JOURNÉES SCIENTIFIQUES DU GERICCO

POITIERS – 29 MARS 2019

Endocardites : pour ou contre le relais oral

Pour: Louis Bernard, Tours ;

Contre: Pierre Tattevin, Rennes)

Louis BERNARD

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.

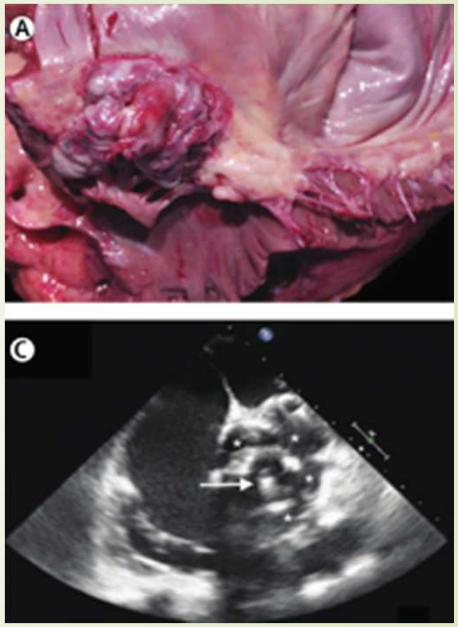
Endocardite

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

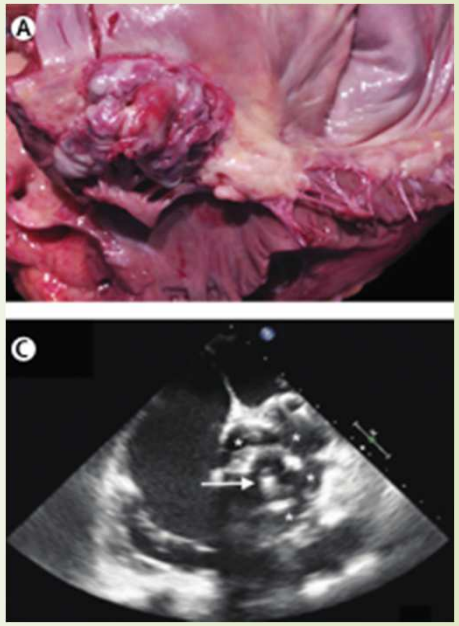


Végétation (2)

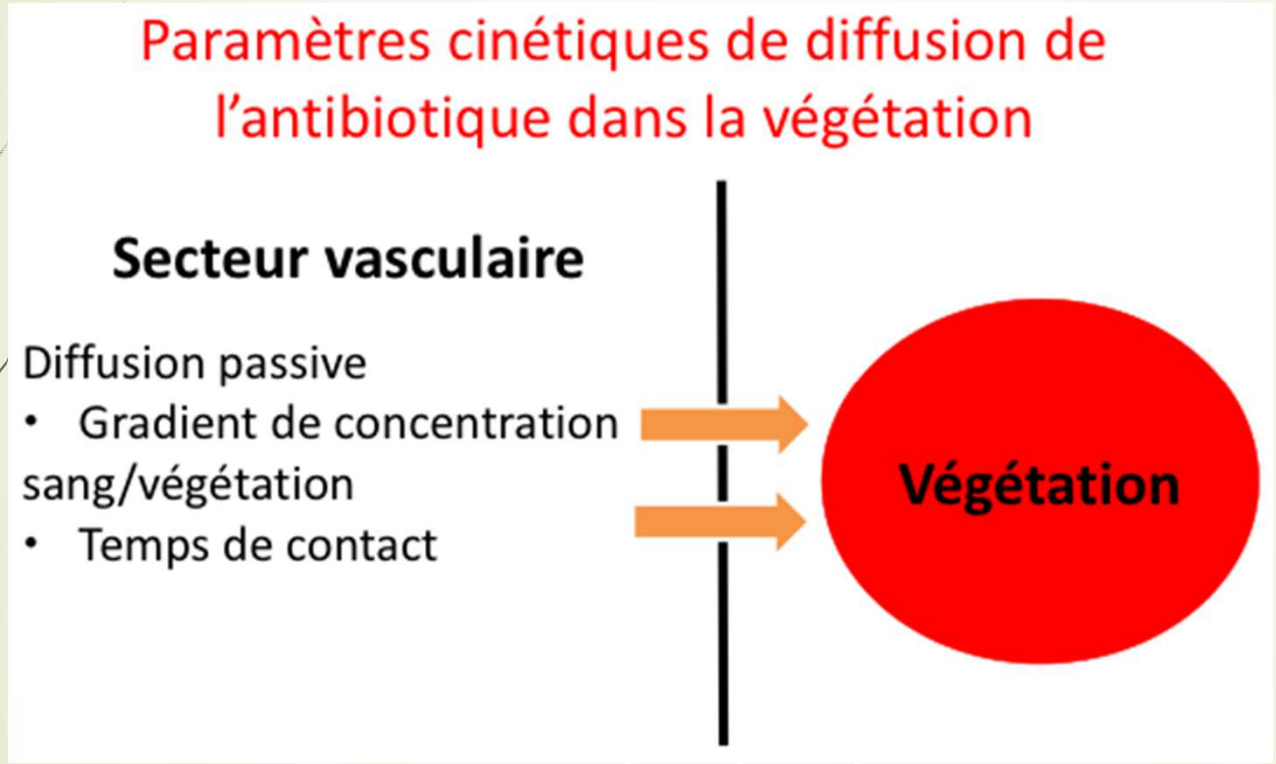
Diffusion dans la végétation: facteurs liés à l'antibiotique et la végétation

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)

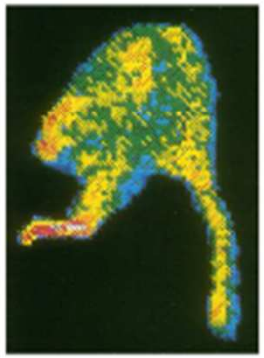
Autoradiographie

- 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

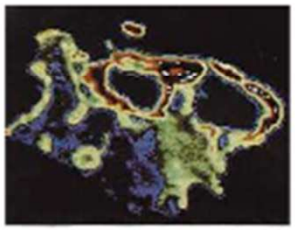
Végétation (7)

Types de diffusion des antibiotiques marqués dans la végétation

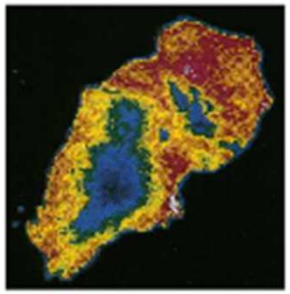
Homogène



Périphérique

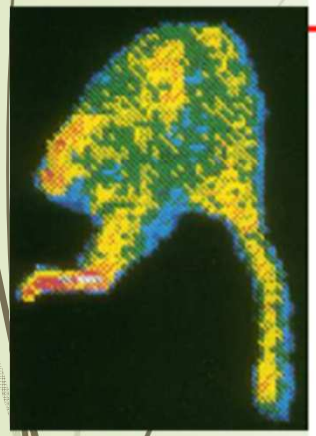


Gradient



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

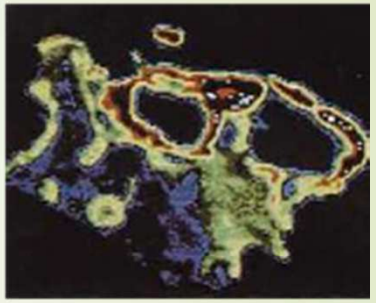
Non homogène

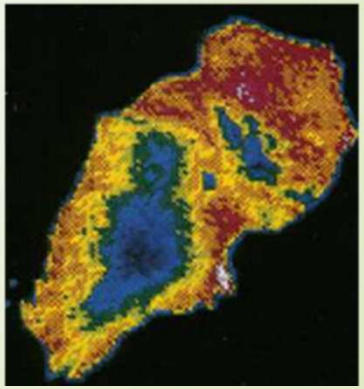
Périphérique

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 Unive

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy
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]													
	0–<5													>160
125 every 48 h	91.													0.0
250 every 48 h	48.													0.0
500 every 48 h	6.4													0.0
750 every 48 h	1.4													0.0
500 every 24 h	2.3													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

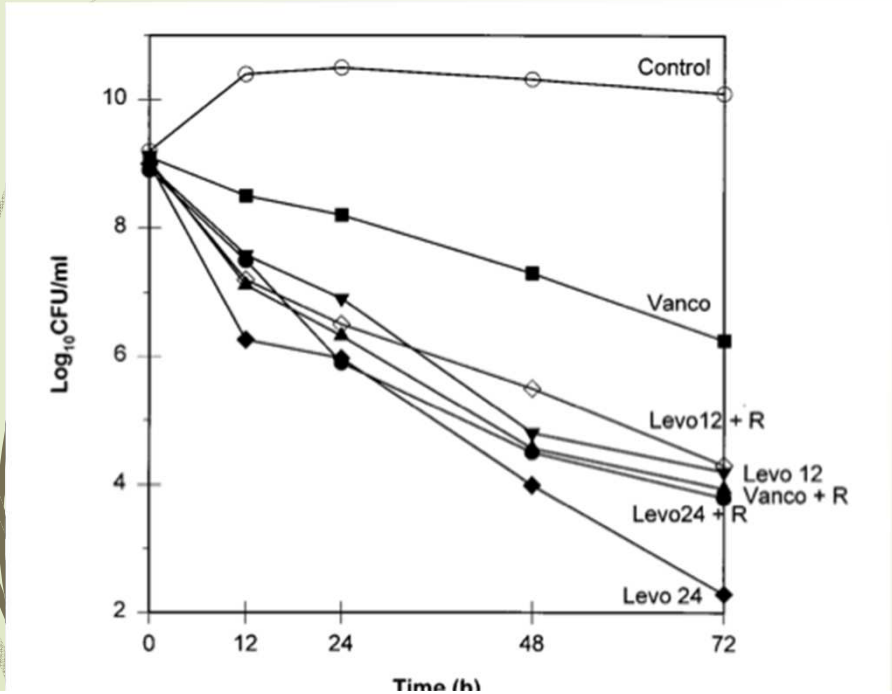
Antibiotiques (2) Lévofloxacine

Pharmacodynamics of Once- or Twice-Daily Levofloxacin versus Vancomycin, with or without Rifampin, against *Staphylococcus aureus* in an In Vitro Model with Infected Platelet-Fibrin Clots

SHIRLEY M. PALMER[1]† AND MICHAEL J. RYBAK[1,2]*

AAC, 1996, p. 701–705

levofloxacin 800 mg /24h ou 400 mg q12h, vancomycin 1 g/12h, and rifampin at 600 mg q24h.
Culture de « Infected platelet-fibrin clots »



Kaatz, AAC 1989,33-8,1184-7
El expérimentale Ciprofloxacine/rifampicine
Si rifampicine seule: mutants

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

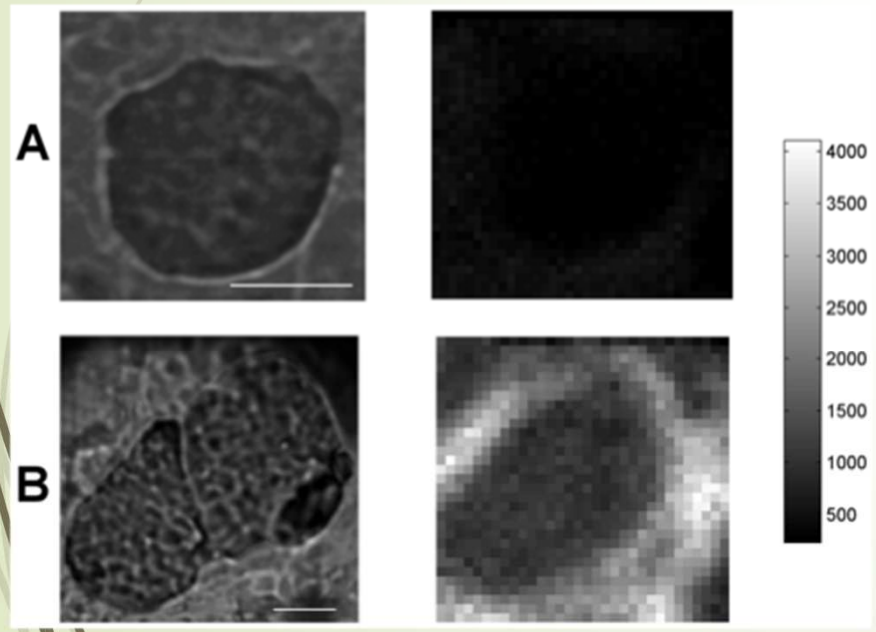


Figure 4. Transmission image (left) and maps of the 390–440 nm peak area (right) of control (A) and ofloxacin treated (B) vegetation maps. The grayscale was the same for both fluorescence maps. White bar = 10 mm.

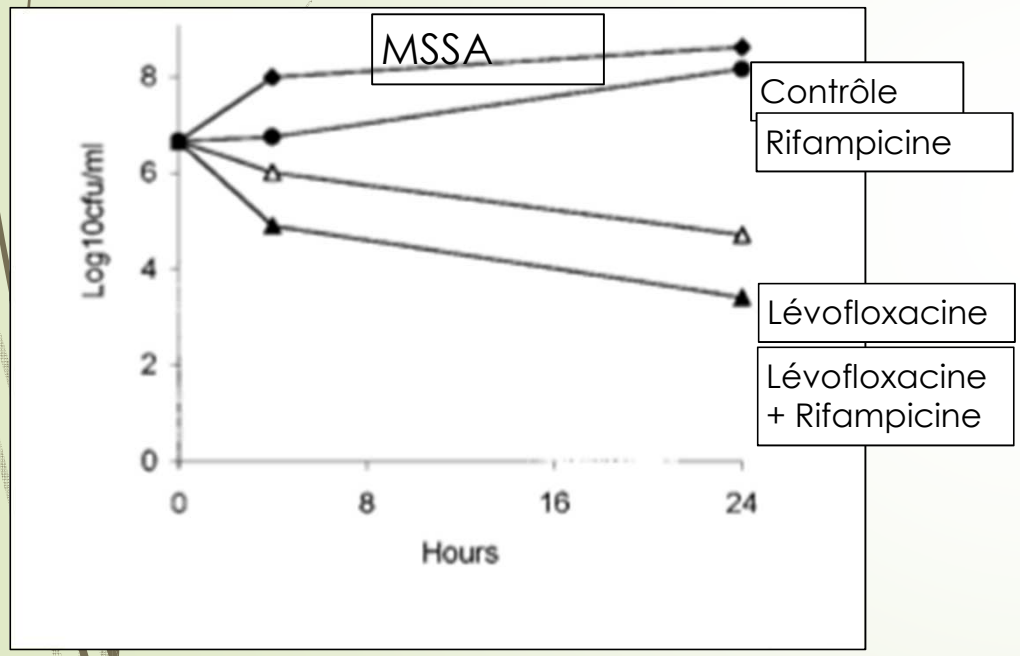
Diffusion immédiate
et en masse de l'ofloxacine

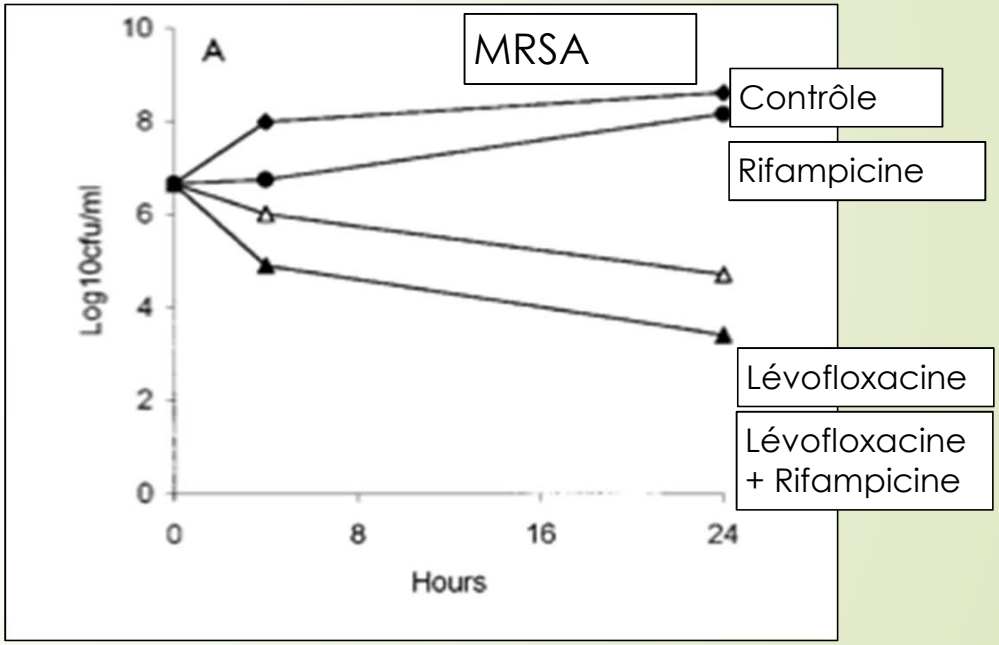
Antibiotiques (5) Lévofloxacine-Rifampicine

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) Lévofloxacine-Rifampicine

Bactericidal Activity of the Combination of Levofloxacin with Rifampin in Experimental Prosthetic Knee Infection in Rabbits Due to Methicillin-Susceptible *Staphylococcus aureus*[▽]

Claudette Muller-Serieys,[1] Azzam Saleh Mghir,[2]† Laurent Massias,[3] and Bruno Fantin[2]*

Laboratoire de Microbiologie, AP-HP, Hôpital Bichat,[1] EA3964, Université Paris Diderot,[2] and Laboratoire de

AAC 2009, p. 2145–2148

TABLE 1. Effects of 7-day treatment regimens of levofloxacin or rifampin, alone or in combination, in rabbits with experimental prosthetic knee infections due to *S. aureus* 17848

Treatment agent (dose[a])	No. of rabbits with sterile bone/no. tested	Log_{10} no. of CFU/g of bone (mean ± SD)	No. of rabb with mutan resistant te rifampin/ne tested[d]
None	0/10	6.36 ± 1.33	2/6
Levofloxacin (25 mg/kg b.i.d. i.v.)	5/12	2.92 ± 1.33[b]	0/12
Rifampin (10 mg/kg b.i.d. i.m.)	5/11	3.20 ± 2.12[b]	4/11
Levofloxacin-rifampin	6/12	1.99 ± 0.52[b,c]	0/12

[a] b.i.d., twice a day; i.m., intramuscularly.
[b] Significantly different from the level for untreated controls ($P < 0.05$).
[c] Significantly different from the level for rifampin alone ($P < 0.05$).
[d] No mutants resistant to levofloxacin were found in rabbits.

Antibiotiques (5) Rifampicine

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

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

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

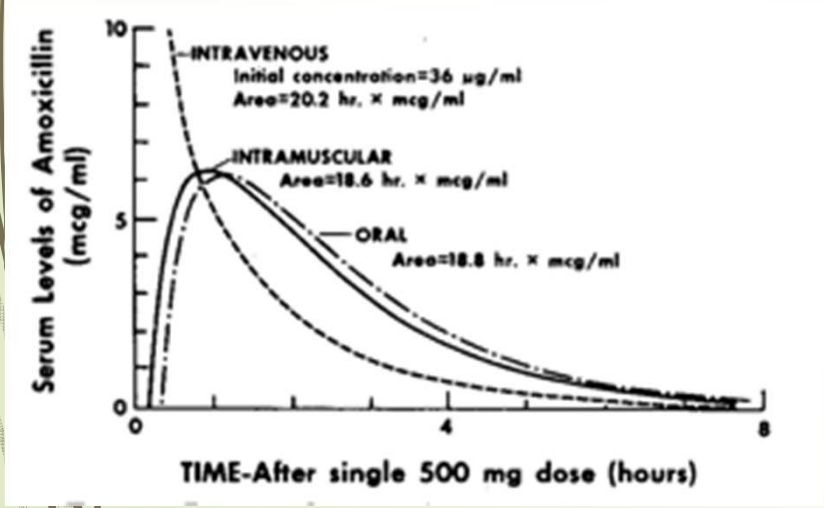
TABLE 3 Summary of frequency of adverse events according to CTCAE criteria[a]

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

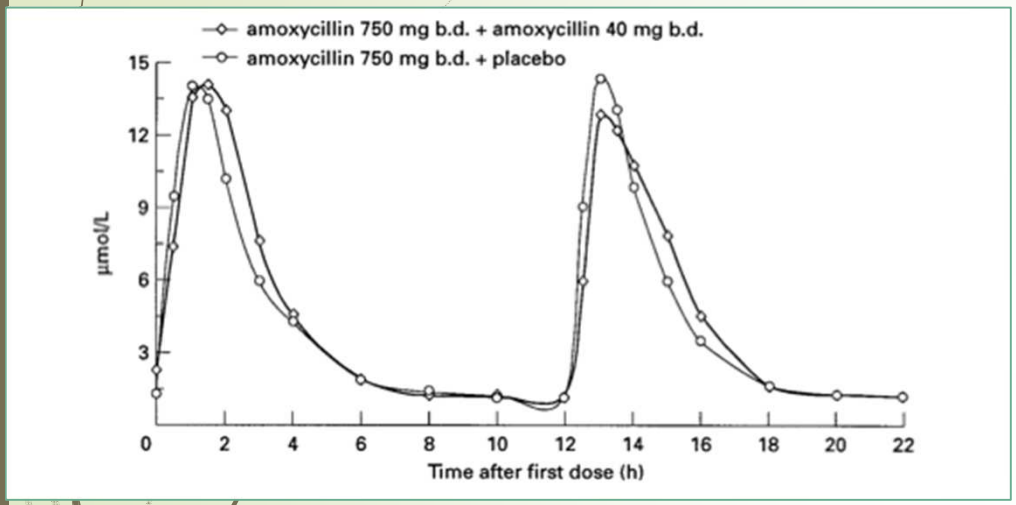


ARANCIBIA, AAC 1980, 199-202

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
$AUC_{[-"]}$	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
$AUC_{"\#\#}$	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

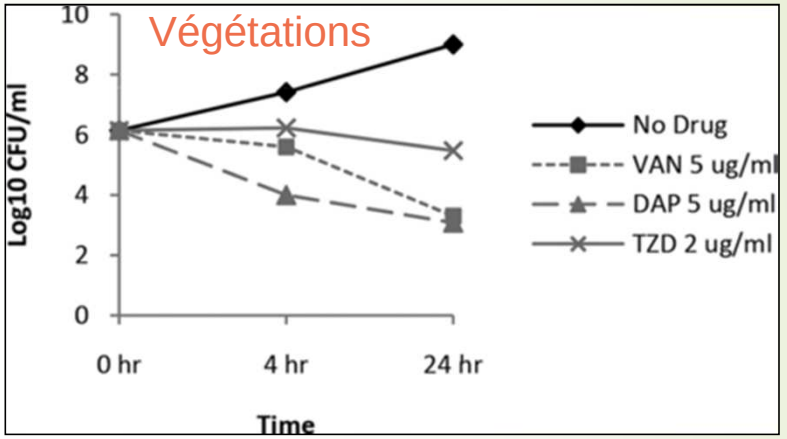


TABLE 1 Comparative study of tedizolid phosphate, daptomycin, and vancomyc

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)

Evaluation 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)

- EI gauche n= 12
- EI 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
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[illegible]

SULFAMIDES

Reference	Cases	Design	[illegible]on	Microbiology	Assessment of antibiotic susceptibility	Therapy	Cure
Schein et al, USA [17]	81 NVE (right-sid[illegible] vs. left-sided [illegible] specified)	[illegible]ed [illegible]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)

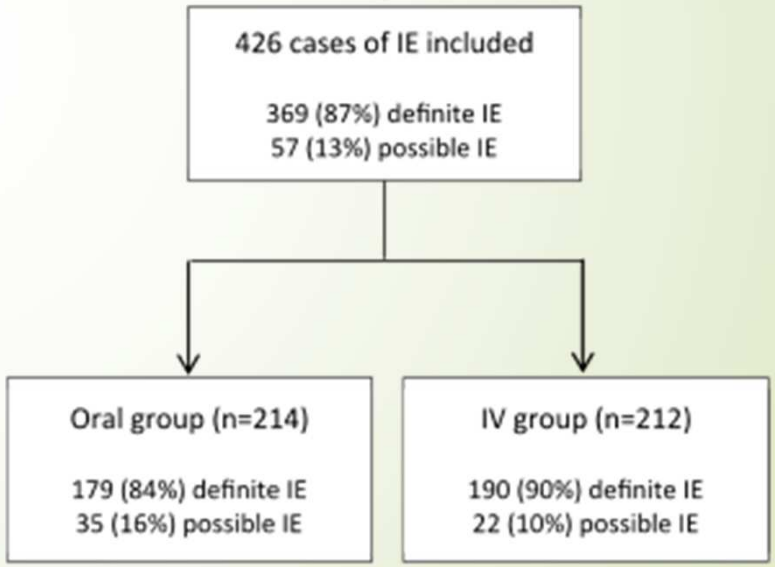
La réalité in vivo (6)

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
  - Enterocoque 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

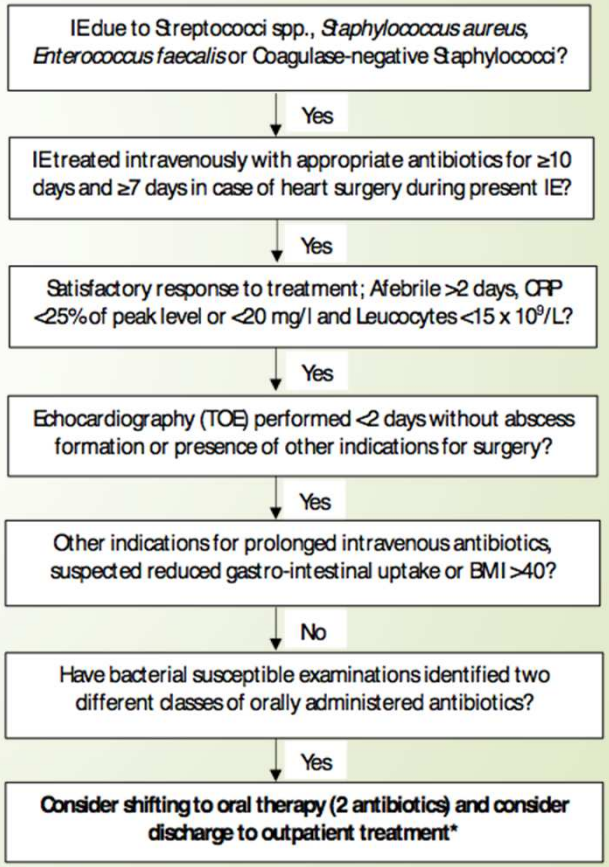
Suivi 6 mois post arrêt ATB .

The NEW ENGLAND JOURNAL of MEDICINE

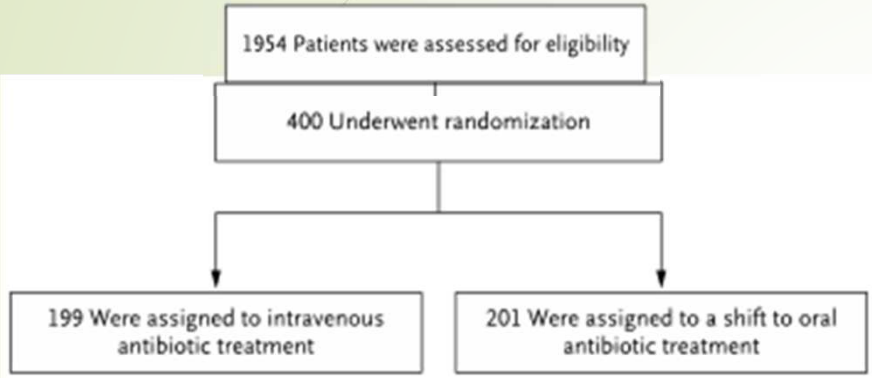
Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

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)

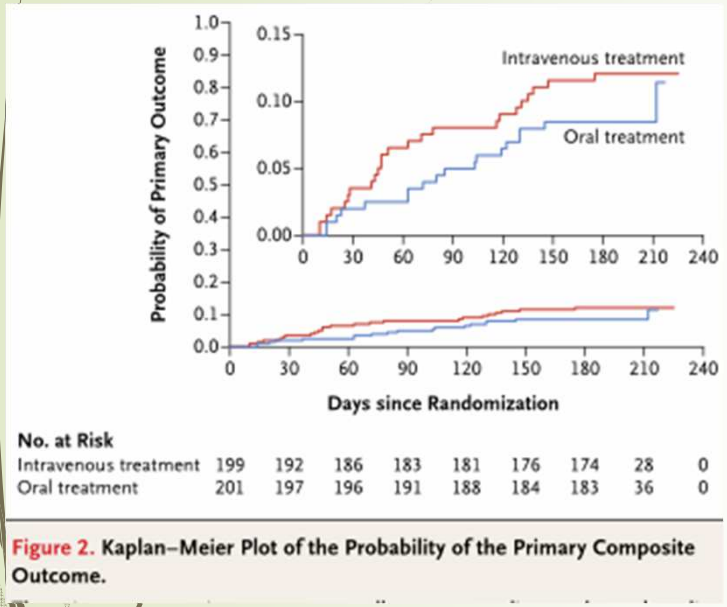
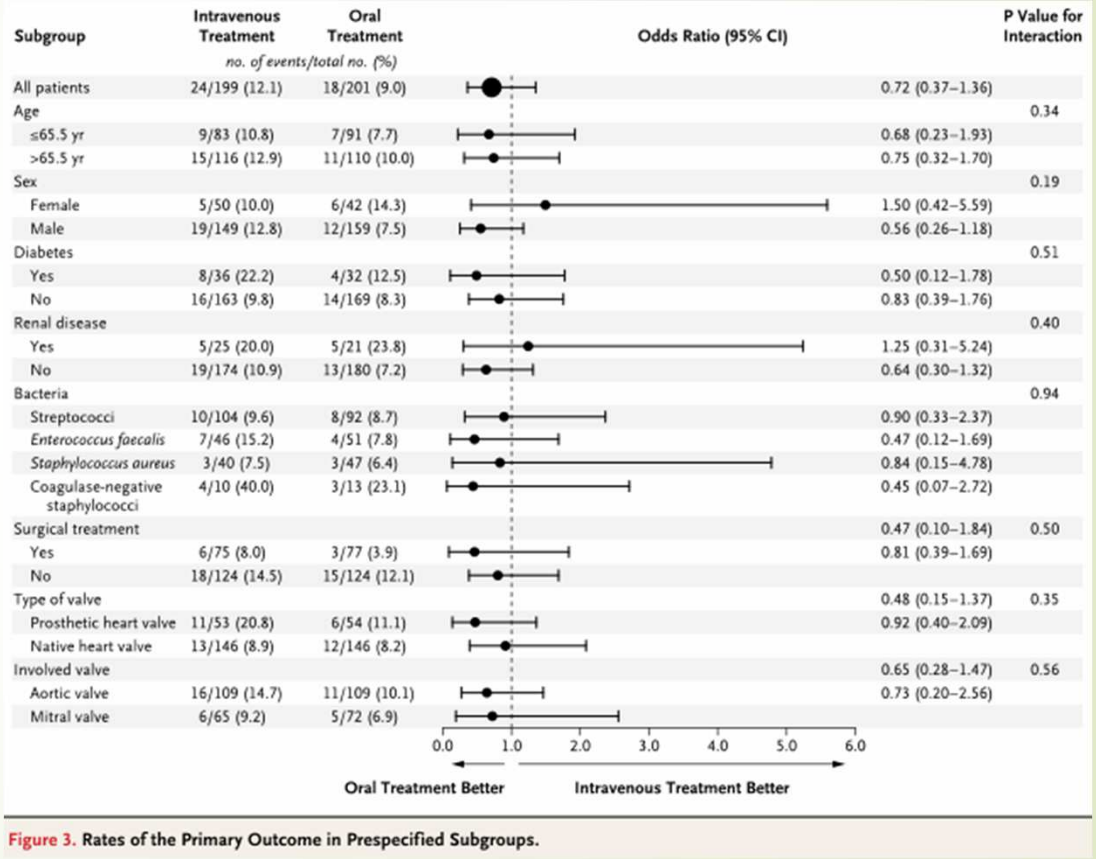


Figure 2. Kaplan–Meier Plot of the Probability of the Primary Composite Outcome.

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.

La réalité in vivo (13)

Penicillin and MS *S. aureus* and CNS:

- Amoxicillin 1 g x 4 and fusidic acid 0.75 g x 2
- Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2
- Linezolid 0.6 g x 2 and fusidic acid 0.75 g x 2
- Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

MSSA and CNSMS

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

MR CNS

- Linezolid 0.6 g x 2 and fusidic acid
- Linezolid 0.6 g x 2 and rifampicin 0.6 g x2

Enterococcus faecalis:

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

Streptococci CMI penicillin <1 mg/L:

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

Streptococci - CMI penicillin ≥1 mg/L:

- Linezolid 0,6 g x2 and rifampicin 0.6 g x 2
- Moxifloxacin 0.4 g x 1 and rifampicin 0.6 g x 2
- Moxifloxacin 0.4 g x 1 and clindamycin 06 g x3

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

Susceptibility to penicillin, ampicillin or methicillin for the bacterial groups included

	Penicillin susceptibility streptococci (MIC< 1 mg/L)	Penicillin susceptibility staphylococci (large and tapered penicillin zone. Penicillinase induction test)	Ampicillin susceptibility (MIC≤ 4 mg/L)	Methicillin resistance (Cefoxitin or oxacillin screening. Confirmed by mec gene analysis)
*Streptococcus spp**	194 susceptible 2 resistant			
Enterococcus faecalis			96 susceptible 1 resistant	
Staphylococcus aureus		27 susceptible 60 resistant		87 susceptible 0 resistant
Coagulase negative staphylococci		7 susceptible 16 resistant		15 susceptible 8 resistant

* Including 1 isolates of *Abiotrophica defectiva*.

Antibiotic regimens in the POET trial.

	Oral regimens	Frequency n (%)
Staphylococcus aureus	Dicloxacillin and rifampicin	15 (33)
	Amoxicillin and rifampicin	13 (29)
	Moxifloxacin and rifampicin	3 (7)
	Amoxicillin and fusidic acid	2 (4)
	Dicloxacillin and fusidic acid	2 (4)
	Fusidic acid and linezolid	2 (4)
	Rifampicin and linezolid	2 (4)
	Penicillin and rifampicin	1 (2)
	Amoxicillin and clindamycin	1 (2)
	Ampicillin and rifampicin	1 (2)
	Moxifloxacin and fusidic acid	1 (2)
	Moxifloxacin and linezolid	1 (2)
	Linezolid and clindamycin	1 (2)
Enterococcus faecalis	Amoxicillin and moxifloxacin	24 (47)
	Amoxicillin and linezolid	13 (25)
	Amoxicillin and rifampicin	6 (12)
	Moxifloxacin and linezolid	5 (10)
	Amoxicillin and ciprofloxacin	2 (4)
	Amoxicillin	1 (2)

	Oral regimens	Frequency n (%)
Streptococci	Amoxicillin and rifampicin	47 (52)
	Amoxicillin and moxifloxacin	12 (13)
	Rifampicin and linezolid	8 (9)
	Moxifloxacin and linezolid	8 (9)
	Amoxicillin and linezolid	7 (8)
	Penicillin	3 (3)
	Ampicillin and moxifloxacin	1 (1)
	Ampicillin and rifampicin	1 (1)
	Dicloxacillin and moxifloxacin	1 (1)
	Moxifloxacin and clindamycin	1 (1)
	Moxifloxacin and vancomycin	1 (1)
Coagulase negative staphylococci	Fusidic acid and linezolid	5 (38)
	Rifampicin and linezolid	4 (31)
	Amoxicillin and linezolid	1 (8)
	Dicloxacillin and rifampicin	1(8)
	Moxifloxacin and linezolid	1(8)
	Rifampicin and Fusidic acid	1(8)

Discussion

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

- **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 0,5-1 g + Rifampicine 600-900 mg / jour

29 mars 2019: Le nombre d'inclusion : **224/610** 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