JOURNÉE CLAUDE BERNARD

PARIS – 28 NOVEMBRE 2019

Endocardites : relais oral / IV .....à la maison

Louis BERNARD, Tours

Conflit d'intérêt : aucun sauf PHRC RODEO

Merci

Bruno FANTIN

Anne-Claude CREMIEUX

Pierre TATTEVIN

INTRODUCTION

A Microbiologie

B Endocarde- Endocardite

C Antibiothérapie : CMI/B PK/PD

D La réalité in vivo

Microbiologie

Microbiologie (1)

426 patients

Microorganisms	
Streptococci	171 (40)
Oral streptococci	99 (23)
Streptococcus bovis/gallolyticus	42 (10)
Pyogenic streptococci	24 (6)
Other Streptococcaceae	6 (1)
Staphylococci	129 (30)
Staphylococcus aureus	81 (19)
Methicillin-susceptible *S. aureus*	67 (16)
Methicillin-resistant *S. aureus*	14 (3)
Coagulase-negative staphylococci	48 (11)
Enterococci	50 (12)
Enterococcus faecalis	49 (12)
Enterococcus faecium	1
HACCEK group	21 (5)
Bartonella spp.	14 (3)
Coxiella burnetii	8 (2)
Other microorganisms	28 (7)
No microorganism identified	5 (1)

A. Mzabi et al. / Clinical Microbiology and Infection 22 (2016) 607–612

40% Streptocoques

35-40% Staphylocoque

10% Entérocoque

10% autres

497 patients

Panel 1: **Proportion of cases of infective endocarditis caused by different microorganisms from a French population-based cohort of 497 patients[2]**

Staphylococci
Staphylococcus aureus: 26·6%
Coagulase-negative staphylococci: 9·7%

Streptococci and enterococci
Oral streptococci: 18·7%
Non-oral streptococci: 17·5%
Enterococci: 10·5%
Other: 1·6%

HACEK (haemophilus, aggregatibacter, cardiobacterium, *Eikenella corrodens*, kingella) microorganisms
1·2%

***Candida* species**
1·2%

Other*
6·0%

Polymicrobial (≥2 microorganisms)
1·8%

No microorganism identified
5·2%

Selton-Suty C, *Clin Infect Dis* 2012; **54:** 1230–39.

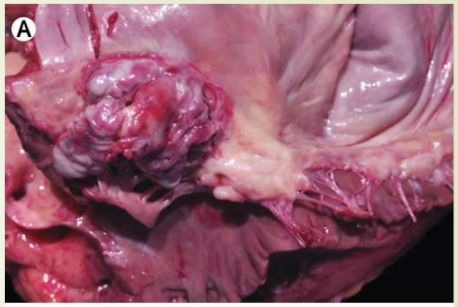
Endocardite

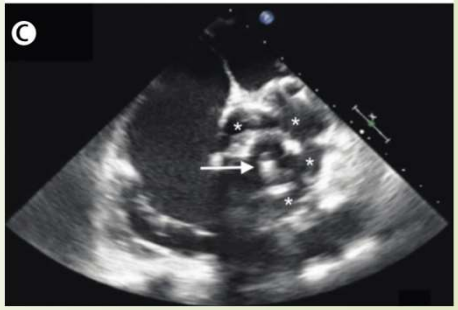
Végétation (1)
Présentation B Fantin RICAI 2017

Population bactérienne: synthèse

- Hétérogénéité de la localisation
- Densité:
  - Effet inoculum
  - Sélection de mutants résistants
- Phase de croissance
- Biofilm

Carbon, Crémieux , Fantin, Infect Dis Clin North Am, 1993



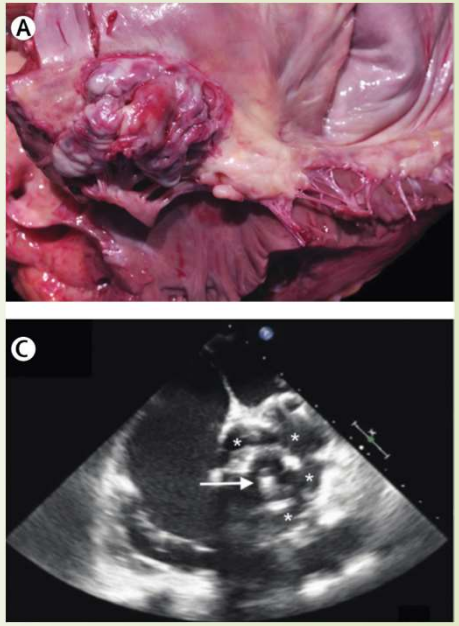


Végétation (2)

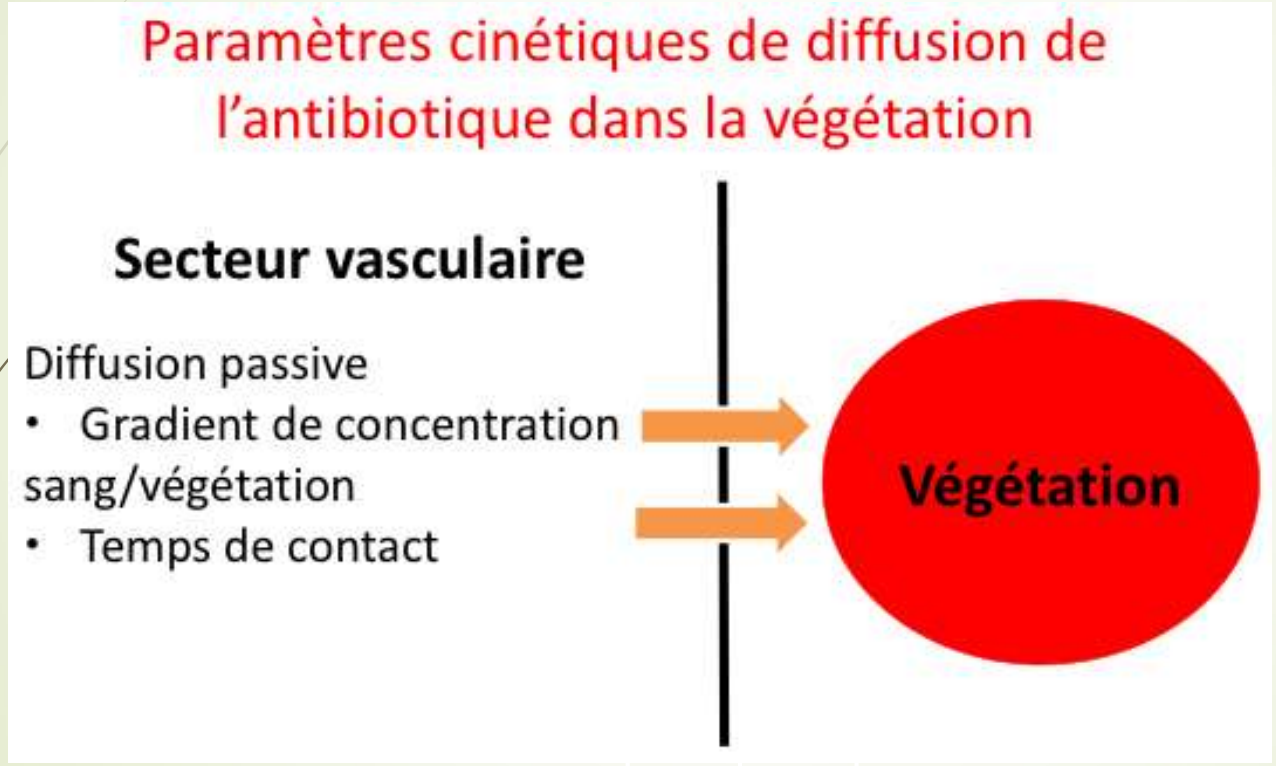
Diffusion dans la végétation: facteurs liés à l'antibiotique et la végétation

Antibiotique	Végétation
• Taille de la molécule	• Taille de la végétation
• Fixation protéique	• Infection de la végétation

Eng et al, Chemotherapy 1982



Végétation (3)



Végétation (4)

Méthodes d'évaluation de la diffusion

- Diffusion de l'antibiotique seul
  - Modélisation
  - Dosage global
  - Autoradiographie
- Interaction antibiotique - bactérie

Végétation (5)

Modélisation = simplification extrême

- Végétation= sphère
- Répartition homogène de l'antibiotique
- Diffusion selon gradient
- AB avec T1/2 de 30 min après 5 inj q 4h

Taille de la végétation	Rapport cion centre végétation/cion libre sérique
0,5 cm	37%
1 cm	22%
2 cm	18%

Eng et al, Chemotherapy 1982

Végétation (6)

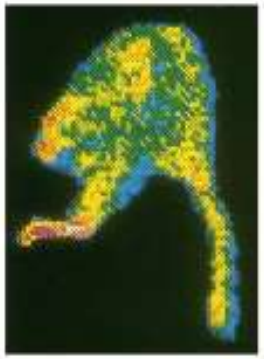
Autoradiographie

- Modèle d'endocardite expérimentale du lapin
- Injection iv. de produit marqué [14C]
- Sacrifice à temps variables
- Analyse:
  - Qualitative: aspect de la diffusion
  - Quantitative: relative aux autres structures

Végétation (7)

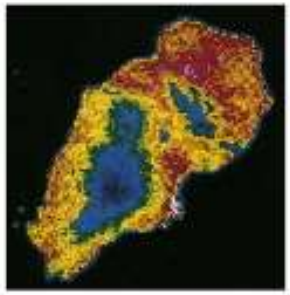
Types de diffusion des antibiotiques marqués dans la végétation

Homogène



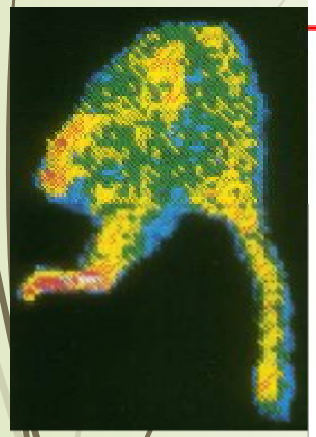
Périphérique

Gradient



Crémieux, JID 1989; Fantin, AAC 1994; Saleh-Mghir AAC 1999

Végétation (8)



Types de diffusion des antibiotiques marqués dans la végétation

Homogène

- Amoxicilline, clavulanate
- Péfloxacine, téma, sparflo
- Tobramycine
- Spiramycine, quinupristine
- Daptomycine
- Tigecycline

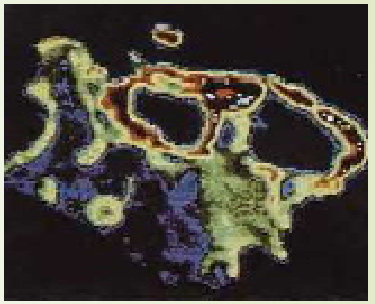
Non homogène

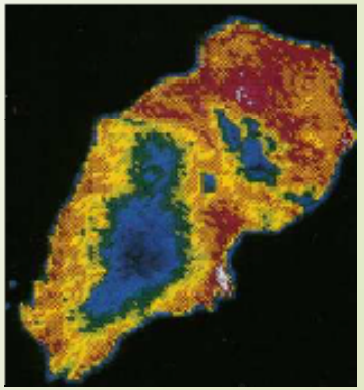
Périphérique

Teicoplanine

Gradient de diffusion

- Ceftriaxone, pénicilline
- Dalfoprisitine





Antibiotiques

Antibiotiques (1) Lévofloxacine

Population Pharmacokinetics and Pharmacodynamics of Levofloxacin in Acutely Hospitalized Older Patients with Various Degrees of Renal Function

Pier Giorgio Cojutti,[a,b] Virginia Ramos-Martin,[c] Isabella Schiavon,[d] Paolo Rossi,[d] Massimo Baraldo,[a,b] William Hope,[c] Federico Pea[a,b]
Institute of Clinical Pharmacology, Santa Maria della Misericordia University Ho

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March 2017 Volume 61 Issue 3 e02134-16

168 patients
Mesures sériques:
330 résiduelles
239 pics

TABLE 3 Probabilities of achieving underexposure, normal target exposure, and overexposure with different levofloxacin dosing regimens in older patients in relation to different classes of renal function

Levofloxacin regimen (mg)	Probability[a]													>160
125 every 48 h														0.0
250 every 48 h														0.0
500 every 48 h														0.0
750 every 48 h														0.0
500 every 24 h														0.3
750 every 24 h	1.1	17.1	81.8	1.7	51.3	47.0	5.8	82.8	11.4	23.2	73.1	3.7	50.3	47.6	2.1
500 every 12 h	0	3.6	96.4	0.2	12.3	87.5	0.1	39.0	60.9	1.5	70.1	28.4	2.8	82.8	14.4

[a]Probability of achieving underexposure (AUC_{24} < 50 mg · h/liter), normal target exposure (AUC_{24} between 50 and 160 mg · h/liter), and overexposure (AUC_{24} > 160 mg · h/liter) with different levofloxacin dosing regimens in older patients in relation to different classes of renal function. The classes of renal function (ml/min/1.73 m²) are shown in the top row, and those of levofloxacin AUC_{24} (mg · h/liter) are shown in the bottom row in the header.

AUC_{24}/MIC target of 87 = microbiological eradication
Efficacité optimisée si rapport AUC/CMI > 125 (BGN) > 35 CG+

Zhang J Infect Chemother (2009) 15:293–300: 163 Chinois: Lévofloxacine 500 mg/j : PK-PD favorable

Antibiotiques (3)

Diffusion of Ofloxacin in the Endocarditis Vegetation Assessed with Synchrotron Radiation UV Fluorescence Microspectrocopy

Eric Batard[1]*, Fréderic Jamme[2,3], Sandrine Villette[4], Cédric Jacqueline[1], Marie-France de la Cochetière[1], Jocelyne Caillon[1], Matthieu Réfrégiers[2]

Plos One 2011 | Vol 6 , 4 | e19440

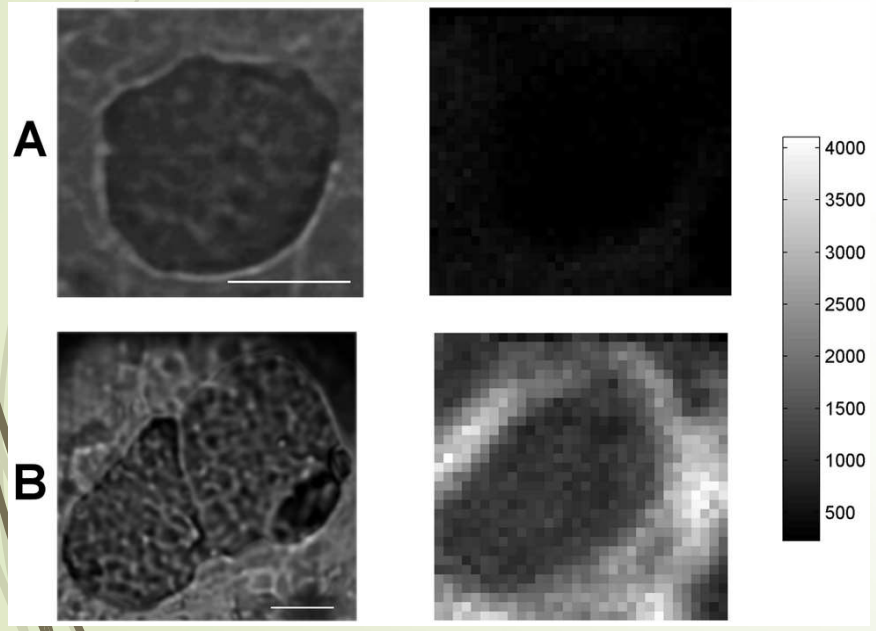


Figure 4. Transmission image (left) and maps of the 390–440 nm peak area (right) of control (A) and ofloxacin treated (B) vegetation maps. The grayscale was the same for both fluorescence maps. White bar = 10 mm.

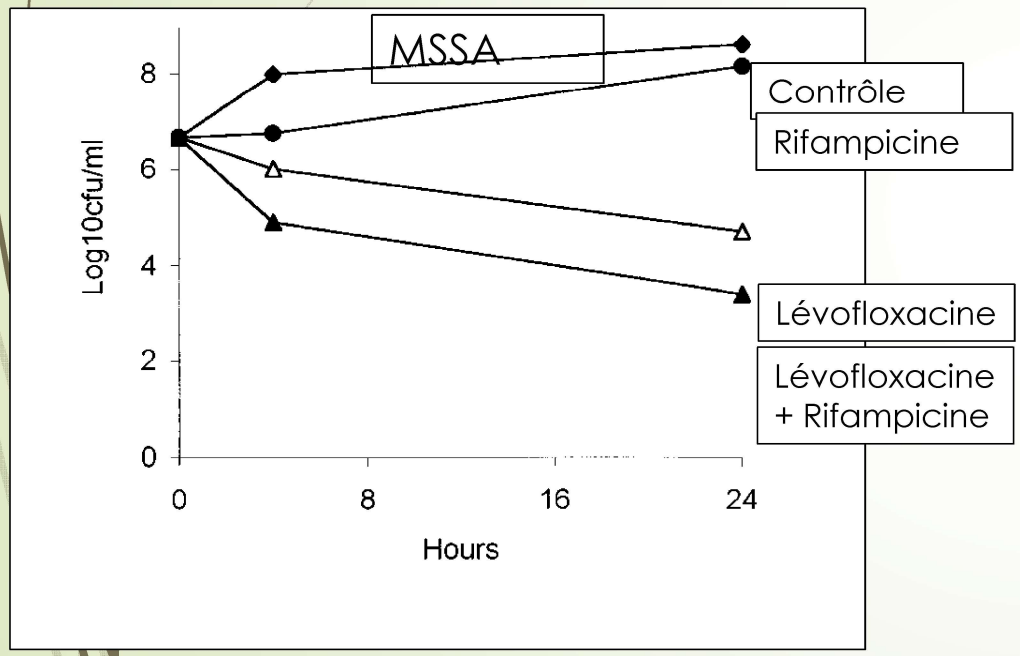
Diffusion immédiate
et en masse de l'ofloxacine

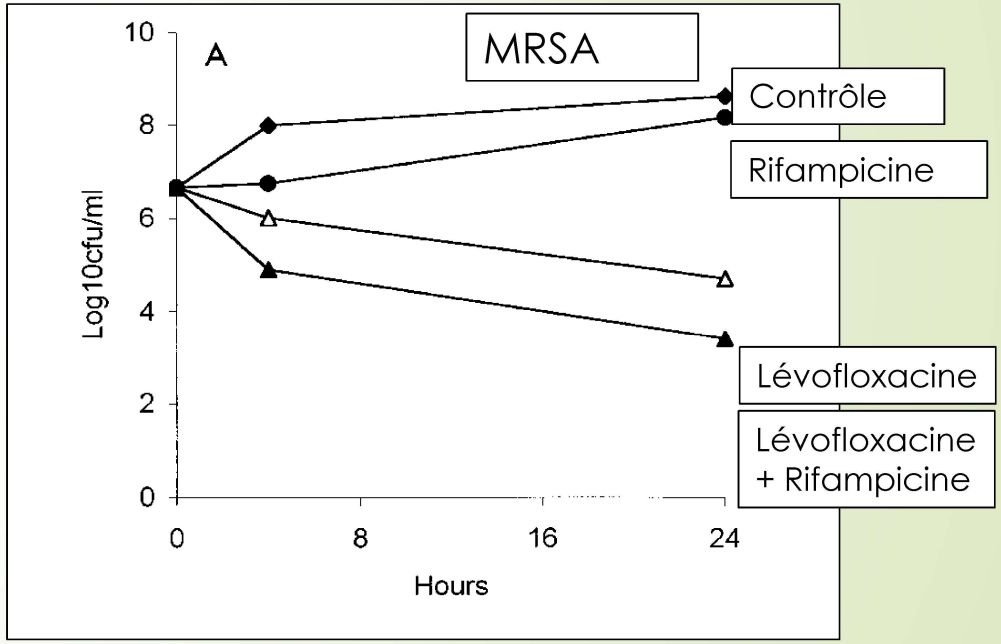
Antibiotiques (5) Lévofloxacine-Rifampicine

Efficacy of Levofloxacin for Experimental Aortic-Valve Endocarditis in Rabbits Infected with Viridans Group Streptococcus or *Staphylococcus aureus*

HENRY F. CHAMBERS,* QING XIANG LIU, LUCIAN LIUXIN CHOW, AND CORINNE HACKBARTH

AAC 1999, 2742–2746





Moreillon, JAC1999 44(6):775-86
EI experimentale Streptocoque: Lévofloxacine 500 mg/j = ceftriaxone
si CMI limite : Lévofloxacine 500 mg x 2/j.

Antibiotiques (5) Rifampicine

Pharmacokinetics, Tolerability, and Bacteriological Response of Rifampin Administered at 600, 900, and 1,200 Milligrams Daily in Patients with Pulmonary Tuberculosis

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Aarnoutse 2017 Vol 61 Issue 11 e01054-17

TABLE 2 Doses and pharmacokinetics of TB drugs[a]

Drug	Pharmacokinetic parameter	Values for subjects receiving: 600 mg rifampin (n = 23)[b]	900 mg rifampin (n = 21)	1,200 mg rifampin (n = 19)	P value[c]
Rifampin	Dose (mg/kg)	10.7 (8.3–12.0)	16.7 (14.1–17.7)	21.4 (17.1–23.5)	
	AUC_{0-24} (mg · h/liter)	23.9 (9.1–118.5)	50.8 (18.9−153.6)	76.1 (43.5–167.0)	<0.001
	C_{max} (mg/liter)	5.3 (2.0–23.3)	9.1 (4.9–15.4)	14.1 (8.1–29.0)	<0.001
	T_{max} (h)	4.0 (2.0–6.1)	4.0 (2.0–6.1)	4.0 (2.5–6.2)	0.879
	CL/F (liters/h)	24.4 (5.1–65.6)	17.2 (5.9–47.7)	15.8 (7.2–27.6)	0.013
	V/F (liters)	77.0 (17.6–212.7)	70.4 (41.8–130.6)	54.8 (34.0–97.0)	0.1
	$t_{1/2}$ (h)	1.9 (1.1–4.5)	2.8 (1.4–7.2)	2.4 (1.4–3.4)	0.02

TABLE 3 Summary of frequency of adverse events according to CTCAE criteria[a]

AE grade	No. of AEs for subjects receiving: All subjects (n = 150)	600 mg rifampin (n = 50) All	Related	Unrelated	900 mg rifampin (n = 50) All	Related	Unrelated	1,200 mg rifampin (n = 50) All	Related	Unrelated
Grade 1 (mild AEs)	821	273	120	153	239	110	129	309	105	204
Grade 2 (moderate AEs)	160	48	16	32	48	10	38	64	9	55
Grade 3 (severe AEs)	20	6	5	1	5	1	4	9	5	4
Grade 4 (life-threatening AEs)	0	0			0			0		
Grade 5 (death related to AE)	3	1		1	1		1	1		1

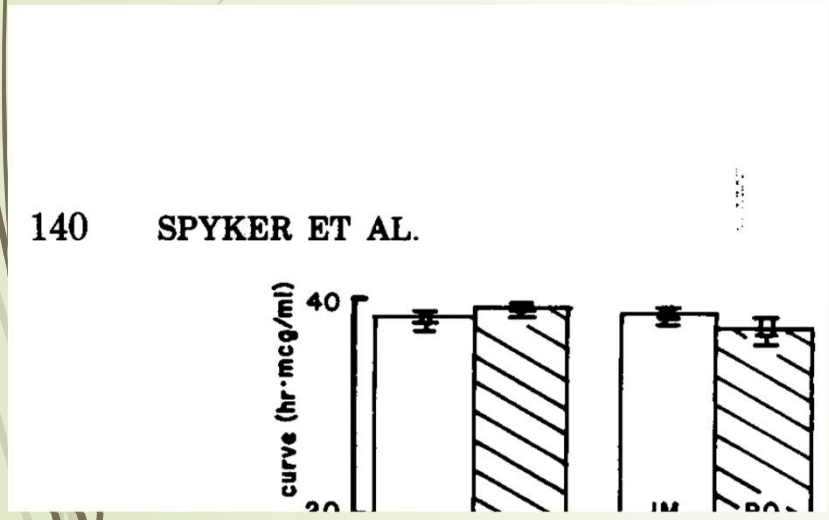
[a]The CTCAE criteria are described elsewhere (24). AE, adverse event; related, the AE is considered associated with the use of the investigational product if the attribution is possible, probable, or very likely.

Amoxicilline

SPYKER AAC 1977, 132-41

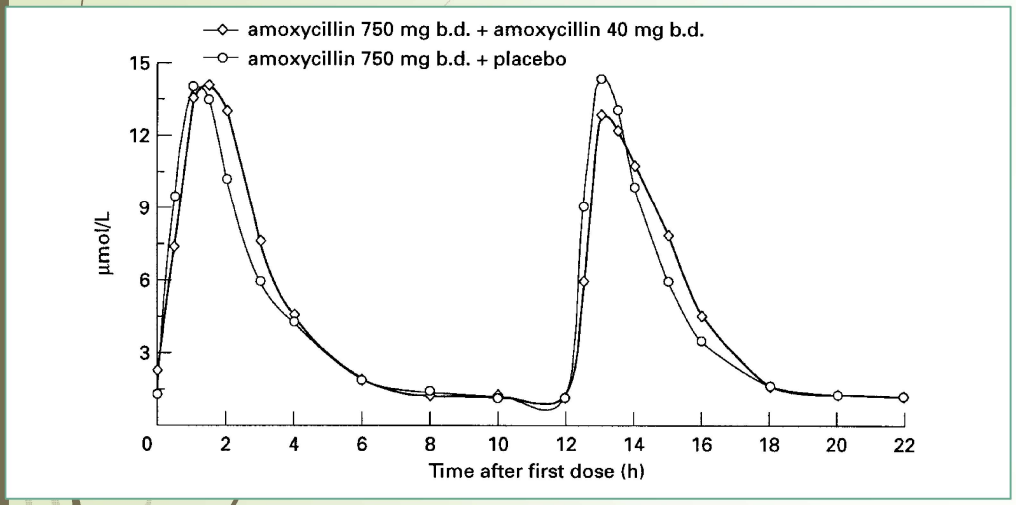
ARANCIBIA, AAC 1980, 199-202

AUC après administration orale = 77.4% IV AUC.



Amoxicilline

Pharmacokinetic and pharmacodynamic interactions between omeprazole and amoxycillin in Helicobacter pylori*-positive healthy subjects*



Pommerien, Aliment Pharmacol Ther 1996; 10: 295–301.

Table 3. Pharmacokinetic parameters (mean, s.d.) of omeprazole 40 mg and amoxycillin 750 mg after twice daily dosing as monotherapy or combined treatment

	Omeprazole		Amoxycillin	
	Monotherapy	Combined therapy	Monotherapy	Combined therapy
Morning dose				
C_{max}	5.0≥ 2.5 µmol}L	4.2≥ 2.0 µmol}L	16.1≥ 4.2 µmol}L	16.3≥ 4.5 µmol}L
t_{max}	1.4≥ 1.4 h	1.6≥ 1.7 h	1.4≥ 0.8 h	1.4≥ 0.6 h
$AUC_{\text{–"!}}$	13.2≥ 9.6 µmol\h}L*	11.6≥ 6.0 µmol\h}L†	44.9≥ 10.2 µmol\h}L‡	45.9≥ 17.6 µmol\h}L‡
Evening dose				
C_{max}	3.7≥ 2.5 µmol}L	3.2≥ 1.7 µmol}L	15.9≥ 5.6 µmol}L	15.6≥ 5.5 µmol}L
t_{max}	1.5≥ 1.4 h	2.0≥ 1.7 h	1.2≥ 0.3 h	1.4≥ 0.5 h
$AUC_{\text{###}}$	9.9≥ 6.7 µmol\h}L*	9.4≥ 5.9 µmol\h}L†	41.2≥ 9.5 µmol\h}L‡	42.8≥ 17.1 µmol\h}L‡

TEDIZOLIDE-ENDOCARDITE

- Modèle expérimental
  - Endocardite gauche du lapin blanc
    - implantation KT coeur gauche
    - H48: 1ml de 10^7 *S. aureus* (IV périphérique)
    - Le lendemain:
      - Tedizolide : 15mg/kg x2/j
      - Daptomycine: 18 mg/Kg x1/j
      - Vancomycine: 30 mg/kg x 2/j
    - A J5 : on tue les lapins
      - Rate, reins, végétations

NON

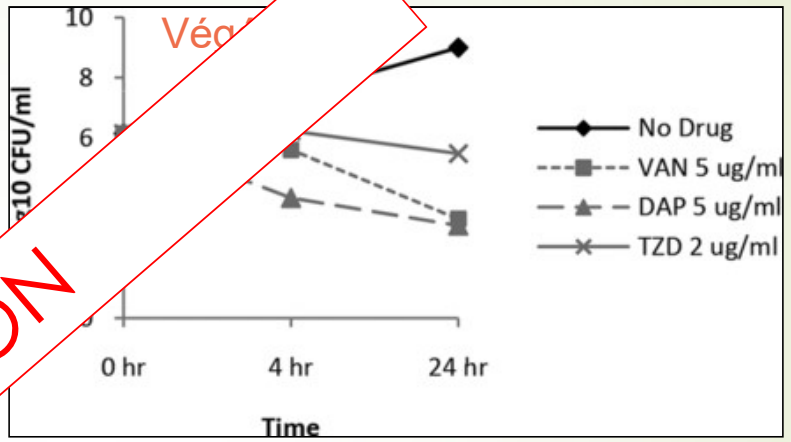


TABLE 1 Comparative study of tedizolid phosphate, daptomycin, and vancomyci

Treatment (no. of rabbits)	Median organism titer, log_{10} CFU/g (IQD)[a]		
	Vegetation	Spleen	Kidney
Control (8)	7.9 (2.2)	4.7 (1.3)	3.4 (2.8)
Tedizolid phosphate, 15 mg/kg i.v. b.i.d. (15)	6.4 (3.4)	3.0 (2.5)	2.3 (1.3)
Daptomycin, 18 mg/kg i.v. q.d. (14)	2.7 (1.4)	1.8 (0.2)	1.7 (0.2)
Vancomycin, 30 mg/kg i.v. b.i.d. (14)	5.5 (3.9)	2.7 (3.8)	2.0 (1.6)

Chan LC et al. *AAC 2015; 59:3252-6*

La réalité in vivo

La réalité in vivo (1)

Évaluation de la qualité de l'antibiothérapie chez 66 patients ayant une endocardite infectieu

E. Demonchy [a], P. Dellamonica [a,b], P.M. Roger [a,b], E. Bernard [a], E. Cua [a], C. Pulcini [a,□,b]

[a] *Service d'infectiologie, hôpital l'Archet 1, CHU de Nice, 151, route Saint-Antoine-de-Ginestière, BP 3079, 06202 Nice cedex 3, France*
[b] *Faculté de médecine de Nice, université de Nice Sophia-Antipolis, 28, avenue de Valombrose, 06107 Nice cedex 2, France*

Received 2 February 2011; received in revised form 21 March 2011; accepted 8 August 2011

Médecine et maladies infectieuses 41 (2011) 602–607

- **66 patients inclus**
- Etude rétrospective
- Respect des recommandations: 14%
- Non respect
  - Gentamicine OD
  - Ajout inutile de rifampicine
  - **Relais per os : 29% (n=19)**

Relais per os : 29% (n=19)

- El gauche n= 12
- El gauche et/ou compliquée n= 15
- **Pas de différence de mortalité**
  - inapproprié (14% vs non 22%, P = 0.62)
  - **(0% oral switch vs. 21%,IV P = 0.052).**

La réalité in vivo (2)

Oral antibiotic therapy for the treatment of infective endocarditis: a systematic review

Awad Al-Omari[1], D William Cameron[2,3,4], Craig Lee[2,4] and Vicente F Corrales-Medina[2,3,4,5*]

BMC Infectious Diseases
BMC Infectious Diseases
2014, 14:140

9 études rétrospectives:
effectif faible sauf 1 (trimétoprime)
2 Etudes prospectives

Switch to oral antibiotics in the treatment of infective endocarditis is not associated with increased risk of mortality in non–severely ill patients☆

A. Mzabi [1, 2], S. Kernéis [1, 2, 3], C. Richaud [1, 2, 3], I. Podglajen [1, 2, 3], M.-P. Fernandez-Gerlinger [1, 2, 3], J.-L. Mainardi [1, 2, 3, 4, *]

CMI CLINICAL MICROBIOLOGY AND INFECTION ESCMID
22 (2016) 607e612

Etude rétrospective
effectif important: 369 patients

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.,

The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med 2019;380:415-24.

Etude prospective randomisée
effectif important: 400 patients
200 patients/bras IV ou PO

10 Etudes rétrospectives dont 2 avec effectif suffisant
3 Etudes prospectives randomisées

La réalité in vivo (3)

8 études rétrospectives à faible effectif

	Cas	Bactériologie	Traitement	Efficacité
Colli et al, Italy	12 EI native + 2 EI-prothèse	MRSA (60%) S. viridans (30%) Enterococcus sp (10%)	Vancomycine 5j puis Linézolide 3s	100%
Dworkin et al, USA		S. aureus (100%)	Cipro.-rifampicine IV 1 s / 3s per os	77%
Chetty et al, South Afr.	15 EI natives	Streptococcus sp (60%) Non documentée (40%)	Amox. Haute dose + probénécide (47%)	87%
Pinchas et al, Israel	11 EI natives gauches	Strepto. viridans (100%)	Amox. Haute dose 6s + probénécide 4s + streptomycine 2 s	100%
Phillips et al, UK	13 EI	Staphylocoque (23%) Streptocoque (62%) Enterococcus sp (15%)	IV 3j (92%) puis per os (amox, péni M) 6 s	100%
Gray et al, UK	13 EI	S. viridans (63%) Enterococcus sp (1%) Non documentée (37%)	Amox. Ou propicillin +/- probénécide	92%
Campeau et al, Canada	10 EI	S. viridans (60%) Enterococcus sp (10%) Anaérobie (40%)	phenithicillin + probénécide 4s + streptomycine 2 s	80%
Friedberg et al, USA	11 EI	S. viridans (57%) Enterococcus sp (18%) Non documentée (27%)	Aureomycin 5-8 s	36%

La réalité in vivo F

études rétrospectives à eff nt

SULFAMIDES

Reference	Cases	Design	ion	Microbiology	Assessment of antibiotic susceptibility	Therapy	Cure
Schein et al, USA [17]	81 NVIE (right-sid vs. left-sided specified)	ied ears	Not specified	negative (27%) *Streptococcus sp.* (94%) *S. aureus* (1%) *Enterococcus sp.* (1%) *H. influenza* (4%)	Not specified	Oral sulfonamides (sulfanilamide, sulfapyridine, sulfathiazole or sulfadiazine) for 10 days-14 weeks	10%

Trimethoprim-sulfamethoxazole versus vancomycin for severe infections caused by meticillin resistant *Staphylococcus aureus*: randomised controlled trial

Mical Paul,[1,2] Jihad Bishara,[1,2] Dafna Yahav,[2,3] Elad Goldberg,[2,4] Ami Neuberger,[5,6] Nesrin Ghanem-Zoubi,[7] Yaakov Dickstein,[6,8] William Nseir,[9] Michael Dan,[2,10] Leonard Leibovici[2,3]

BMJ 2015;350:h2219

252 patients
91 (36%) bactériémiques

Décès

- trimethoprim-sulfamethoxazole: 14/41 (34%)
- Vancomycine 9/50 (18%)

(risk ratio 1.90, 0.92 to 3.93).

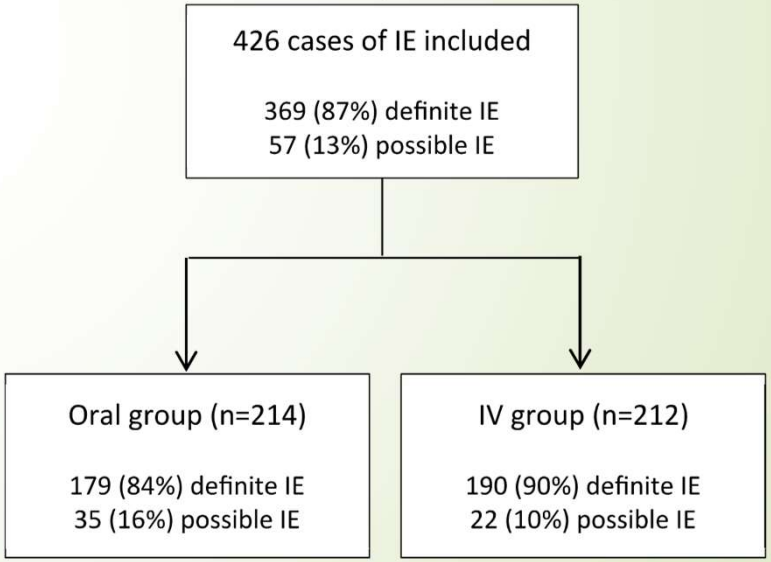
La réalité in vivo (6)

Switch to oral antibiotics in the treatment of infective endocarditis is not associated with increased risk of mortality in non–severely ill patients☆

A. Mzabi [1, 2], S. Kernéis [1, 2, 3], C. Richaud [1, 2, 3], I. Podglajen [1, 2, 3], M.-P. Fernandez-Gerlinger [1, 2, 3], J.-L. Mainardi [1, 2, 3, 4, *]

CMI CLINICAL MICROBIOLOGY AND INFECTION
ESCMID
22 (2016) 607e612

- **426 patients inclus**
- Etude rétrospective
- 246 patients (58%) avec chirurgie
  - 156 (64%) with native valve,
  - 50 (20%) with prosthetic valve
  - 40 (16%) with pacemaker or intracardiac device.
- Relais per os (médiane: 21 jours)
  - Streptocoque oraux: 14 jours
  - *S. aureus*: 28 j
  - Entérocoque 28 jours
  - Autres: 21 jours



La réalité in vivo (7)

Oral antibiotic regimen according to microorganism identified

Microorganism	Antibiotic regimen
Streptococci ($n = 91$)	• Amoxicillin ($n = 84$; 92%) • Amoxicillin—clindamycin ($n = 4$; 4%) • Amoxicillin—rifampin ($n = 3$; 3%)
Staphylococci ($n = 54$)	• Clindamycin—(rifampin or fluoroquinolone) ($n = 15$; 28%) • Fluoroquinolone—rifampin ($n = 13$; 24%) • Amoxicillin—(rifampin or fluoroquinolone or clindamycin) ($n = 9$; 17%) • Fluoroquinolone ($n = 4$; 7%) • Amoxicillin ($n = 4$; 7%) • Clindamycin ($n = 4$; 7%) • Rifampin—(Bactrim or doxycycline) ($n = 2$; 4%) • Linezolid ($n = 2$; 4%) • Rifampin ($n = 1$; 2%)
Enterococci ($n = 23$)	• Amoxicillin ($n = 21$; 91%) • Amoxicillin—rifampin ($n = 2$; 9%)

La réalité in vivo (8)

Main characteristics of patients who switched to oral route compared to those who received exclusively intravenous therapy

Characteristic	Oral antibiotic switch ($n = 214$)	Exclusively intravenous route ($n = 212$)	p[a]
Temperature >38°C	183 (86)	183 (86)	0.89
Acute heart failure	60 (28)	94 (44)	$<10^{-4}$
Shock	9 (4)	36 (17)	$<10^{-4}$
Cerebral emboli	27 (13)	42 (20)	0.05
CRP, mg/L	81 (10–512)	88 (10–525)	0.06
Serum creatinine >100 µmol/L	76 (36)	110 (52)	$<10^{-4}$
Surgery	120 (56)	126 (59)	0.49
Streptococci	91 (43)	80 (38)	0.32
Coagulase-negative staphylococci	26 (12)	22 (10)	0.64
Enterococci	23 (11)	26 (12)	0.65
Staphylococcus aureus	28 (13)	53 (25)	0.002
No. of deaths/No. of patients followed up after diagnosis			
Day 10	0/214	18/212	
Day 30	1/188	25/200	
Day 90	4/144	20/170	

RECHUTES : 11 patients (3%) Médiane 20 mois
groupe per os n= 2/ groupe IV n=9

REINFECTION : 12 patients (3%) Médiane 28 mois
groupe per os n= 4/ groupe IV n=8

La réalité in vivo (9)

études prospectives à effectif important (n=3)

Table 2 Clinical trials of oral antibiotic therapy for infective endocarditis

Reference	Cases	Design	Case definition	Microbiology	Therapy	Results
Heldman et al, USA [18]	85 IVDUs with NVIE (all right-sided with no systemic metastases), 40 in the oral therapy arm and 45 in the IV therapy arm	Prospective, randomized, open label. 1-month follow-up	- ≥2 positive blood cultures AND any of the following: Valvular vegetations on echocardiogram (definite – 15 cases) OR evidence of pulmonary emboli on chest X-ray or tricuspid insufficiency murmur (probable – 26 cases) OR no other identifiable source for the infection (possible – 44 cases)	MRSA (5%) MSSA (89%) CoNS (6%)	Oral ciprofloxacin and rifampin for 4 weeks vs. IV oxacillin or vancomycin (IV gentamicin for the first 5 days) for 4 weeks	Cure rate: 90% (oral therapy) vs. 91% (IV therapy), $p = 0.9$ Treatment toxicity: 3% (oral therapy) vs. 62% (IV therapy), $p < 0.001$
Stamboulian et al, Argentine [19]	30 NVIE (all left-sided), 15 in each arm	Prospective, randomized, open label. 3 to 6-motnh follow-up	- ≥2 positive blood cultures AND any of the following: New or changing regurgitant murmur OR predisposing heart disease OR vascular phenomena OR valvular vegetation on echocardiogram	S. viridans (50%) S. bovis (50%)	IV or IM ceftriaxone for 2 weeks followed by high dose oral amoxicillin for 2 weeks vs. IV or IM ceftriaxone for 4 weeks	Cure rate: 100% in both arms. Treatment toxicity not reported

NVIE denotes cases of native valve infective endocarditis. IV denotes intravenous. IM denotes intramuscular. IVDUs denotes intravenous drug users. MSSA denotes methicillin-sensitive *S. aureus*. MRSA denotes methicillin-resistant *S. aureus*. CoNS denotes coagulase-negative staphylococcus. All reports reported follow-up ≥2 months.

BMC Infectious Diseases 2014, 14:140

La réalité in vivo (10)

- **DUKE avec hémocultures +**
  Streptococcus, *Enterococcus faecalis*, *Staphylococcus aureus*, CNS
- **Traitement antibiotique IV> 10 jours**
- **Dosage sérique ATB si PO** (0,5 h, 1 h, 2, 4 et 6 h)
- **CMI** (Etest ou Vitek)

Critère principal d'évaluation : composite de
- Toute cause de mortalité
- Chirurgie cardiaque non programmée,
- Evénement(s) embolique(s),
- Rechute de bactériémie au même germe

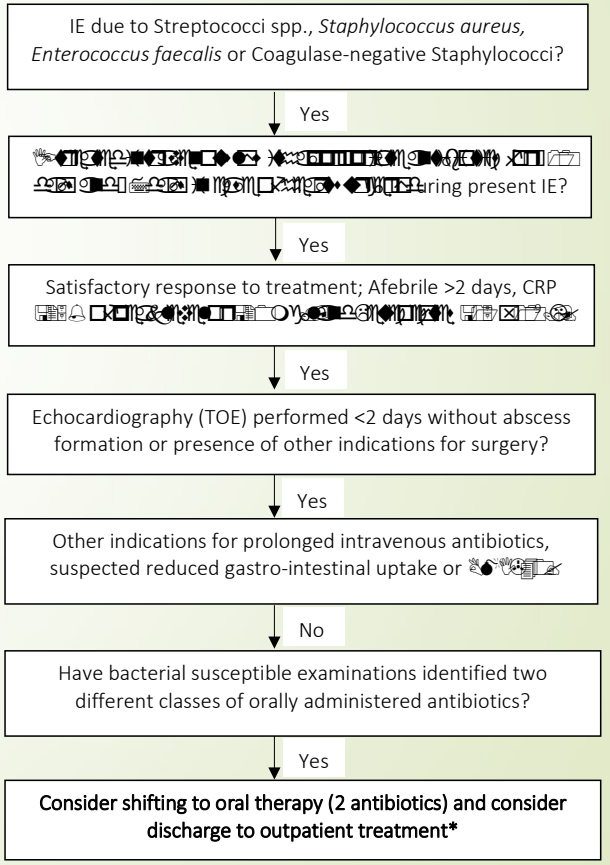
Suivi 6 mois post arrêt ATB .

The NEW ENGLAND JOURNAL of MEDICINE

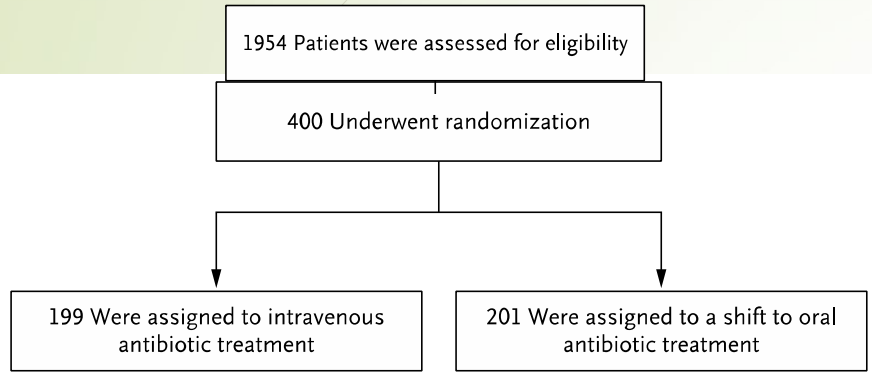
Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Kasper Iversen, M.D., D.M.Sc., Nikolaj Ihlemann, M.D., Ph.D., Sabine U. Gill, M.D., Ph.D.,

N Engl J Med 2019;380:415-24.



La réalité in vivo (11)



Randomisation J17 (médiane/ diagnostic EI)
Durée de traitement
PO: 17 jours IV : 19 jours
Durée de séjour après la randomisation:
IV:19 jours
PO: 3 jours ((P<0.001).

Preexisting prosthesis, implant, or cardiac disease — no. (%)		
Prosthetic heart valve	53 (26.6)	54 (26.9)
Pacemaker	15 (7.5)	20 (10.0)
Other known valve disease	82 (41.2)	90 (44.8)
Cardiac involvement at randomization — no. (%)§		
Mitral-valve endocarditis	65 (32.7)	72 (35.8)
Aortic-valve endocarditis	109 (54.8)	109 (54.2)
Mitral-valve and aortic-valve endocarditis	23 (11.6)	20 (10.0)
Endocarditis in other locations§	2 (1.0)	0
Pacemaker endocarditis	6 (3.0)	8 (4.0)
Vegetation size >9 mm	7 (3.5)	11 (5.5)
Moderate or severe valve regurgitation	19 (9.5)	23 (11.4)
Valve surgery during current disease course	75 (37.7)	77 (38.3)

N Engl J Med 2019;380:415-24.

La réalité in vivo (12)

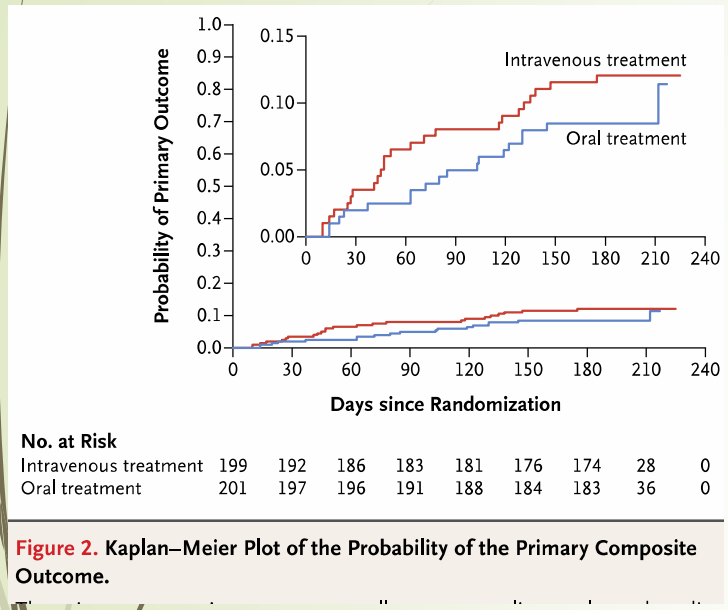


Figure 2. Kaplan–Meier Plot of the Probability of the Primary Composite Outcome.

ECHECS

ITT

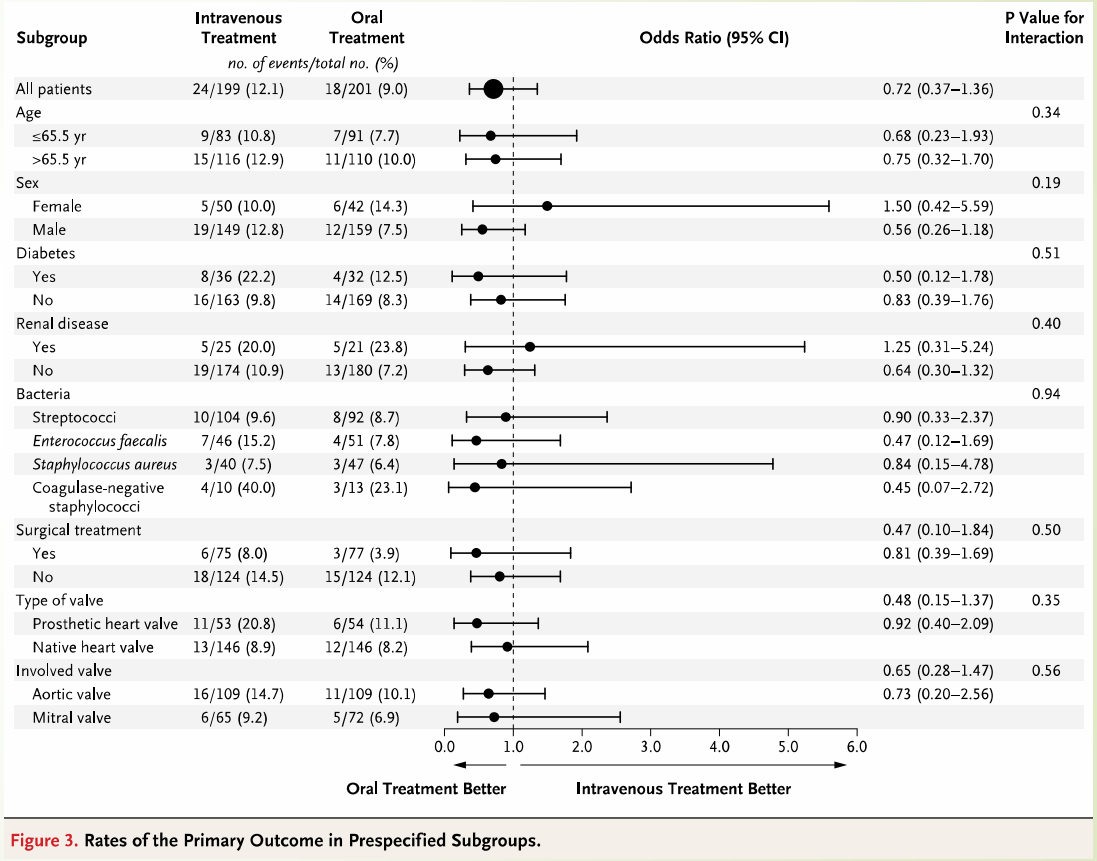
24 patients (12.1%) IV

18 patients (9.0%) PO

Per Protocole

24/199 patients (12.1%) IV

18/197 (9.1%) PO



Subgroup	Intravenous Treatment	Oral Treatment	Odds Ratio (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
All patients	24/199 (12.1)	18/201 (9.0)	0.72 (0.37–1.36)	
Age				0.34
≤65.5 yr	9/83 (10.8)	7/91 (7.7)	0.68 (0.23–1.93)	
>65.5 yr	15/116 (12.9)	11/110 (10.0)	0.75 (0.32–1.70)	
Sex				0.19
Female	5/50 (10.0)	6/42 (14.3)	1.50 (0.42–5.59)	
Male	19/149 (12.8)	12/159 (7.5)	0.56 (0.26–1.18)	
Diabetes				0.51
Yes	8/36 (22.2)	4/32 (12.5)	0.50 (0.12–1.78)	
No	16/163 (9.8)	14/169 (8.3)	0.83 (0.39–1.76)	
Renal disease				0.40
Yes	5/25 (20.0)	5/21 (23.8)	1.25 (0.31–5.24)	
No	19/174 (10.9)	13/180 (7.2)	0.64 (0.30–1.32)	
Bacteria				0.94
Streptococci	10/104 (9.6)	8/92 (8.7)	0.90 (0.33–2.37)	
Enterococcus faecalis	7/46 (15.2)	4/51 (7.8)	0.47 (0.12–1.69)	
Staphylococcus aureus	3/40 (7.5)	3/47 (6.4)	0.84 (0.15–4.78)	
Coagulase-negative staphylococci	4/10 (40.0)	3/13 (23.1)	0.45 (0.07–2.72)	
Surgical treatment			0.47 (0.10–1.84)	0.50
Yes	6/75 (8.0)	3/77 (3.9)	0.81 (0.39–1.69)	
No	18/124 (14.5)	15/124 (12.1)		
Type of valve			0.48 (0.15–1.37)	0.35
Prosthetic heart valve	11/53 (20.8)	6/54 (11.1)	0.92 (0.40–2.09)	
Native heart valve	13/146 (8.9)	12/146 (8.2)		
Involved valve			0.65 (0.28–1.47)	0.56
Aortic valve	16/109 (14.7)	11/109 (10.1)	0.73 (0.20–2.56)	
Mitral valve	6/65 (9.2)	5/72 (6.9)		

Figure 3. Rates of the Primary Outcome in Prespecified Subgroups.

N Engl J Med 2019;380:415-24.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Table S2
Oral regimens recommended in the POET trial

Methicillin sensitive *Staphylococcus aureus* and coagulase-negative staphylococci

1) Dicloxacillin 1 g x 4 and fusidic acid 0.75 g x 2
2) Dicloxacillin 1 g x 4 and rifampicin 0.6 g x 2
3) Linezolid 0.6 g x 2 and fucidic acid 0.75g x 2
4) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

Enterococcus faecalis:

1) Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2
2) Amoxicillin 1 g x 4 and moxifloxacin 0.4 g x 1
3) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2
4) Linezolid 0.6 g x 2 and moxifloxacin 0.4 g x 1

Streptococci with a minimal inhibitory concentration for penicillin of <1 mg/L:

1) Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2
2) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2
3) Linezolid 0.6 g x 2 and moxifloxacin 0.4 g x1

Iversen K et al. New Engl J Med 2018

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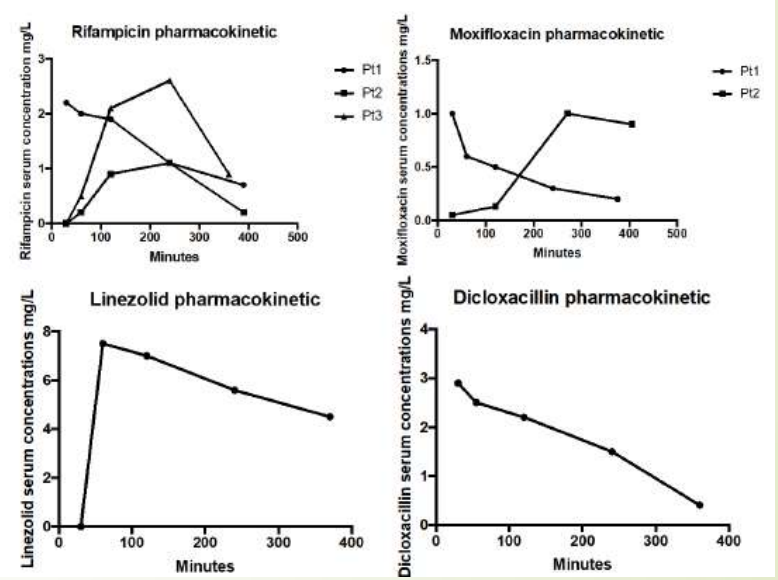
ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Table S3

Applied cut-off levels for therapeutic plasma concentrations

Antibiotic	Applied cut-off levels for therapeutic plasma concentration
Rifampicin	<3 mg/L
Moxifloxacin	<2 mg/L
Linezolid	<8 mg/L
Fusidic acid	< 4 mg/L
Amoxicillin, Streptococcus spp	≤2 mg/L in <50% of the dosing interval
Amoxicillin, E. faecalis	≤8 mg/L in <50% of the dosing interval
Dicloxacillin	≤2 mg/L in <50% of the dosing interval
Clindamycin	<0.5 mg/L



Iversen K et al. New Engl J Med 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Patients très sélectionnés !
25% des patients
Traitement hétérogène
Mortalité 4,5%

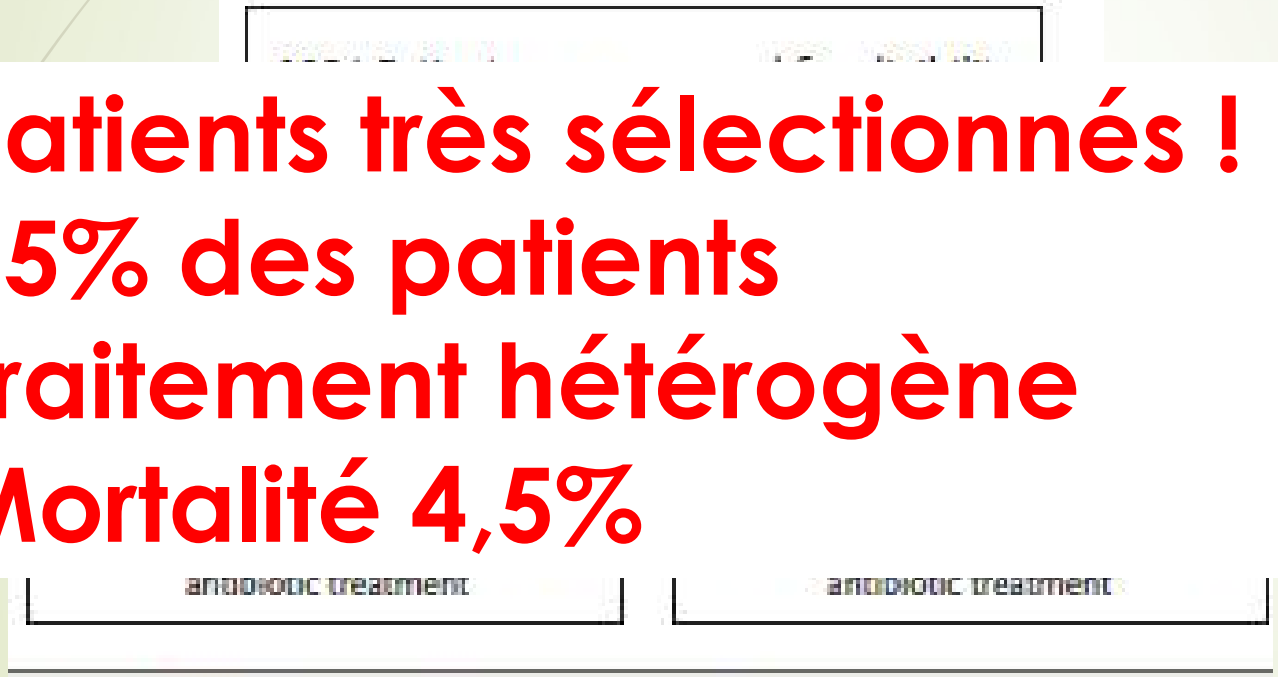


Figure 1. Enrollment and Randomization of Patients.

Iversen K et al. New Engl J Med 2018

IV à la maison….

18 études
- 18 à 133 patients
- 0 à 33% d'échec
- Molécules variables
- Beaucoup de rétrospectif…

Conclusion : ……..difficile !

Clinical Infectious Diseases

MAJOR ARTICLE

Outpatient Parenteral Antibiotic Treatment for Infective Endocarditis: A Prospective Cohort Study From the GAMES Cohort

Juan M. Pericàs,[1,a] Jaume Llopis,[1,a] Víctor González-Ramallo,[2] Miguel Á. Goenaga,[3] Patricia Muñoz,[2] M. Eugenia García-Leoni,[2] M. Carmen Fariñas,[4] Marcos Pajarón,[4] Juan Ambrosioni,[1] Rafael Luque,[5] Josune Goikoetxea,[6] José A. Oteo,[7] Enara Carrizo,[8] Marta Bodro,[1] José M. Reguera-Iglesias,[9] Enrique Navas,[10] and Carmen Hidalgo-Tenorio,[11] José M Miró[1]; for the Spanish Collaboration on Endocarditis-Grupo de Apoyo al Manejo de la Endocarditis Infecciosa en España (GAMES) investigators[b]

[1]Hospital Clínic de Barcelona, Institut de Recerca Augusti Pi i Sunyer, Universitat de Barcelona, [2]Hospital General Universitario Gregorio Marañón, Madrid, Instituto de Investigación Sanitaria, Gregorio Marañón. Centro de Investigación Biomédica en Red Enfermedades Respiratorias (CIBERES, CB06/06/0058), Department of Medicine, Universidad Complutense de Madrid, [3]Hospital Donostia, San Sebastián, [4]Hospital Universitario Marqués de Valdecilla, Universidad de Cantabria, Santander, [5]Hospital Universitario Virgen del Rocío, Sevilla, [6]Hospital de Cruces, Barakaldo, [7]Hospital San Pedro de la Rioja, Logroño, [8]Hospital Universitario de Araba-Txagorritxu, Gasteiz, [9]Hospital Regional Universitario de Málaga, [10]Hospital Universitario Ramón y Cajal, Madrid, and [11]Hospital Virgen de las Nieves, Complejo Hospitalario de Granada, Granada, Spain

(See the Editorial Commentary by Tattevin and Revest on pages 1701–2.)

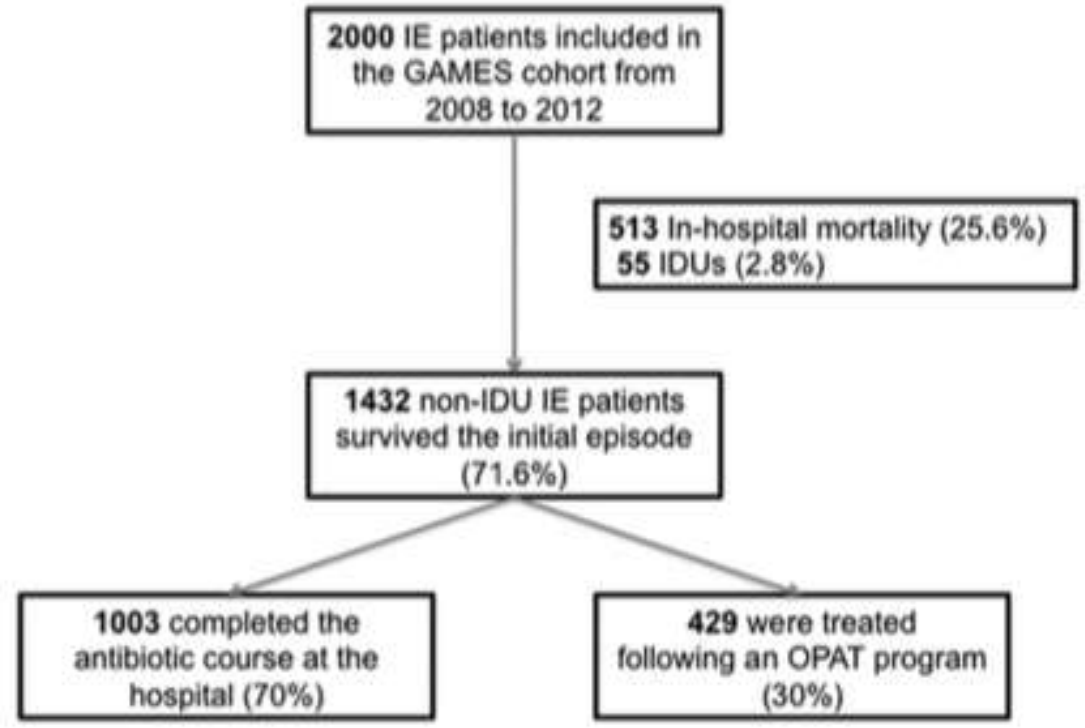


Figure 1. Flowchart of patient treatment. Abbreviations: IDU, intravenous drug user; IE, infective endocarditis; OPAT, outpatient parenteral antibiotic treatment.

Clinical Infectious Diseases® 2019;69(10):1690–700

Comparaison Baseline

- Groupe « traitement hospitalier » : 23,3% critères IDSA(+) pour OPAT
  - Plus d'insuffisances hépatique et rénale (3,6 vs 14%;)
  - Plus d'endocardite native (65,6 % vs 57,1%)
  - Plus entérocque (15,7% vs 9,3%)

- Groupe « OPAT » : 21,7% critères IDSA (+) pour OPAT
  - Plus d'IE sur PM ou défibrilateur (18,6% vs 11,7%)
  - Plus de traitement immunosuppresseur 4.1% vs 7%

RESULTATS

Variables	Hospital-based Antibiotic Treatment (N = 1003)	Outpatient Parenteral Antibiotic Treatment (N = 429)	*P* Value
Symptomatic	200 (25.7%)	74 (20.7%)	.034
oNYHA I	48 (24%)	23 (31.1%)	.019
oNYHA II	102 (51%)	37 (50%)	.965
oNYHA III	50 (25%)	14 (20.3%)	.047
oNYHA IV	10 (5%)	0	<.001
Outcomes			
Readmissions during first 3 months after discharge	101 (10%)	47 (10.9%)	.614
Infective endocarditis related	58 (57.4%)	20 (42.5%)	.091
Catheter/antibiotic related	5 (4.9%)	5 (10.6%)	.199
Other complications	38 (37.6%)	22 (46.8%)	.289
Surgery within first year after discharge	80 (8%)	45 (10.5%)	.142
Relapse	32 (3.2%)	6 (1.4%)	.053
Mortality at 1 year	125 (12.5%)	33 (7.7%)	.004

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Multivarié: uniquement score de CHARLSON !

Clinical Infectious Diseases

EDITORIAL COMMENTARY

Outpatient Parenteral Antibiotic Treatment for Infective Endocarditis: Insights From Real Life

Pierre Tattevin and Matthieu Revest

Infectious Diseases and Intensive Care Unit, Pontchaillou University Hospital, Rennes, France

- Pas un mot sur le relais oral !!!

Discussion

El gauche: Relais per os semble possible

EI gauche: Relais per os semble possible

- Pour qui :
  -Taille de l'inoculum (végétation)
  -CMI
- Quand : J2 ou J5 d'apyrexie
- Quelles molécules ?
  - amoxiclline (absorption per os saturable)
  - quinolones (moxifloxacine ?)
  - rifampicine
- Bithérapie?
- Quelle durée ?
- Critères d'arrêt des antibiotiques

EI gauche: Relais per os semble possible

- **PHRC RODEO : Relais par voie Orale des EI cœur Gauche**
  - Etude Randomisée IV versus per os
  - Streptocoque/Entérocoque (CMI < 0,5 mg/l):
    - amoxiclline 1,5-2 g x 3/jour
  - Staphylocoque:
    - Lévofloxacine 0,5-0,75 g + Rifampicine 600-900 mg / jour

28 nov 2019: Le nombre d'inclusion : **285/610** attendus

-> Répartition des germes :
* Staphylocoque : 75
* Entérocoque : 16
* Streptocoque : 133

-> 178 patients ont terminés l'étude => dans l'eCRF, la visite a été saisie et faite pour 137 patients: visite a été saisie

merci

Réduction de la durée ?

Combien de temps pour stériliser des valves pour les EI chez l'homme ?

Etude rétrospective de tous les patients opérés pour EI infectieuse

- Auckland, Nouvelle Zélande, 1963-1999, **n=506**

Quelle est la proportion de valves non stériles en fonction du moment de la chirurgie par rapport au traitement ATB ?

Morris AJ et al. Clin Infect Dis 2003

Combien de temps pour stériliser des valves pour les EI chez l'homme ?

Variable	No. of episodes	Microbiological findings: No. of positive Gram stain results/ total no. of samples stained (%)	Microbiological findings: No. of positive culture results/ total no. of cultures (%)
Proportion of standard duration antibiotic treatment completed at time of operation			
≤25%	106	88/100 (88)	76/106 (72)
26%–50%	113	85/101 (84)	40/108 (37)
51%–75%	57	37/50 (74)	7/54 (13)
76%–100%	41	21/34 (62)	2/38 (5)

Morris AJ et al. Clin Infect Dis 2003

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