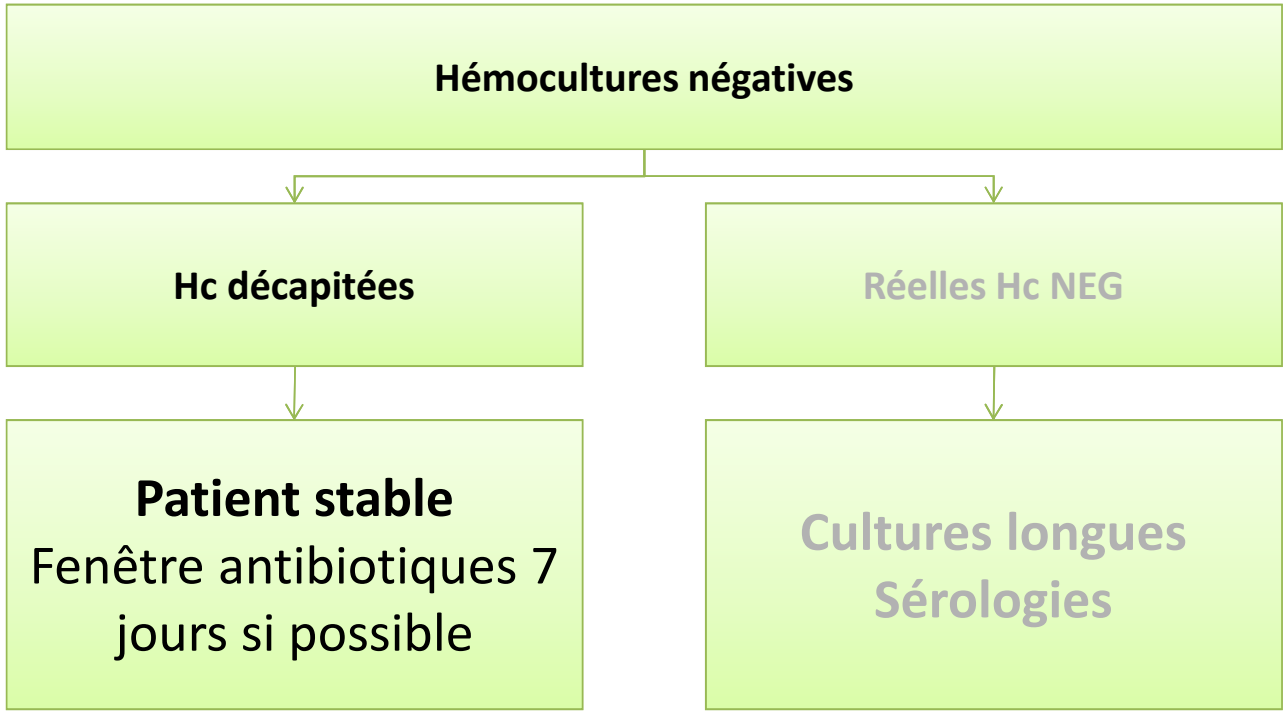
≈ 15%

Hoen B, Duval X, N Eng J Med 2013;368:1425-33

Hémocultures Négatives



Hémocultures Négatives



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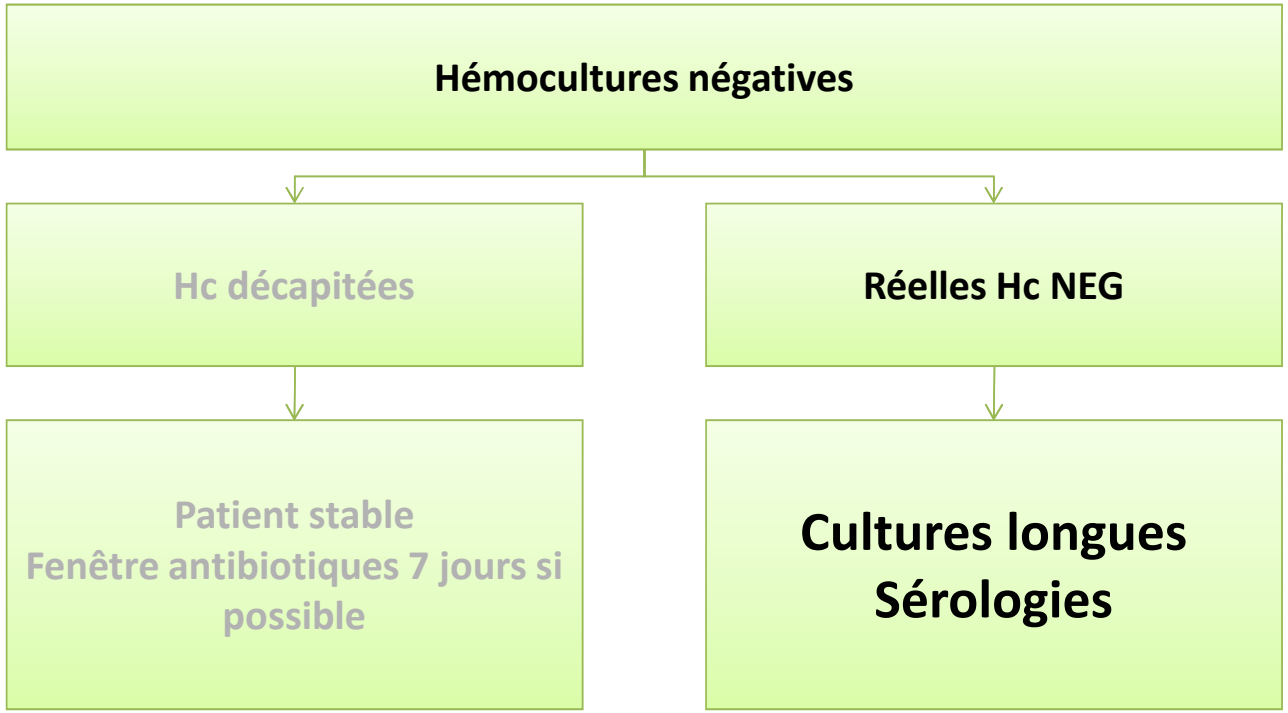
Hc décapitées

15%

Hoen B, Duval X, N Eng J Med 2013;368:1425-33


Hémocultures négatives
Hc décapitées
Réelles Hc NEG
Patient stable
Fenêtre antibiotiques 7 jours si possible
Cultures longues
Sérologies

Les micro-organismes responsables des EI à HN

- **La cause la plus fréquente**
  - ***Coxiella burnetti***
- **Les causes fréquentes**
  - *Abiotrophia*
  - *Actinobacillus actinomycetemcomitans*
  - ***Bartonella***
  - ***Brucella***
- **Les causes rares**
  - *Cardiobacterium hominis*
  - ***Erisipelothrix rhusiopathiae***
  - *Hæmophilus aphrophilus*
  - *Haemophilus parainfluenzae*
  - ***Listeria monocytogenes***

- **Les causes très rares**
  - *Campylobacter*
  - *Eikenella*
  - *Francisella*
  - *Gemella*
  - *Gronulicatella*
  - *Kingella*
  - *Legionella*
  - *Mycobactéries*
  - *Mycoplasma*
  - *Neisseria*
  - *Pasteurella*
  - *Tropheryma whipplei*

D'après Raoult, Communication personnelle, ICAAC 2011

Schémas de référence pour EI à germes intra cellulaire

2023

Micro-organisme	Schéma thérapeutique	Commentaires
Coxiella burnetii	**Doxycycline (200 mg/j)** + hydroxychloroquine (200–600 mg/j) pendant au moins 18 mois	Critères de guérison : titre d'IgG de phase I <1:400 et des titres d'IgM et d'IgA <1:50

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Bartonella spp.	**Doxycycline (100 mg × 2/j)** 4 sem + gentamicine (3 mg/kg/j) 2 sem	Taux de guérison attendu supérieur à 90 %

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Brucella spp.	**Doxycycline (200 mg/j)** + cotrimoxazole (800/160 mg × 2/j) + rifampicine (300–600 mg/j) pendant au moins 3–6 mois +/- gentamicine pendant les 3 premières semaines	Critères de guérison : titre d'anticorps < 1:60

Schémas de référence pour EI à germes intra cellulaire

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T. whipplei	**Doxycycline (200 mg/j)** + hydroxychloroquine (200–600 mg/j) pendant au moins 18 mois	?

Endocardite à Bacille gram négatif

HACEK

Haemophilus parainfluenzae, H. aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, et *Kingella kingae.*

Si producteur de betalactamase

- **Ceftriaxone** 2 g/24 h IV/IM en 1 dose 6 semaines (PVE)
- Ou **Ciprofloxacin** 1000 mg/24 h PO ou 800 mg/24 h IV en 2 doses

Si NON producteur de betalactamase:

- **Amoxicilline + gentamicine**

4 semaines (NVE) 6 semaines (PVE)

Autres BGN

- Bithérapies betalactamines + aminosides (+/- FQ)
- Traitement prolongé: 6 semaines
- Chirurgie systématique ?

Endocardite à Streptocoques « rares »

Endocardite à Streptocoques « rares »

- **EI Pneumocoque**
  - Associée à méningite chez 30% des patients
  - Si souche sensible: TT idem EI strepto (bithérapie 2 semaines puis monothérapie 2-4 semaines ??).
  - Si souche résistante: choix en fonction de CMI
  - Si méningites, forte doses de C3G dans l'attente des CMI

Endocardite à Streptocoques « rares »

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- **Streptocoques A, B, C, G** (dont anginosus): bithérapie 2 semaines puis monothérapie 2-4 semaines

  Chirurgie systématique si Si Gpe B sur prothèse

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  Chirurgie systématique si Si Gpe B sur prothèse
- **Streptocoques déficients (Granulicatella, Abiotrophia)**

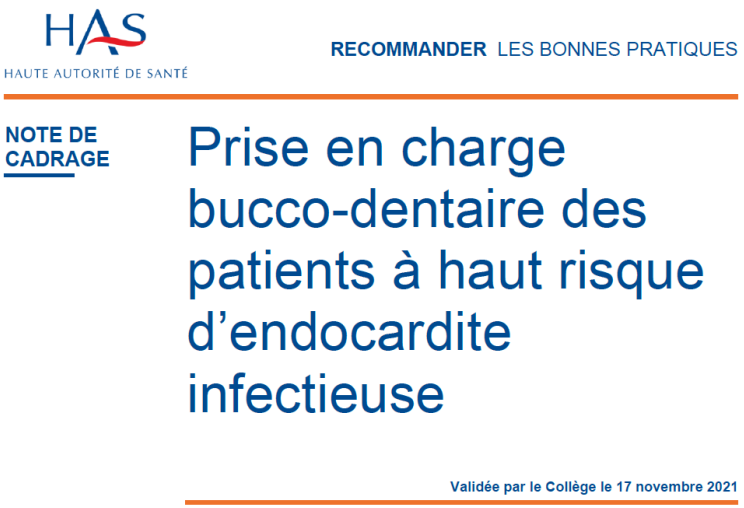
  bithérapie 2 semaines puis monothérapie 2-4 semaines

Traitements prolongés suppressifs …

Endocardite infectieuse
Prophylaxie

https://www.endocardite.org

French Health Authority GPC guidelines - March 2024


HAUTE AUTORITÉ DE SANTÉ

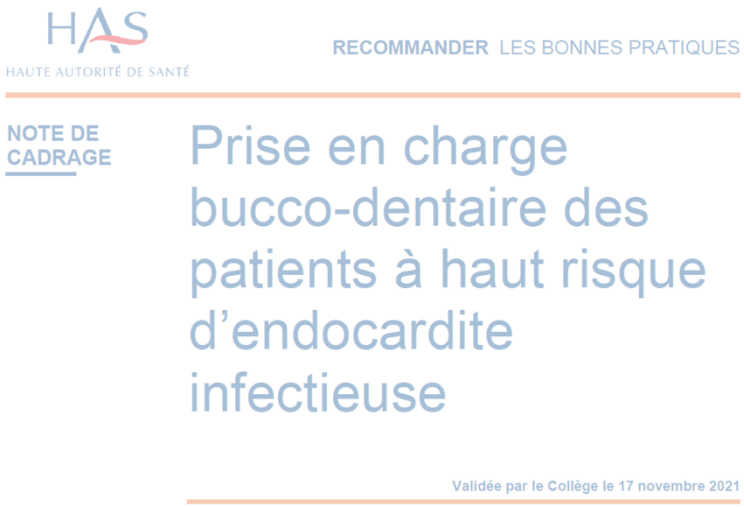
RECOMMANDER LES BONNES PRATIQUES

NOTE DE CADRAGE

Prise en charge bucco-dentaire des patients à haut risque d'endocardite infectieuse

Validée par le Collège le 17 novembre 2021

HAS
HAUTE AUTORITÉ DE SANTÉ



- Activity on oral streptococci
- Drug adverse effect
- Drug interactions
- Narrow antibiotic spectrum

Clindamycin withdrawnfrom the list of antibiotics eligible for AP

Prophylactic antibiotic regime for high-risk dental procedures

Situation	Antibiotic	Single-dose 30–60 min before procedure	
		Adults	Children
No allergy to penicillin or ampicillin	Amoxicillin	2 g orally	50 mg/kg orally
	Ampicillin	2 g i.m. or i.v.	50 mg/kg i.v. or i.m.
	Cefazolin or ~~ceftriaxone~~	1 g i.m. or i.v.	50 mg/kg i.v. or i.m.
Allergy to penicillin or ampicillin	~~Cephalexin~~[a,b]	2 g orally	50 mg/kg orally
	Azithromycin or ~~clarithromycin~~	500 mg orally	15 mg/kg orally
	~~Doxycycline~~ **Pristinamycine 1 g**	100 mg orally	<45 kg, 2.2 mg/kg orally >45 kg, 100 mg orally
	Cefazolin or ~~ceftriaxone~~[b]	1 g i.m. or i.v.	50 mg/kg i.v. or i.m.

Contents lists available at ScienceDirect

Infectious Diseases Now

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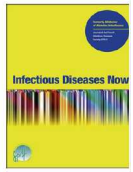

Guidelines

Antibiotic therapy and prophylaxis of infective endocarditis – A SPILF-AEPEI position statement on the ESC 2023 guidelines

No antibiotic prophylaxis for extra oral procedures (including prosthetic valve patients or history of IE)

ESC European Society of Cardiology
European Heart Journal (2023) **00**, 1–95
https://doi.org/10.1093/eurheartj/ehad193

2023 ESC Guidelines for the management of endocarditis

Recommendations for IE prevention in high-risk patients

Recommendations	Class[a]	Level[b]
Antibiotic prophylaxis is recommended in dental extractions, oral surgery procedures, and procedures requiring manipulation of the gingival or periapical region of the teeth.[11,49,51,108]	I	B
Systemic antibiotic prophylaxis may be considered for high-risk[c] patients undergoing an invasive diagnostic or therapeutic procedure of the respiratory, gastrointestinal, genitourinary tract, skin, or musculoskeletal systems.[6,11]	IIb	C

[c] This recommendation does not apply to patients with intermediate risk for IE or to the general population

Prophylaxie de l'endocardite

CONSEILS PENDANT LA DURÉE DU TRAITEMENT ANTICOAGULANT

SFC
SFCTCV

Traitement : ❑ Temporaire ❑ Définitif

INR CIBLE : entre ..... **et** ..... Contrôlez l'INR au moins une fois par mois

Notez les INR sur votre carnet de traitement anticoagulant

- Ne prenez aucun autre médicament sans avis médical (risques d'interactions)
- Consultez votre médecin en urgence en cas de saignement ou d'hématome ou si l'INR est supérieur à 5
- Prenez l'avis de votre médecin si l'INR est en dehors des valeurs cibles
- Signalez que vous êtes sous anticoagulant à tout médecin/professionnel de santé
- Ne modifiez pas ou n'interrompez pas le traitement sans avis médical

Cardiologue traitant ..... Médecin traitant .....

Fédération Française de Cardiologie

PRÉVENTION DE L'ENDOCARDITE INFECTIEUSE

SPILF
SFC / FFC
SFCTCV ADF

Actualisation 2011 des recommandations

Nom, prénom : .....

Cardiopathies à haut risque d'endocardite infectieuse :
- ❑ Prothèse valvulaire cardiaque ou anneau valvulaire
- ❑ Antécédent d'endocardite infectieuse
- ❑ Cardiopathie congénitale cyanogène

Remis par le Dr : .....

le : ..... à : .....

tél. : ..... email : .....

www.infectiologie.com
www.adf.asso.fr
www.sfcardio.fr
www.fedecardio.com

ASSOCIATION POUR L'ETUDE ET LA PREVENTION DE L'ENDOCARDITE INFECTIEUSE

Fédération Française de Cardiologie

Cette carte doit être systématiquement montrée à votre médecin et / ou votre dentiste

En cas de soin dentaire à risque*, traitement antibiotique préventif **impératif :**
Prenez en une prise, par la bouche, dans l'heure précédant les soins

En l'absence d'allergie connue aux B-lactamines : **Amoxicilline : 2 g** (enfant : 50 mg/kg)

Si allergie connue aux B-lactamines : ~~**Clindamycine : 600 mg** (enfant 20 mg/kg)~~

En cas de fièvre (avec ou sans soin dentaire préalable) :
- prévenez systématiquement votre médecin
- présentez-lui cette carte
- ne prenez pas d'antibiotique sans son avis et/ou avant la recherche de germes dans le sang par une hémoculture

Brossage quotidien des dents, visite semestrielle systématique chez le chirurgien dentiste sont également indispensables pour une bonne prévention

* consultez votre cardiologue, votre médecin traitant et/ou les sites indiqués au verso

SFC
SFCTCV

CHIRURGIE VALVULAIRE

Date d'implantation : .....

Lieu d'implantation : .....

Nom du chirurgien : .....

Aortique	Mitrale	Autres
❑ Mécanique ❑ Biologique ❑ Réparation Modèle/ref. : ..... N° de série : ..... Diamètre :	❑ Mécanique ❑ Biologique ❑ Réparation Modèle/ref. : ..... N° de série : ..... Diamètre :	❑ Mécanique ❑ Biologique ❑ Réparation Modèle/ref. : ..... N° de série : ..... Diamètre : .....

PREVENTION DE L'ENDOCARDITE INFECTIEUSE

Nom, prénom

Vous avez une **cardiopathie à haut risque d'endocardite infectieuse**

- □ Prothèse valvulaire (dont TAVI), clip, anneau ou tout autre matériel valvulaire, implanté par voie chirurgicale ou percutanée
- □ Antécédents d'endocardite infectieuse
- □ Cardiopathie congénitale cyanogène
- □ Pompe d'assistance ventriculaire

Carte remise par le Dr : à le

tel Email :

fedecardio.org infectiologie.com sfcardio.com adf.asso.fr ufsbd.fr endocardite.fr sfctcv.org

Fédération Française de Cardiologie

AEPEI, Association pour l'Etude et la Prévention de l'Endocardite Infectieuse

Cette carte doit être systématiquement montrée à votre médecin / votre dentiste

Les mesures d'hygiène sont les plus importantes

- brossez-vous les dents 2 à 3 fois / jour
- consultez votre dentiste 2 fois / an ou en cas de saignement au brossage
- nettoyez toute plaie cutanée, évitez tatouage et piercing

En cas de soin dentaire à risque*, le **traitement antibiotique préventif est impératif**

- Il consiste en une prise d'antibiotique, par la bouche, une heure avant les soins

Absence d'allergie aux pénicillines :

Amoxicilline : 2 g (enfant : 50 mg/kg)

Allergie aux pénicillines :

Azithromycine : 20 mg/kg**

Ou **Pristinamycine : 1g** (enfant ≥ 6 ans : 25 mg/kg)

En cas de fièvre (avec ou sans soin dentaire préalable)

- prévenez systématiquement votre médecin et présentez-lui cette carte
- ne prenez pas d'antibiotique sans son avis et/ou avant réalisation d'hémoculture

* consultez votre dentiste, cardiologue, et/ou médecin traitant (ou les sites internet listés au verso)
** contre-indiqué si allongement de l'intervalle QT connu

PREVENTION DE L'ENDOCARDITE INFECTIEUSE

Nom, prénom

Vous présentez l'une des cardiopathies suivantes

- insuffisance aortique, insuffisance mitrale, rétrécissement aortique, bicuspidie aortique, rétrécissement mitral
- cardiopathie congénitale non cyanogène
- cardiomyopathie hypertrophique obstructive
- stimulateur (pace maker, défibrillateur)

Cette cardiopathie peut être associée à la survenue d'une endocardite infectieuse, mais ne justifie pas l'administration préventive d'antibiotiques avant un soin dentaire.

Carte remise par le Dr : à

le

tel email

fedecardio.org infoelio.com sfcardio.com adf.asso.fr ufsbd.fr endocardite.fr sfctcv.org

Fédération Française de Cardiologie

AEPEI, Association pour l'Etude et la Prévention de l'Endocardite Infectieuse

Cette carte doit être systématiquement montrée à votre médecin / votre dentiste

Votre cardiopathie NE nécessite PAS d'antibiotique à visée préventive en cas de soin dentaire

MAIS les mesures suivantes d'hygiène cutanée et bucco-dentaire sont indispensables

Pour une prévention efficace

- brossez-vous les dents 2 à 3 fois par jour
- consultez votre dentiste 2 fois par an ou si saignement au brossage
- nettoyez toute plaie cutanée, évitez tatouage et piercing

En cas de fièvre (avec ou sans soin dentaire préalable) :

- prévenez systématiquement votre médecin et présentez-lui cette carte
- ne prenez pas d'antibiotique sans son avis et/ou avant réalisation d'une hémoculture

Adhésion à la Prophylaxie de l'Endocardite chez les Patients à Haut Risque

98 patients with a history of definite infective endocarditis in the 39 preceding months

9/10 patients know that	but	Only 4/10 patients	
Tooth brushing prevents endocarditis		brush their teeth ≥ twice a day	1/2 patients have dental caries
Dental visits are recommended twice a year		went to the dentist ≥ once a year	1/3 patients have oral foci of infection

Considered adherent to prophylaxis guidelines

Characteristics less frequent in adherent patients	Characteristics not associated with adherence	Characteristics more frequent in adherent patients
Tobacco use	Age	Surgery performed after discharge
Depressive symptoms	Quality of life	Self-evaluation of correct adherence to prophylaxis guidelines
Cognitive decline	Prophylaxis guidelines knowledge	Search for information on IE
	Oral origin of prior endocarditis	

Celestin B. Arch Cardiovasc Dis 2023;116:176-82

Prevention

- Stabilité recommandations
- Antibioprophylaxie limitée
  - Cardiopathies à haut risque
  - Procédures dentaires à haut risque
- Mesure d’hygiène générale +++

Adhérence par les patients aux mesures de prophylaxie

Etude POST IMAGE

Transversale, monocentrique, Bichat Paris
Convocation de 100 patients à distance de l'EI pour bilan exhaustif

Visite chez le dentiste ≥ 2 fois par an
Brossage des dents ≥ 2 fois par jour
Port d'une carte de prophylaxie de l'EI

} **27/ 100 patients**

Déterminant de la non adhésion: Dépression présente chez 30% des patients

Celestin B. Arch Cardiovasc Dis 2023;116:176-82

Recommendations for infective endocarditis prevention in cardiac procedures

Trans catheter valvular procedures

2023 ESC Guidelines for the management of endocarditis
(European Heart Journal; 2023 – doi: 10.1093/eurheartj/ehad193)

Recommendations for infective endocarditis prevention in cardiac procedures

Trans catheter valvular procedures

Recommendations	Class	Level
Antibiotic prophylaxis covering for common skin flora including *Enterococcus* spp. and *S. aureus* should be considered before TAVI and other transcatheter valvular procedures.	IIa	C

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Conclusion- endocardites infectieuses

1. Toujours l'évoquer
2. Diagnostiquer le plus tôt possible
3. Evaluation chirurgicale systématique **et répétée**
4. Centres de référence: prise en charge multidisciplinaire
5. Antibiothérapie: longue, complexe
   - CMI, complication, type de valve
   - gentamicine en perte de vitesse

Conclusion- endocardites infectieuses

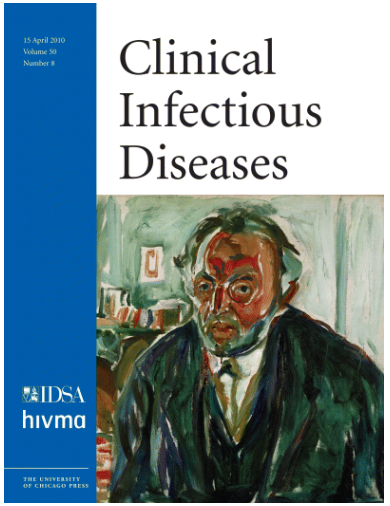
6. Place du traitement ambulatoire
7. EI sur TAVI : diagnostic et prise en charge compliqués
8. Importance de la prophylaxie
9. Suivi

	Fixation protéique	Cut off (valeur CMI maximale) souche sensible		Cible (100% fraction libre > 4 CMI)	
Amoxicilline	20%	Enterocoque	4 mg/L	20 mg/L	
		Strepto	2 mg/L	10 mg/L	
Cefazoline	80%	S. aureus	2 mg/L	40 mg/L	
Cloxacilline	90%	S. aureus	0,5 mg/L	20 mg/L	< 50
Ceftriaxone	95%	Strepto pneumoniae	0,5 mg/L	20 mg/L	

Cefazoline: 80 – 100 mg/kg/day administered in 3 doses or by continuous infusion after a loading dose of 30 mg/kg over 1 hour.

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

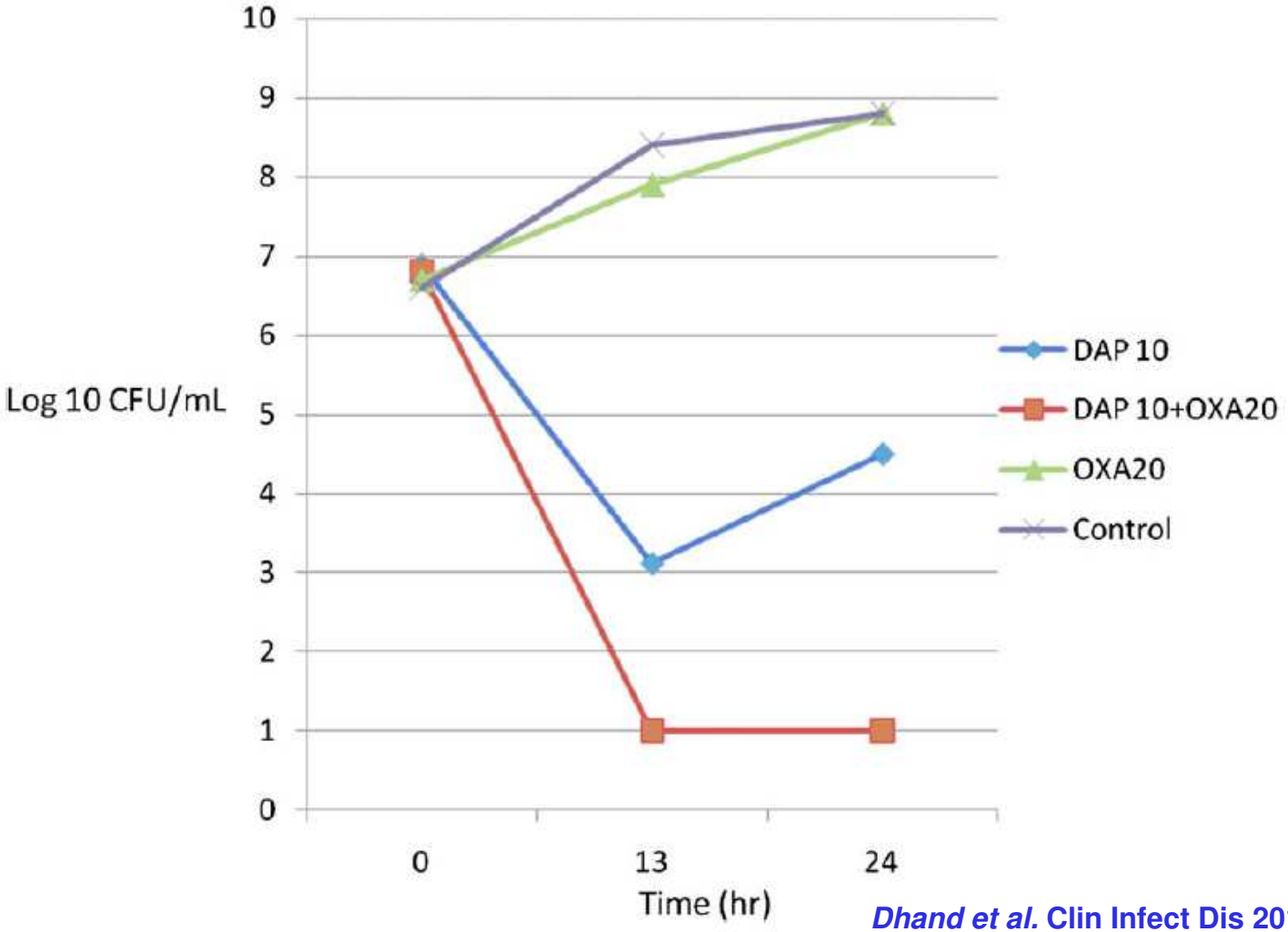
Abhay Dhand,[1] Arnold S. Bayer,[3,4] Joseph Pogliano,[5] Soo-Jin Yang,[3,4] Michael Bolaris,[3] Victor Nizet,[5] Guiquing Wang,[2] and George Sakoulas[1,5,6]



- **7 patients 'bactériémie SARM réfractaire'**
  - **7 à 22 jours bactériémie sous vanco, avec associations et relais divers (gentamicine, rifampicine, daptomycine)**
    - **Pas de foyer persistant évident**
    - **CMI vanco et dapto restées < 1 (n=6)**
    - **Une souche => VISA (CMI vanco 3; dapto 2-4 mg/L)**

Tous ont rapidement négativé HC sous dapto + pénicilline M

Courbe de bactéricidie



Dhand et al. Clin Infect Dis 2011

(Flu)(o)cloxacillin	12 g/day i.v. in 4–6 doses
Cefazolin	6 g/day i.v. in 3 doses
Rifampin	900-1200 mg/day i.v. or orally in 3 equally divided doses
Gentamicin	3 mg/kg/day i.v. or i.m. in 1
Daptomycin	10 mg/kg/day i.v. in 1 dose
Ceftaroline OR **Fosfomycin**	1800 mg/day i.v. in 3 doses 8-12 g/day i.v. in 4 doses (apport Na+)
Vancomycin	30 mg/kg/day i.v. in 2 doses