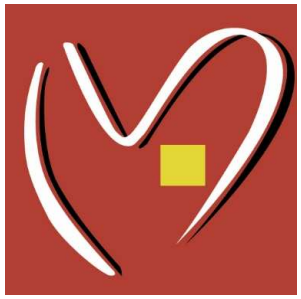
Antibiothérapie par voie orale dans l'endocardite infectieuse

Comment les résultats de POET vont changer nos pratiques ?



AVANT POET

Dans l'EI du cœur droit chez l'UDIV

- Dworkin RJ, Lee BL, Sande MA, Chambers HF. Treatment of right-sided *Staphylococcus aureus* endocarditis in intravenous drug users with ciprofloxacin and rifampicin. Lancet 1989; 2: 1071-3
- Heldman AW, Hartert TV, Ray SC, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. Am J Med 1996; 101: 68-76.

TREATMENT OF RIGHT-SIDED STAPHYLOCOCCUS AUREUS ENDOCARDITIS IN INTRAVENOUS DRUG USERS WITH CIPROFLOXACIN AND RIFAMPICIN

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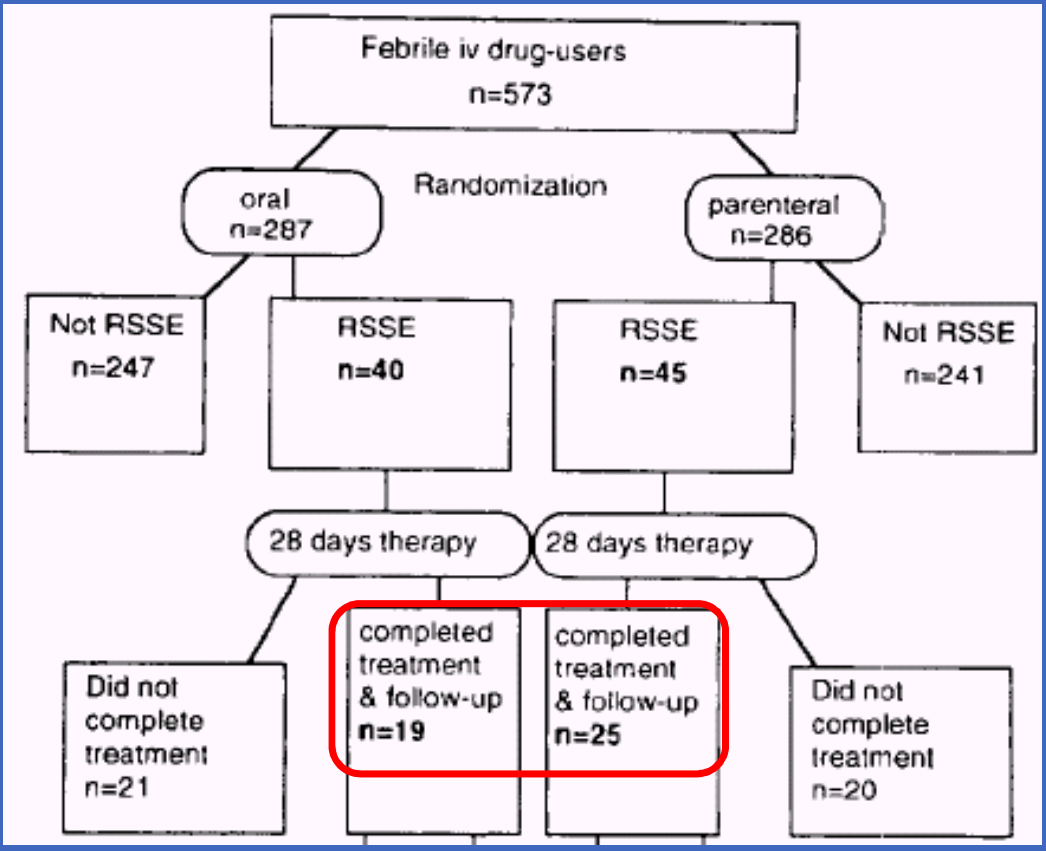
Summary A combination of ciprofloxacin (intravenous then oral) and oral rifampicin was tested in 14 intravenous drug users with right-sided *Staphylococcus aureus* endocarditis. All 10 patients who completed therapy were cured based on resolution of symptoms and negative blood cultures at 4 weeks post therapy.

Study by Dworkin et al.

- Highly-selected patients
  - community acquired right-sided native valve IE in IVDUs older than 18
  - MIC ≤ than 1 mg/L for both study drug
  - Ab Rx for less than 3 days
  - No evidence of mitral or aortic valve infection
  - No clinically significant liver disease
  - neither pregnancy nor breastfeeding
- Antibiotic regimen – 21 days
  - Rifampicin 300 mg bid orally
  - Ciprofloxacin 300 mg bid intravenously for 7 days, then 750 mg bid orally

Oral Antibiotic Treatment of Right-sided Staphylococcal Endocarditis in Injection Drug Users: Prospective Randomized Comparison with Parenteral Therapy

- Oral Ab Rx:
  - Ciprofloxacin 750 mg BID +
  - Rifampin 300 mg BID
- IV Ab Rx:
  - Oxacillin or Vancomycin +
  - Gentamicin for the first 5 days
- Trial design
  - 28 days inpatient Rx
  - Test of cure
    - » Inpatient: 7 d after end of Ab Rx
    - » Outpatient follow-up 1 month later



Heldman et al, Am J Med 1996

Oral Antibiotic Treatment of Right-sided Staphylococcal Endocarditis in Injection Drug Users: Prospective Randomized Comparison with Parenteral Therapy

Efficacy of Oral Versus Parenteral Antibiotics

	Oral	Intravenous
a. Bacteriologic evaluation of outcome		
Cured	18	22
Failed	1	3($P = 0.6$)
b. Combined bacteriologic and projected clinical evaluations of outcome		
Cured	26	30
Failed	3	3($P = 0.9$)

Heldman et al, Am J Med 1996

Dans une série observationnelle monocentrique française d'EI "tout venant"

- Mzabi A, Kernéis S, Richaud C, Podglajen I, Fernandez-Gerlinger MP, Mainardi JL. Switch to oral antibiotics in the treatment of infective endocarditis is not associated with increased risk of mortality in non-severely ill patients. Clin Microbiol Infect 2016; 22: 607-12

Dans une série observationnelle monocentrique française d'EI "tout venant"

Clinical Microbiology and Infection 22 (2016) 607–612

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Original article

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, *]

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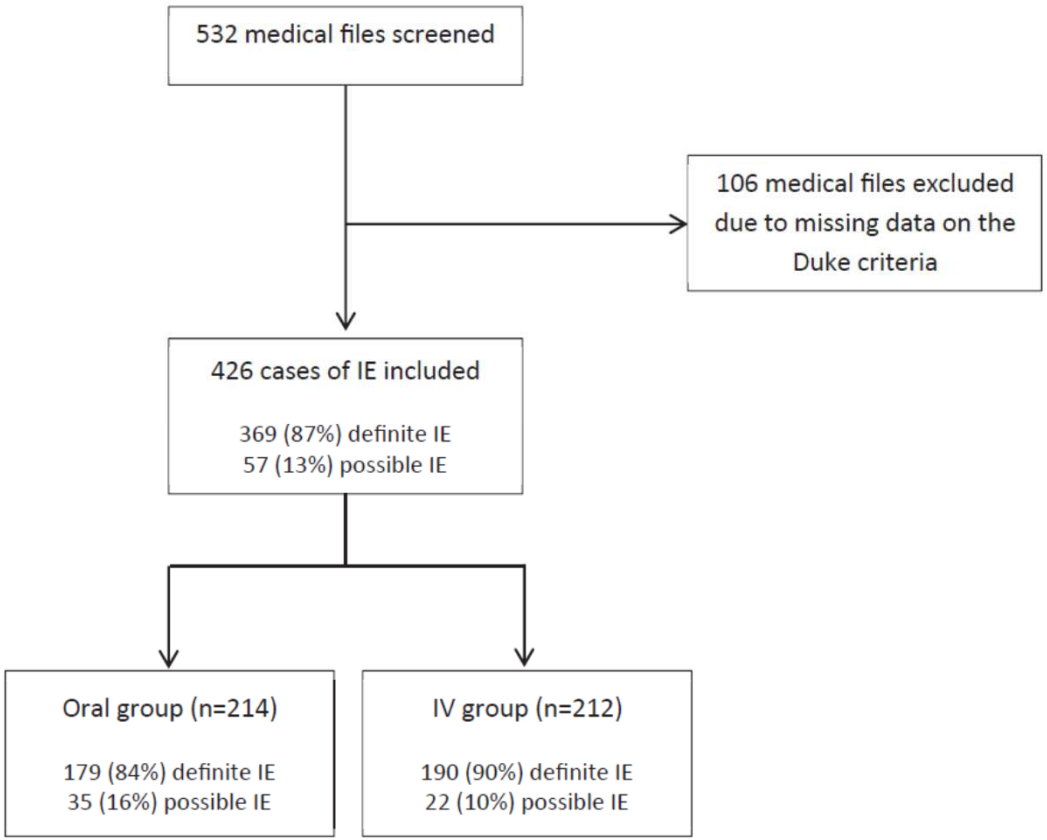
Local management strategy

- After a minimum duration of 7 days IV, the following criteria are evaluated every day
  - general condition of patient
  - resolution of fever
  - reduction in C-reactive protein levels
  - negative blood cultures
  - normalization of leukocytosis
  - normalization of serum creatinine and imaging data (disappearance or reduction of abnormalities).
- If all criteria are fulfilled, then an antibiotic regimen targeting the microorganism is started by oral route until the end of treatment.



Location of IE	
Left heart	335 (79)
Right heart	27 (6)
Permanent pacemaker	52 (12)
Intracardiac device[a]	12 (3)
Native valve	262 (62)
Prosthetic valve	100 (23)
Bioprosthesis	53 (12)
Mechanical prosthesis	47 (11)
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)

Oral antibiotic regimens

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%)

Main results

- Six independent predictors of mortality were identified: age >65 years, type 1 diabetes, immunosuppression, shock, disinsertion of a prosthetic valve and S. aureus as the causative microorganism
- Death occurred in 76 (36%) and 16 (8%) patients of IV and oral groups, respectively
- After adjustment for the six predictors identified above, switch to oral administration was not associated with an increased risk of mortality
- Relapse of IE
  - occurred in 11 patients (3%)
  - was observed at a median (range) time of 20 months after the first episode
  - two had received an oral treatment during the first (*E. faecalis*, CNS)
  - the other nine received complete parenteral therapy

POET

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.

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Methods (1)

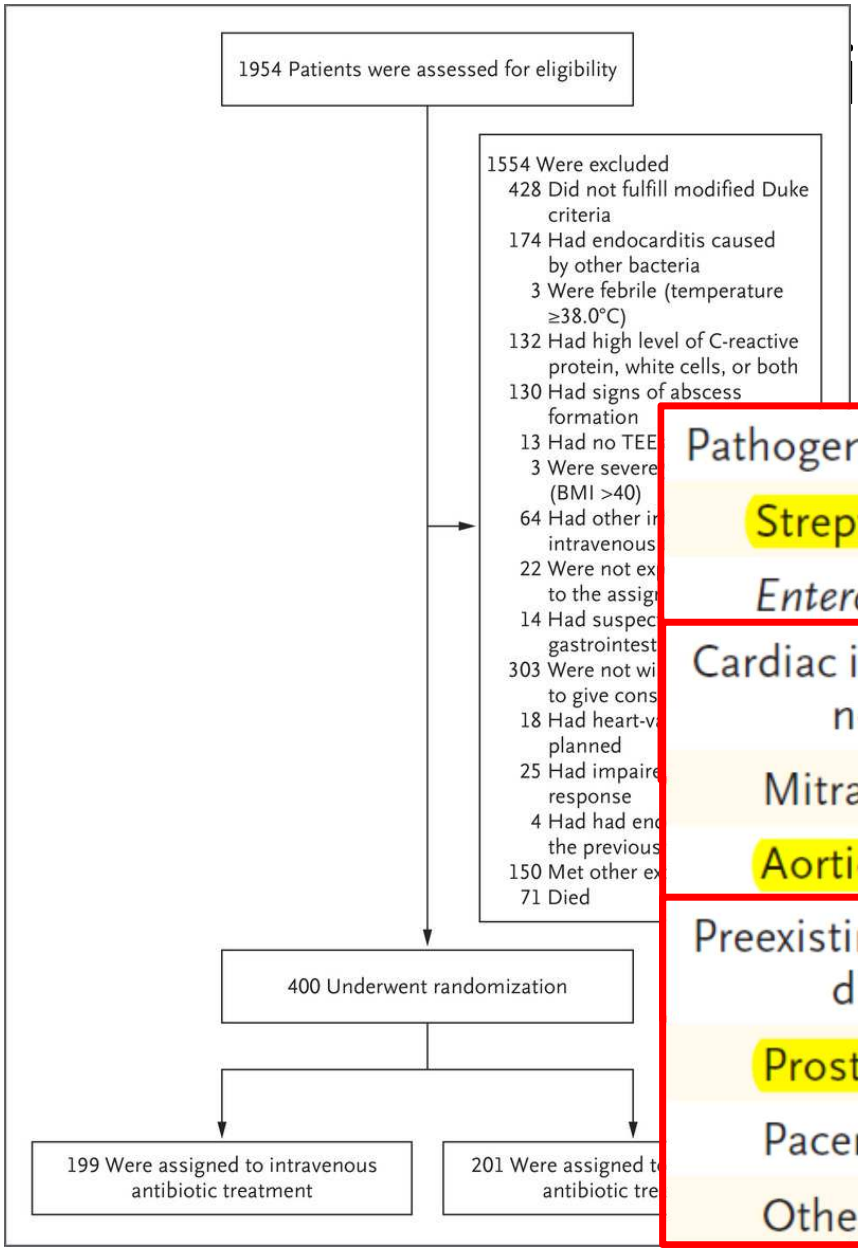
- Nationwide investigator-initiated, multicenter, randomized, unblinded, noninferiority trial performed in Denmark
- Eligibility criteria
  - Adults in stable condition who were receiving IV Ab Rx for left-sided NV or PV IE
  - fulfilled the modified Duke criteria
  - blood cultures positive for streptococci, *E. faecalis*, *S. aureus*, or CNS
  - satisfactory clinical responses to initial treatment, including antibiotic treatment administered intravenously for at least 10 days and, among patients who had undergone valve surgery, for at least 7 days after the surgery
  - TEE performed before randomization had to show no signs of abscess or valve abnormalities that would require surgery
- Follow-up
  - Patients assigned to receive IV Rx remained in the hospital until the end of Ab Rx
  - If feasible, patients assigned to receive oral Rx were treated in the outpatient clinics and were seen two to three times per week

Methods (2) – Oral regimens recommended

- Penicillin and methicillin-susceptible *S aureus* and CNS
  - Amoxicillin 1 g x 4 and fusidic acid 0.75 g x 2 or rifampicin 0.6 g x 2
  - Linezolid 0.6 g x 2 and fusidic acid 0.75 g x 2 or rifampicin 0.6 g x 2
- MS SA and MS CNS
  - Dicloxacillin 1 g x 4 and fusidic acid 0.75 g x 2 or rifampicin 0.6 g x 2
  - Linezolid 0.6 g x 2 and fucidic acid 0.75g x 2 or rifampicin 0.6 g x 2
- Methicillin resistant coagulase-negative staphylococci
  - 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 x2
- *Enterococcus faecalis*
  - Amoxicillin 1 g x 4 and rifampicin 0.6 g x 2 or moxifloxacin 0.4 g x 1
  - Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2 or moxifloxacin 0.4 g x 1
- Streptococci with a MIC for penicillin of <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 or moxifloxacin 0.4 g x1
- Streptococci with a minimal inhibitory concentration for penicillin of ≥1 mg/L:
  - Linezolid 0,6 g x 2 and rifampicin 0.6 g x 2
  - Moxifloxacin 0.4 g x 1 and rifampicin 0.6 g x 2 or clindamycin 0.6 g x3

Methods (3) – PK analyses and outcomes

- PK in patients switched to oral Ab
  - blood sampled for measurement of plasma levels of orally administered Ab obtained
    - on day 1 after the first dose (30 minutes and 1, 2, 4, and 6 hours after administration)
    - on day 5, after the administration of multiple doses
- Primary outcome: from randomization through 6 months after end of antibiotic treatment, composite of
  - all cause mortality
  - unplanned cardiac surgery
  - clinically evident embolic events
  - relapse of bacteremia with the primary pathogen



ICS

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Intravenous Treatment (N=199)	Oral Treatment (N=201)
Mean age — yr	67.3±12.0	67.6±12.6
Female sex — no. (%)	50 (25.1)	42 (20.9)
Body temperature — °C	36.9±0.45	37.0±0.44
Coexisting condition or risk factor — no. (%)		
Diabetes	36 (18.1)	31 (15.4)
Renal failure	25 (12.6)	21 (10.4)
Dialysis	13 (6.5)	15 (7.5)
COPD	17 (8.5)	9 (4.5)
Pathogen — no. (%)†		
Streptococcus	104 (52.3)	92 (45.8)
Enterococcus faecalis	46 (23.1)	51 (25.4)
Cardiac involvement at randomization — no. (%)§		
Mitral-valve endocarditis	65 (32.7)	72 (35.8)
Aortic-valve endocarditis	109 (54.8)	109 (54.2)
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)

Patients' disposition

	Intravenous	Oral
Median time from diagnosis to Rando, days	17	17
Median time of Rx after Rando, days	19	17
Median length of hospital stay after Rando, days	19	3
% patients treated as outpatients	-	80
% switched to a different Rx, w/o cross-over	22	12*
% cross-over	0	2**

* : $p < 0.01$

** : n=4, new incident bacteremia with a different pathogen, nausea, patient's choice (n=2)

Susceptibility of microorganisms to β-lactams

	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

Antibiotic regimens for oral treatment

	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)
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)

	Oral regimens	Frequency n (%)
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)
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)

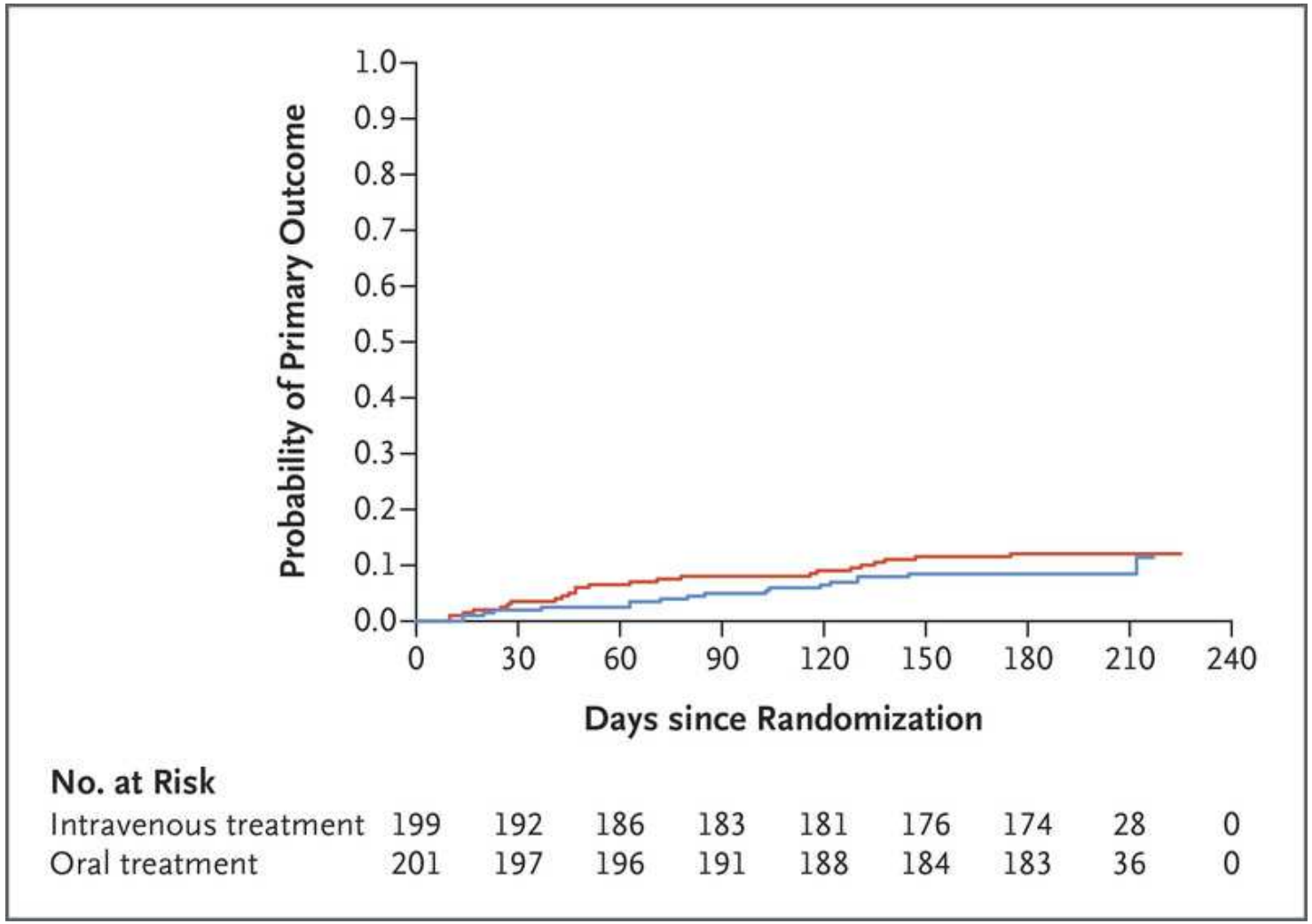
Results: primary outcome (1)

- The primary composite outcome occurred in 42 patients (10.5%)
  - 24 patients (12.1%) in the intravenously treated group
  - 18 patients (9.0%) in the orally treated group (OR 0.72; 95% CI 0.37 to 1.36)
- Between-group Δ 3.1 percentage points (95% CI, –3.4 to 9.6; P = 0.40) in favor of oral treatment, meeting the criterion for noninferiority

Table 2. Distribution of the Four Components of the Primary Composite Outcome.*

Component	Intravenous Treatment (N=199)	Oral Treatment (N=201)	Difference	Hazard Ratio (95% CI)
	number (percent)		*percentage points (95% CI)*	
All-cause mortality	13 (6.5)	7 (3.5)	3.0 (–1.4 to 7.7)	0.53 (0.21 to 1.32)
Unplanned cardiac surgery	6 (3.0)	6 (3.0)	0 (–3.3 to 3.4)	0.99 (0.32 to 3.07)
Embolic event	3 (1.5)	3 (1.5)	0 (–2.4 to 2.4)	0.97 (0.20 to 4.82)
Relapse of the positive blood culture†	5 (2.5)	5 (2.5)	0 (–3.1 to 3.1)	0.97 (0.28 to 3.33)

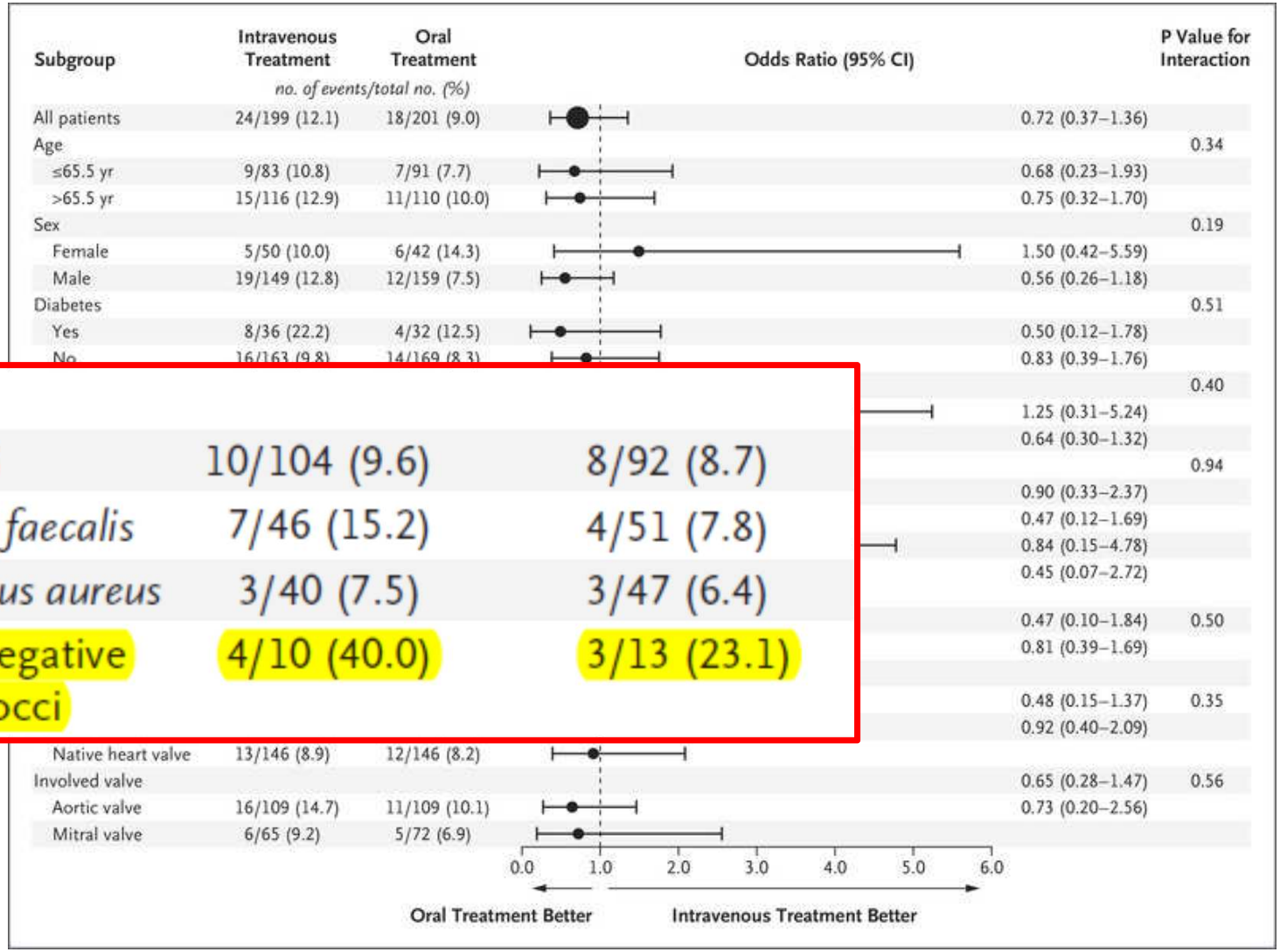
Results: primary outcome (2)



Causes of deaths

	Intravenous treatment	Oral treatment
Causes of death	**12**	**8**
Infection and endocarditis, n (%)	2 (16.7)	2 (25.0)
Infection, not endocarditis, n (%)	2 (16.7)	2 (25.0)
Sudden cardiac death, n (%)	4 (33.3)	0 (0)
Heart failure, n (%)	1 (8.3)	0 (0)
Cerebral haemorrhage, n (%)	1 (8.3)	1 (12.5)
Cancer, n (%)	2 (16.7)	1 (12.5)
Lung disease, (n%)	0 (0)	1 (12.5)
Renal failure, n (%)	0 (0)	1 (12.5)

Results: primary outcome (3)



Bacteria

Streptococci	10/104 (9.6)	8/92 (8.7)
Enterococcus faecalis	7/46 (15.2)	4/51 (7.8)
Staphylococcus aureus	3/40 (7.5)	3/47 (6.4)
Coagulase-negative staphylococci	4/10 (40.0)	3/13 (23.1)

PK data

- In seven patients in the orally treated group, the plasma concentration of one of the two administered antibiotics was suboptimal, as assessed by peak levels and time above the MIC
  - rifampicin in 3 patients,
  - moxifloxacin in 2 patients
  - linezolid in 1 patient
  - dicloxacillin in 1 patient)
- In all seven patients, the plasma concentration of the other simultaneously administered antibiotic was appropriate.
- The primary outcome did not occur in any of these patients. No antibiotic regimens were changed on the basis of PK findings

Side effects after randomization

Side effects	Intravenous treatment n=12	Oral treatment n=10
Gastro-intestinal symptoms, n (%)	0 (0)	3 (30.0)
Renal failure, n (%)	0 (0)	1 (10.0)
Hepatic failure, n (%)	0 (0)	1(10.0)
Bone marrow suppression, n (%)	2 (16.7)	4 (40.0)
Allergy, n (%)	10 (83.3)	1 (10.0)

The severity of the listed side effects necessitated shift of antibiotics in all cases

Summary

- In patients with LS IE caused by streptococci, *E. faecalis*, *S. aureus*, or CNS, who were in clinically stable condition and who had had an adequate response to initial treatment, a shift from initial IV to oral antibiotic Rx was noninferior to continued IV antibiotic treatment.
- The patients in the orally treated group were shifted from IV to oral treatment on about day 17 (midpoint of the treatment period)
- Thus, during half the treatment period, the patients in the orally treated group were eligible for partial or complete outpatient treatment
- PK is not an issue when offering oral antibiotic Rx if the context of these randomization criteria when two antibiotics with good oral bioavailability are prescribed

APRES POETS

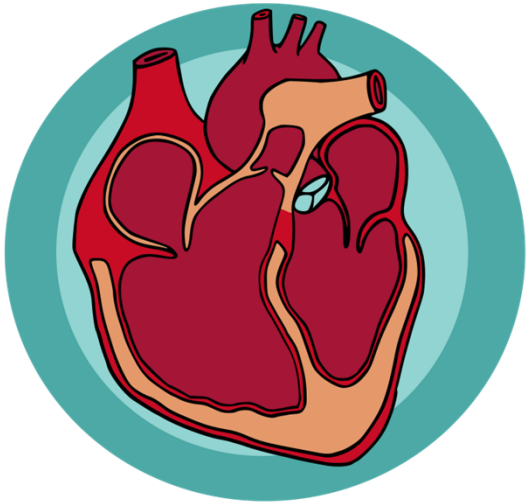
Généralisabilité des résultats de POET

- Limites de POET
  - EI du cœur gauche, peu d'UDIV
  - 4 groupes de micro-organismes, représentant 75% des causes d'EI
  - Seulement 22% d'EI à *S. aureus,* pas de MRSA
  - Biais de sélection non exclu (non inclusion des patients les plus fragiles)
- Perspectives pour notre pratique ?
  - Au moins 2 semaines de traitement IV
  - Bonne réponse clinique et biologique
  - Echo cœur "rassurante" (pas d'abcès, pas de chirurgie prévisible)
  - Microbes testés dans POET
  - Possibilité de construire une antibiothérapie orale
  - Poursuite d'une surveillance spécialisée

Après la poésie le western

RODEO

Relais Oral Dans le traitement des Endocardites à staphylocoques ou streptOcoques multisensibles



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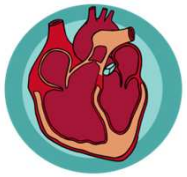


RODEO

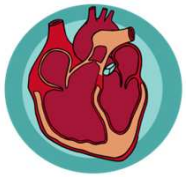
Objectif principal de l'étude :

Evaluer si un passage à la voie orale n'est pas moins efficace que la poursuite d'un traitement IV pour des patients ayant une endocardite à staphylocoque ou streptocoque-entérocoque du cœur gauche, ayant reçu au moins 10 jours de traitements IV, ayant subit une chirurgie valvulaire ou non.

Critère de jugement principal = ECHEC dans les 3 mois suivants la fin de l'antibiothérapie

L'échec correspond à :

- Tout type de décès
- Un évènement embolique symptomatique
- La nécessité d'une chirurgie valvulaire non planifiée
- La rechute microbiologique au germe initialement identifié



RODEO

CHRU
HÔPITAUX DE TOURS

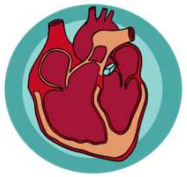
Généralités

Patients randomisés entre J10 et J28 (pour avoir un minimum de 14 jours de traitement PO dans le bras expérimental)
Patients suivis 6 mois après la fin de l'antibiothérapie
Durée totale du traitement 4 ou 6 semaines

Protocole mis en place en 2016
1ère inclusion le 01/03/2016

43 centres ouverts aux inclusions
648 patients attendus au total

A l'heure actuelle 187 inclusions
Fin des inclusions prévue le 28/02/2019 (prolongation possible)



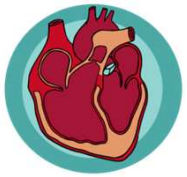
RODEO

CHRU HÔPITAUX DE TOURS

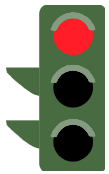
Critères de sélection

Critères d'inclusion

- Endocardite infectieuse (EI) du cœur gauche (critères de Duke) sur valve native ou prothétique
- EI à Staphylococcus sp. (aureus ou à coagulase négative), sensible à la lévofloxacine et la rifampicine OU à Streptococcus sp./Enterococcus sp., sensible à l'amoxicilline (CMI ≤ 0,5mg/L)
- Sujet adulte (18 ans minimum)
- Traitement antibiotique adapté reçu depuis au moins 10 jours en IV
- Si chirurgie valvulaire, traitement antibiotique reçu depuis au moins 10 jours depuis la chirurgie
- Minimum de 14 jours de traitement restant au moment de la randomisation
- Apyrexie (< 38°C) durant les 48 dernières heures avant la randomisation (minimum 2 mesures/jour)
- Hémocultures négatives depuis au moins 5 jours => au moins une hémoculture datant de 5 jours minimum
- Consentement signé
- Patient affilié à un régime de sécurité sociale française



RODEO



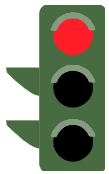
CHRU HÔPITAUX DE TOURS

Critères de sélection

Critères de non-inclusion

- IMC <15 kg/m² ou > 40 kg/m²
- Débit de filtration glomérulaire < 50 ml/min/1,73m2 pour les patients présentant une endocardite due à un *Staphylococcus* sp. (aureus ou à coagulase négative)
- Débit de filtration glomérulaire < 30 ml/min/1,73m2 pour les patients présentant une endocardite due à un *Streptococcus/Enterococcus* sp.
- Patient incapable ou peu disposé à prendre un traitement oral (intolérance digestive, malabsorption significative)
- Difficultés pressenties pour la compliance avec un traitement oral ou le suivi de l'étude (déficience cognitive sévère, maladie psychiatrique sévère…)
- Patient sans entourage en ambulatoire pour surveillance et soutien
- Chirurgie valvulaire prévue dans les 6 mois
- Patient avec dispositif intra-cardiaque (pace-maker, défibrillateur implantable) et suspicion d'EI lié à ce dispositif (si dispositif non retiré)
- Femme enceinte, allaitante ou en âge de procréer sans contraception efficace

RODEO



Critères de sélection

Critères de non-inclusion

- Durée de participation présumée < 7 mois (espérance de vie, patient envisageant de vivre à l'étranger…)
- Antécédent d'EI dans les 3 derniers mois
- Autre infection nécessitant un traitement antibiotique par voie veineuse
- Prise de traitement oestroprogestatif pouvant interagir avec la rifampicine
- Contre indication aux antibiotiques oraux administrés dans le bras expérimental