BEST OF BIBLIO

NATHALIE ASSERAY

MARS 2019

SMIT
CHU NANTES

PARTIAL ORAL VS INTRAVENOUS ANTIBIOTIC TREATMENT OF ENDOCARDITIS

Les Recommandations en vigueur:

- **Traitement oral possible pour les EI du cœur droit**
- **Traitement par voie veineuse, reposant beaucoup sur les B-lactamines, pour une durée de 4 à 6 semaines, par voie veineuse**

Des études observationnelles faisant état de la pratique du relais oral dans les EI du cœur gauche, ont rapporté un bénéfice potentiel

Perspective de diminuer les risques associés aux voies veineuses de longue durée, et à la prolongation d'hospitalisation

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PARTIAL ORAL VS INTRAVENOUS ANTIBIOTIC TREATMENT OF ENDOCARDITIS

Etude POET: prospective, multicentrique, comparative, randomisée, de non-infériorité, en ouvert, services de cardiologie danois.

Patients adultes, critères de Duke, cliniquement stable (réponse favorable à la prise en charge initiale)

Prise en charge par une équipe multidisciplinaire

Hémocultures positives: Streptocoques, *S.aureus*, *E.fecalis*, SCN

Au moins 10 jours de traitement IV, et pour les patients opérés, au moins 7 jours après la chirurgie

ETO avant randomisation: pas d'abcès, pas de valvulopathie chirurgicale

Randomisation 1:1

Bras oral: suivi ambulatoire, 2 à 3 visites/semaines – 201 pts

- **Médiane de la durée de traitement restant: 17j IQ 14-25**
- **Fréquence de survenue de l'outcome composite: 18 (9%)**

Bras IV: ttt hospitalier – 199 pts

- **Médiane de la durée de traitement restant: 19j IQ 14-25**
- **Fréquence de survenue de l'outcome composite: 24 (12%)**

ETO de fin de traitement

Suivi jusqu'à 6 mois après complétude du traitement

PARTIAL ORAL VS INTRAVENOUS ANTIBIOTIC TREATMENT OF ENDOCARDITIS

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Médiane de la dur

Fréquence de surv

Bras IV: ttt hospitalier

Médiane de la dur

Fréquence de surv

ETO de fin de traiteme

Suivi jusqu'à 6 mois a

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)

* Six patients, three in each group, had two outcomes.
† For details about relapse of the positive blood culture, see the Supplementary Appendix.

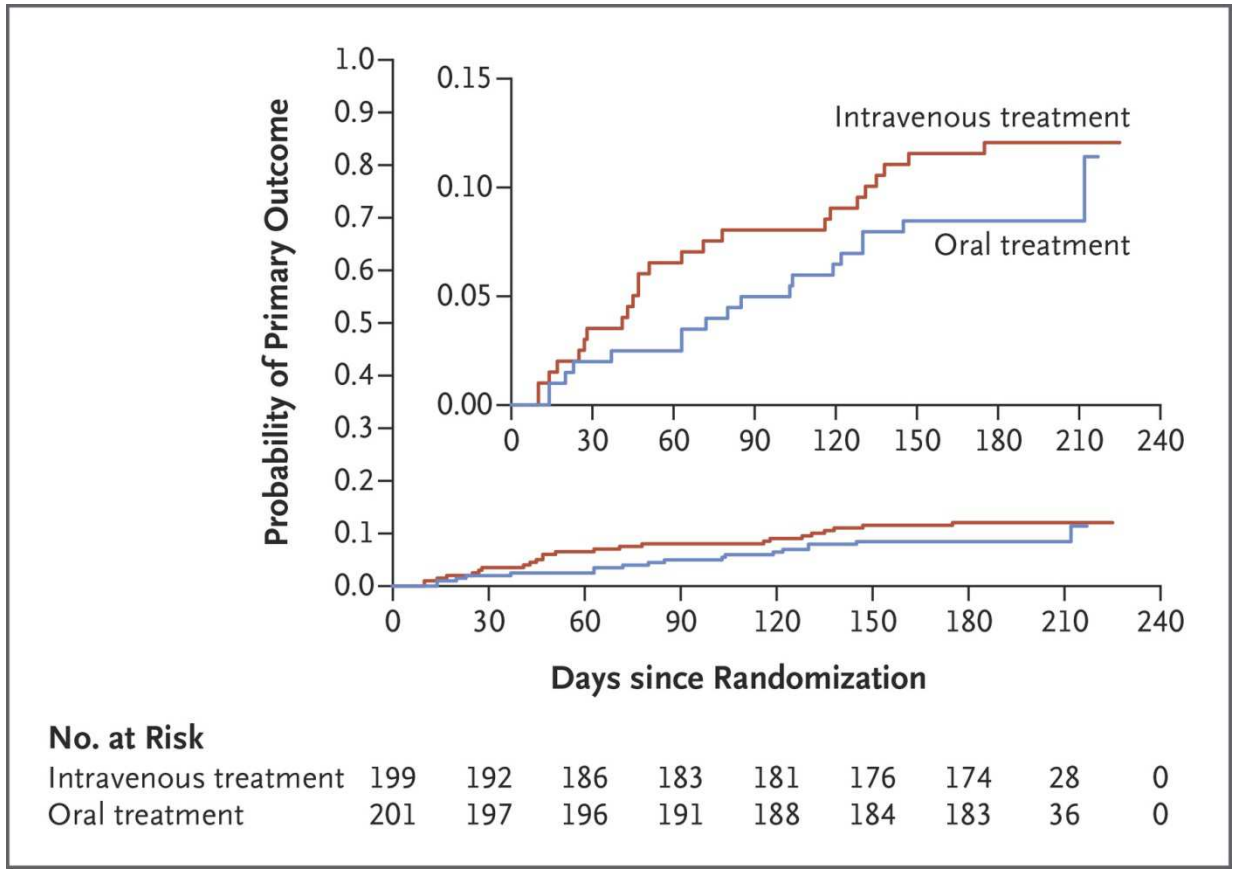
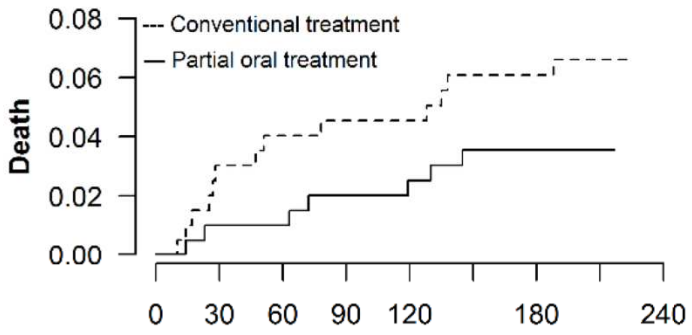


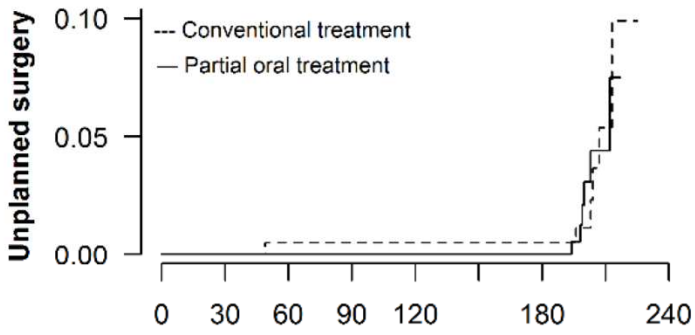
Figure 2. Kaplan–Meier Plot of the Probability of the Primary Composite Outcome. The primary composite outcome was all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with the primary pathogen, from randomization until 6 months after antibiotic treatment was completed. The oral treatment group shifted from intravenously administered antibiotics to orally administered antibiotics at a median of 17 days after the start of treatment.
The inset shows the same data on an enlarged y axis.

POET: SUPPLEMENTARY DATA

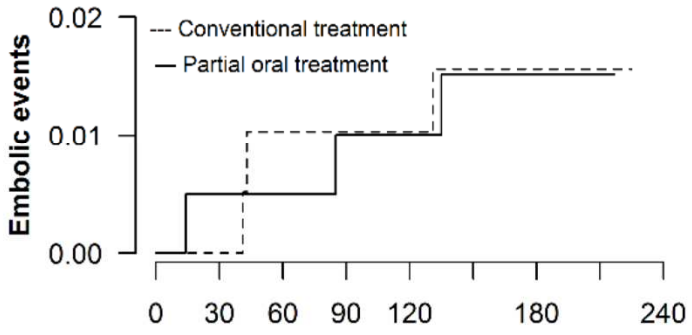
Figure S2



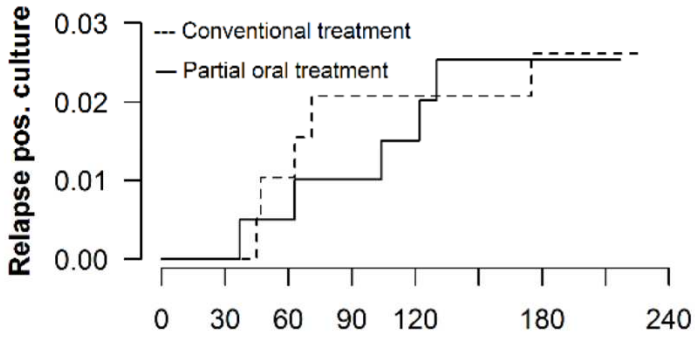
No. at Risk					
Conventional treatment	199	190	186	181	0
Partial oral treatment	201	196	191	187	0



No. at Risk									
Conventional treatment	199	194	191	190	190	187	186	30	0
Partial oral treatment	201	199	199	197	196	194	193	39	0



No. at Risk									
Conventional treatment	199	194	189	188	188	184	183	29	0
Partial oral treatment	201	198	198	195	194	191	190	39	0



No. at Risk									
Conventional treatment	199	194	189	186	186	183	181	29	0
Partial oral treatment	201	199	198	195	193	189	188	36	0

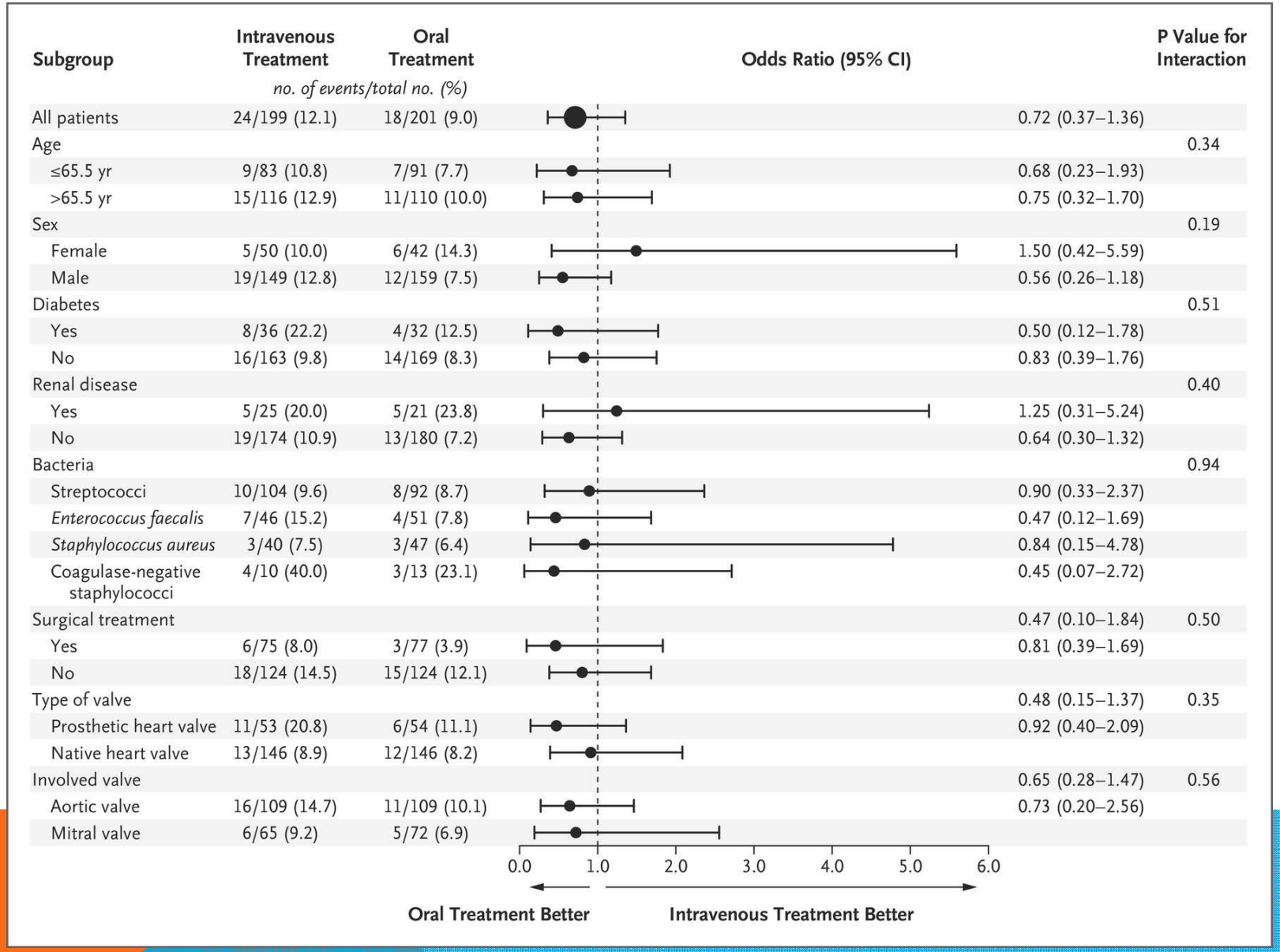


Figure 3. Rates of the Primary Outcome in Pre-specified Subgroups.

POET:
LES RÉGIMES DE TRAITEMENT PO

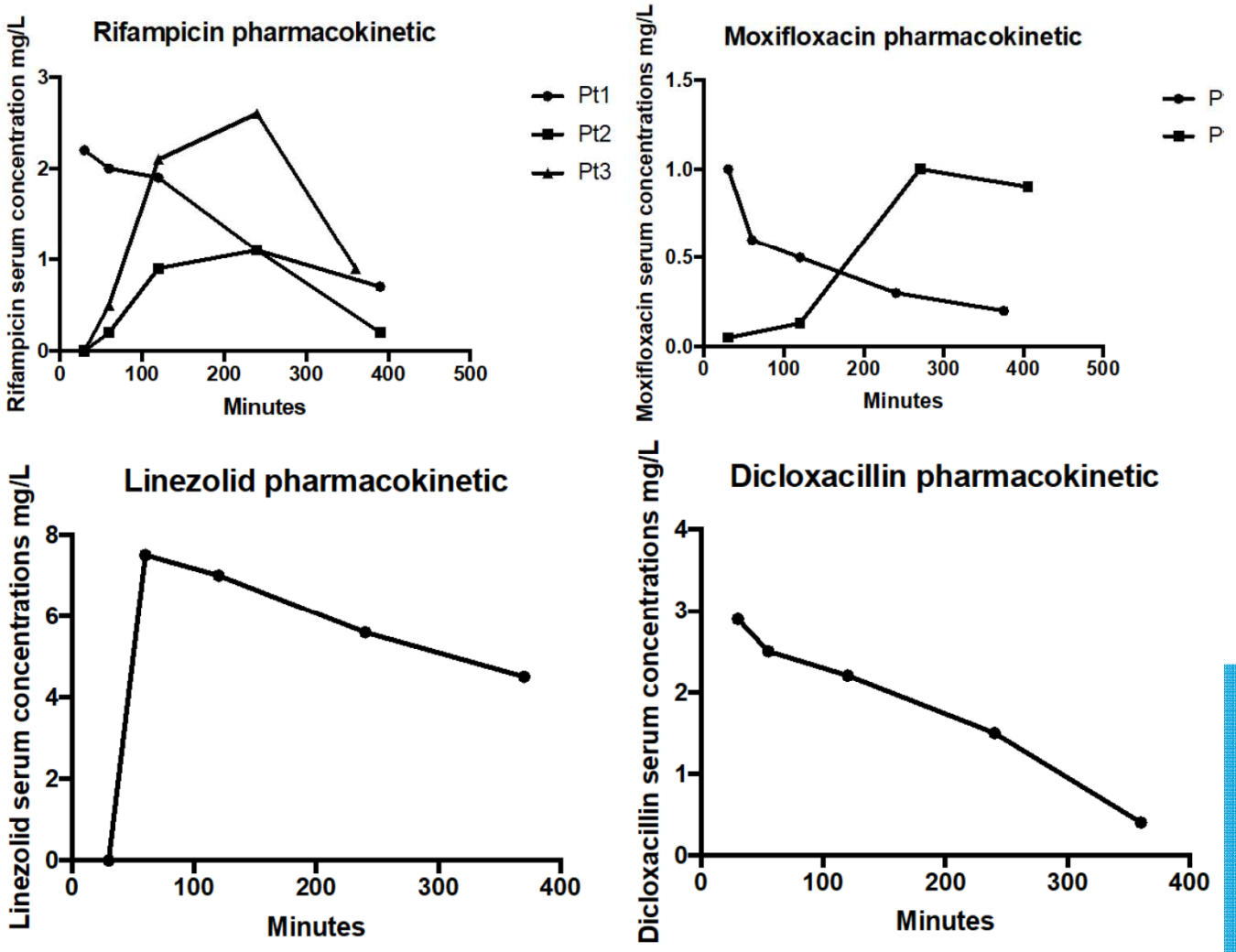
Table S10

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)
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)

POET: SUPPLEMENTARY DATA

Figure S3



ORAL VS INTRAVENOUS ANTIBIOTICS FOR BONE AND JOINT INFECTIONS

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•and Matthew Scarborough, Ph.D.
•for the OVIVA Trial Collaborators

all in UK

Etude OVIVA

“The preference for intravenous antibiotics reflects a broadly held belief that parenteral therapy is inherently superior to oral therapy”

Etude comparative, prospective, multicentrique, en ouvert, groupes parallèles, étude de non-infériorité.

Inclusion de patients adultes: Ostéite des os long (natifs), infection d’ arthroplastie sur articulation native, IPOA, infections d’ostéo-synthèse, discite et spondylodiscite.

Randomisation à au moins 7 jours de la chirurgie septique (ou du début ATB si traitement médical). 1:1

Choix de l’antibiotique par un « infectiologue accrédité »

Dans le bras IV: adjonction possible d’un 2eme ATB PO (ex: Rif), à discrétion du prescripteur.

1054 patients inclus, 2010 - 2015

Durée de traitement:

IV, 523: 78j (IQ 42 – 99)

PO, 526: 71j (IQ 43 – 94)

January 31, 2019
N Engl J Med 2019; 380:425-436
DOI: 10.1056/NEJMoa1710926

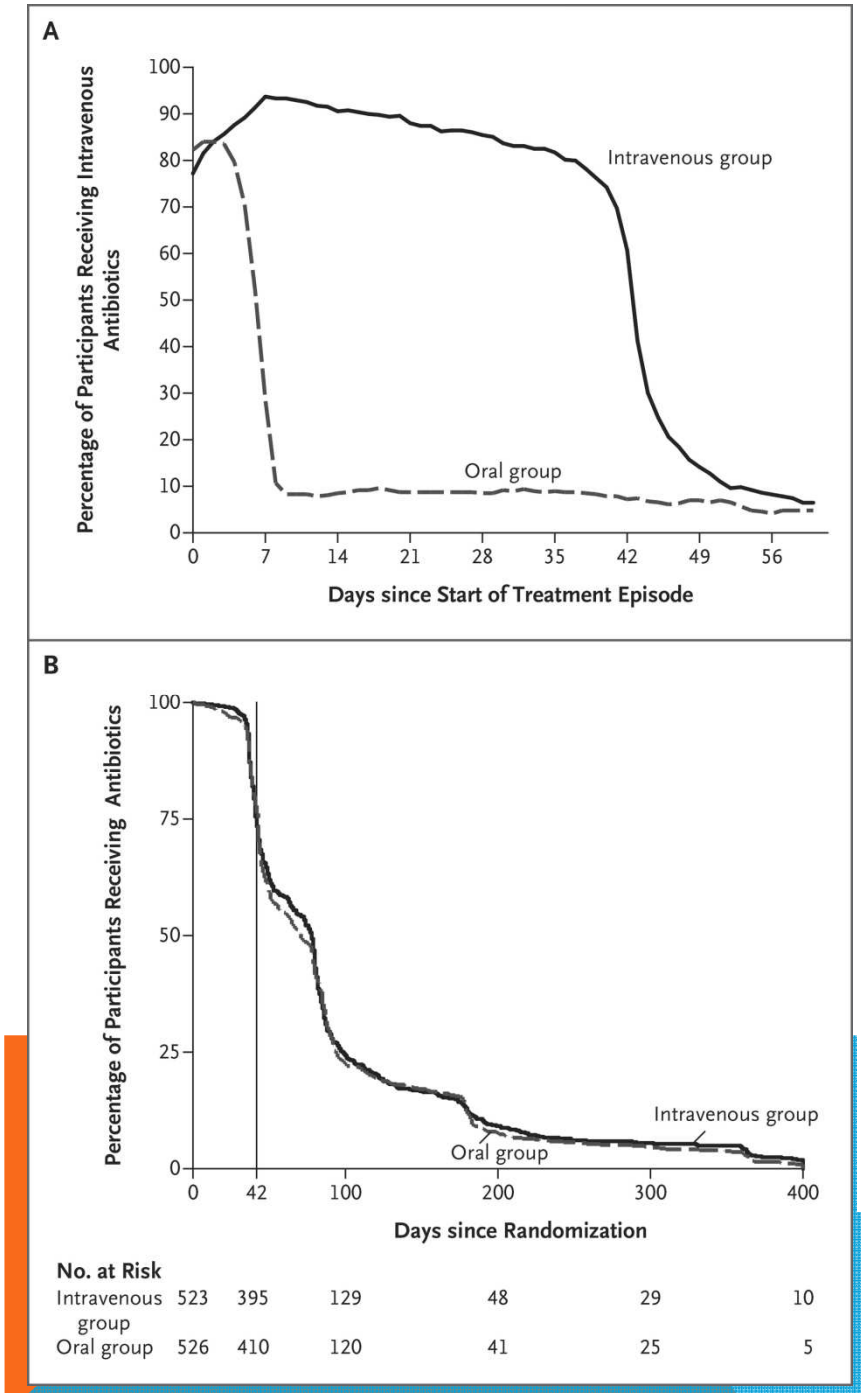


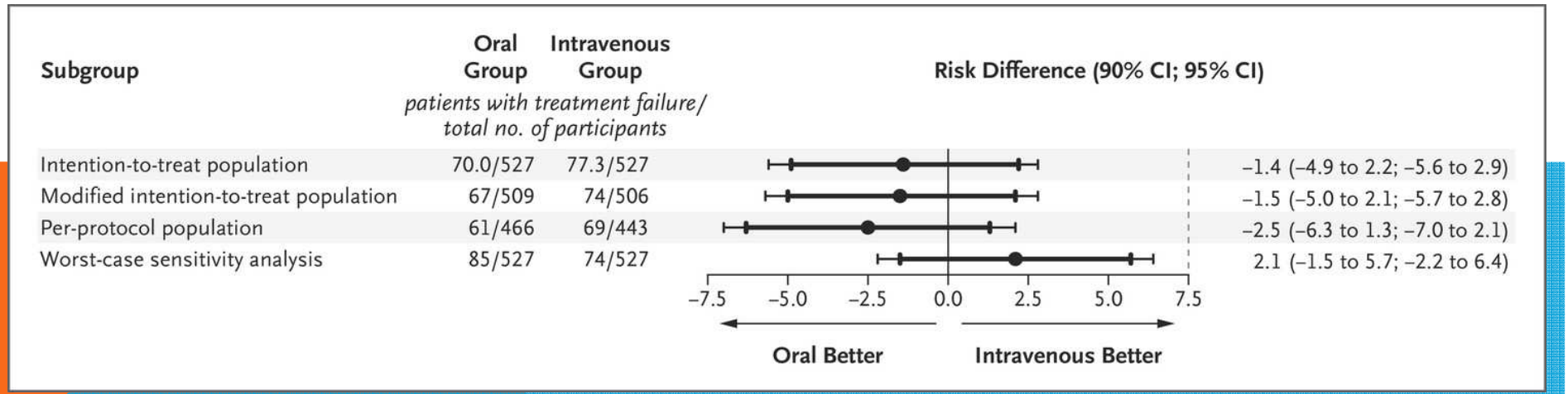
Table S2: Criteria defining primary endpoints (definitive treatment failure)

	IV Antibiotic (N = 74)	PO Antibiotic (N = 67)	Total (N = 141)
Definite treatment failure determination*			
- clinical findings[a] (with or without other findings)	49 (66.2%)	34 (50.7%)	83 (58.9%)
- microbiological findings[b] (with or without other findings) where microbiology samples were submitted	54 (73.0%)	47 (70.1%)	101 (71.6%)
- histological findings[c] (with or without other findings) where histology samples were submitted	18 (24.3%)	11 (16.4%)	29 (20.6%)
Definite treatment failure determination by mutually exclusive category*:			
- clinical and microbiological and histological findings	6 (8.1%)	3 (4.5%)	9 (6.4%)
- clinical and microbiological findings	23 (31.1%)	13 (19.4%)	36 (25.5%)
- clinical and histological findings	4 (4.5%)	1 (1.5%)	5 (3.6%)
- microbiological and histological findings	8 (10.8%)	5 (7.5%)	13 (9.2%)
- clinical findings alone	16 (21.6%)	17 (25.4%)	33 (23.4%)
- microbiological findings alone	17 (23.0%)	26 (38.8%)	43 (30.5%)
- histological findings alone	0 (0.0%)	2 (3.0%)	2 (1.4%)

** Frequency and percentages are displayed*

[a] Defined by a draining sinus tract arising from bone/prosthesis and/or frank pus adjacent to bone/ prosthesis at operation
[b] Defined by indistinguishable bacterial isolates from ≥ 2 deep tissue samples or a pathogenic organism from a single closed aspirate or biopsy
[c] Defined by characteristic inflammatory infiltrate or microorganisms on microscopy

Figure 3. Differences in Risk According to the Analysis Performed.
The point estimates for the differences in failure rates are shown with 90% (thick lines) and 95% (thin lines) two-sided confidence intervals. The non-inferiority margin is indicated by the vertical dashed line. The use of two-sided 90% confidence intervals was pre-specified in the trial protocol in accordance with the sample-size calculation. Because two-sided 95% confidence intervals are also now commonly included in non-inferiority trials, they are shown here to assess the sensitivity of the results to a change in significance level. In the intention-to-treat population, missing data were imputed with the use of multiple imputation by chained equations. The modified intention-to-treat population included only the participants with complete end-point data. The worst-case sensitivity analysis shows the results based on the worst-case assumption that, for participants with missing data, all participants who were randomly assigned to receive oral therapy and no participants who were randomly assigned to receive intravenous therapy had definitive treatment failures, thus introducing the worst possible bias against the oral strategy.



LES ANTIBIOTIQUES DE L'ÉTUDE

Table S10: Overview of actual antibiotics (excluding rifampicin), as defined by agents used for more than one week during the initial six-week treatment period

	Participants randomized to IV Antibiotic* (N = 521)	Participants randomized to PO Antibiotic* (N = 523)	Total* (N = 1044)
Glycopeptides[a] (IV)	214 (41.1%)	22 (4.2%)	236 (22.6%)
Penicillins (IV)	38 (7.3%)	11 (2.1%)	49 (4.7%)
Cephalosporins (IV)	173 (33.2%)	8 (1.5%)	181 (17.3%)
Carbapenems (IV)	41 (7.9%)	5 (1.0%)	46 (4.4%)
Other single IV antibiotic	35 (6.7%)	2 (0.4%)	37 (3.5%)
Combination IV antibiotics	35 (6.7%)	6 (1.1%)	41 (3.9%)
Penicillins (PO)	8 (1.5%)	83 (15.9%)	91 (8.7%)
Quinolones[b] (PO)	33 (6.3%)	191 (36.5%)	224 (21.5%)
Tetracyclines[c] (PO)	4 (0.8%)	57 (10.9%)	61 (5.8%)
Macrolides / Lincosamide [d] (PO)	10 (1.9%)	68 (13.0%)	78 (7.5%)
Other single PO antibiotic (PO)	10 (1.9%)	54 (10.3%)	64 (6.1%)
Combination PO antibiotics (PO)	13 (2.5%)	87 (16.6%)	100 (9.6%)

The categories in this table were not mutually exclusive; 149 participants fell into more than one category and the data do not take account of adjunctive rifampicin which was analysed separately.

**Frequency and percentages are displayed*

[a] *Glycopeptides were either teicoplanin or vancomycin*

[b] *Quinolones were ciprofloxacin in all but two cases, one each of moxifloxacin and levofloxacin. Of 191 participants in the oral arm who were prescribed quinolones, 160 (83.8%) were also prescribed rifampicin at some point during the trial.*

[c] *Doxycycline was the only tetracycline antibiotic prescribed.*

[d] *Macrolides were clarithromycin (4 cases) and erythromycin (2 cases); clindamycin was the only lincosamide used.*

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Table S11: Actual rifampicin use in 1049 participants

Observed rifampicin use[a]	Randomized to IV Antibiotic* (N=523)	Randomized to PO Antibiotic* (N=526)	Total* (N=1049)
No rifampicin use	310 (59.3%)	233 (44.3%)	543 (51.8%)
<2 weeks[b]	21 (4.2%)	36 (6.8%)	57 (5.4%)
2 to 6 weeks[b]	72 (13.8%)	92 (17.5%)	164 (15.6%)
>6 weeks[b]	120 (22.9%)	165 (31.4%)	285 (27.2%)

**Frequency and percentages are displayed*

[a] The most commonly prescribed doses of rifampicic were 300mg BD (388 prescriptions) 450mg BD (133 prescriptions).

[b] Based on the longest continuous period of use.

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

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

- **Gravité des bactériémies à *S.aureus***
- **Hypothèse d'amélioration du pronostic avec la Rifampicine**
  - En améliorant la bactéricidie précoce
  - Stériliser plus vite la bactériémie et les sites infectés
  - Réduire le risque de dissémination et de métastases septiques

*United Kingdom Clinical Infection Research Group (UKCIRG)**

www.thelancet.com **Vol 391 February 17, 2018**
http://dx.doi.org/10.1016/ S0140-6736(17)32456-X

METHODE

- **Inclusion:**
  - Patients adultes
  - Au moins une hémoculture à SASM ou SARM
  - Antibiothérapie efficace ≤ 96h
  - Absence de résistance Rifampicine
  - Absence de contre-indication Rifampicine
- **Non-Inclusion**
  - Hémoculture polymicrobienne
  - Tuberculose suspectée
  - Précédente inclusion dans ARREST
- **Randomisation 1:1, contre placebo, en aveugle**
- **Durée : 2 semaines**
- **Association à un antibiotique principal (« backbone »), à discrétion du clinicien**
- **De 2012 à 2015, 29 centres Royaume Uni.**
- **779 inclusions,**
  396 Placebo 374 Rifampicine
- **758 analysables**
  388 Placebo 370 Rifampicine

RESULTATS

Population de l'étude:

- 495 (65%) d'homme
- Age médian 65 (IQR 50–76) ans
- Charlson médian 2 (0–3)
- 70 (9%) patients en soins intensifs

Site de l'infection:

- Profond N=301 (40%) dont
  - 33 (4%) endocardites
  - 14 (2%) infections de prothèse
- 130 (17%) infections de catheters
- 138 (18%) infections peau et parties molles
- 49 (6%) autres sites
- Non diagnostiqué 139 (18%)

	Placebo (n=388)	Rifampicin (n=370)	Total (N=758)
Trial drug			
Never initiated trial drug	8 (2%)	6 (2%)	14 (2%)
Initiated intravenous trial drug	51 (13%)	45 (12%)	96 (13%)
Initiated oral trial drug	329 (85%)	319 (86%)	648 (85%)
Initiated trial drug once per day	175 (45%)	173 (47%)	348 (46%)
Initiated trial drug twice per day	205 (53%)	191 (52%)	396 (52%)
Initiated trial drug 600 mg per day	74 (19%)	75 (20%)	149 (20%)
Initiated trial drug 900 mg per day	306 (79%)	289 (78%)	595 (78%)
Initial total dose per day (mg/kg; n=741)	11·2 (9·9–12·9)	11·0 (10·0–12·7)	11·1 (10·0–12·9)
Hours from starting active antibiotics to trial drug	69 (49–85)	68 (46–85)	68 (48–85)
Days on trial drug	13·0 (11·3–13·5)	12·6 (6·0–13·2)	12·8 (7·9–13·4)
Backbone active antibiotic treatment*			
Flucloxacillin	321 (83%)	298 (81%)	619 (82%)
Co-amoxiclavulante	122 (31%)	107 (29%)	229 (30%)
Piperacillin or tazobactam	115 (30%)	102 (28%)	217 (29%)
Vancomycin or teicoplanin	188 (48%)	192 (52%)	380 (50%)
Cephalosporin	110 (28%)	104 (28%)	214 (28%)
Fluoroquinolone	47 (12%)	46 (12%)	93 (12%)
Macrolide	30 (8%)	28 (8%)	58 (8%)
Clindamycin	23 (6%)	36 (10%)	59 (8%)
Tetracycline	29 (7%)	26 (7%)	55 (7%)
Gentamicin or amikacin	101 (26%)	98 (26%)	199 (26%)
Stat gentamicin or amikacin	95 (24%)	87 (24%)	182 (24%)
Carbapenem	38 (10%)	35 (9%)	73 (10%)
Other antibiotic†	52 (13%)	52 (14%)	104 (14%)
Number of antibiotics received during *Staphylococcus aureus* infection episode (excluding study drug)	3 (2–4)	3 (2–4)	3 (2–4)
Days of antibiotic treatment for *S aureus* infection episode	30 (18–44)	29 (17–45)	29 (18–45)
Rifampicin used open-label: initiated <14 days from randomisation‡	25 (6%)	18 (5%)	43 (6%)
Rifampicin used open-label: initiated ≥14 days from randomisation	27 (7%)	14 (4%)	41 (5%)

Data are n (%), or median (IQR). *Including active antibiotics taken from the first blood culture sample throughout the illness episode. †Open-label rifampicin excluded. ‡Masked trial drug stopped and open-label rifampicin initiated for clinical reasons.

Table 2: **Trial drug and backbone antibiotic treatment**

Figure 2. Treatment failure, disease recurrence, and death from randomisation to 12 weeks

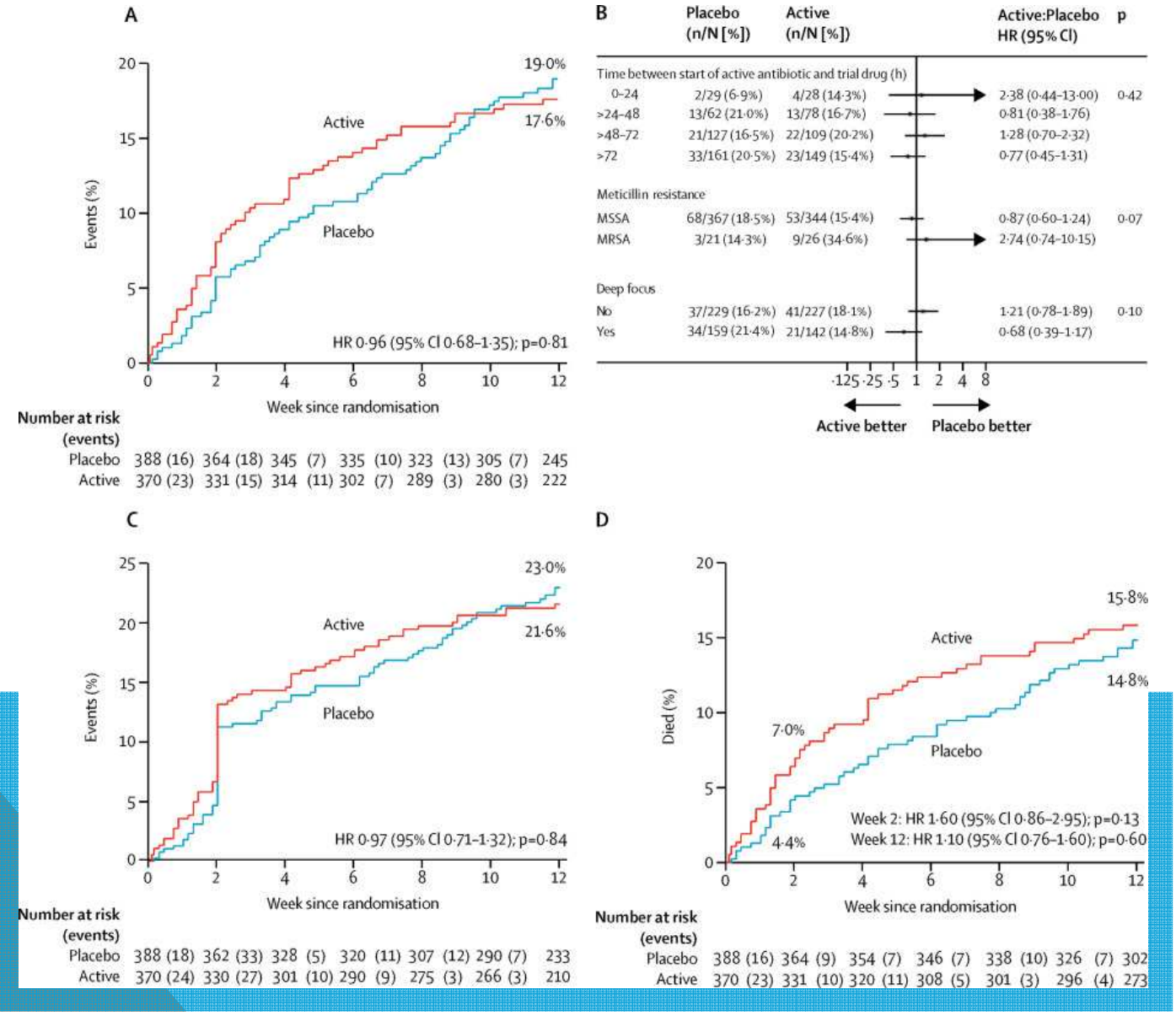

Figure S2a Five priority subgroup analyses for bacteriological failure/recurrence or death through 12 weeks (primary endpoint)

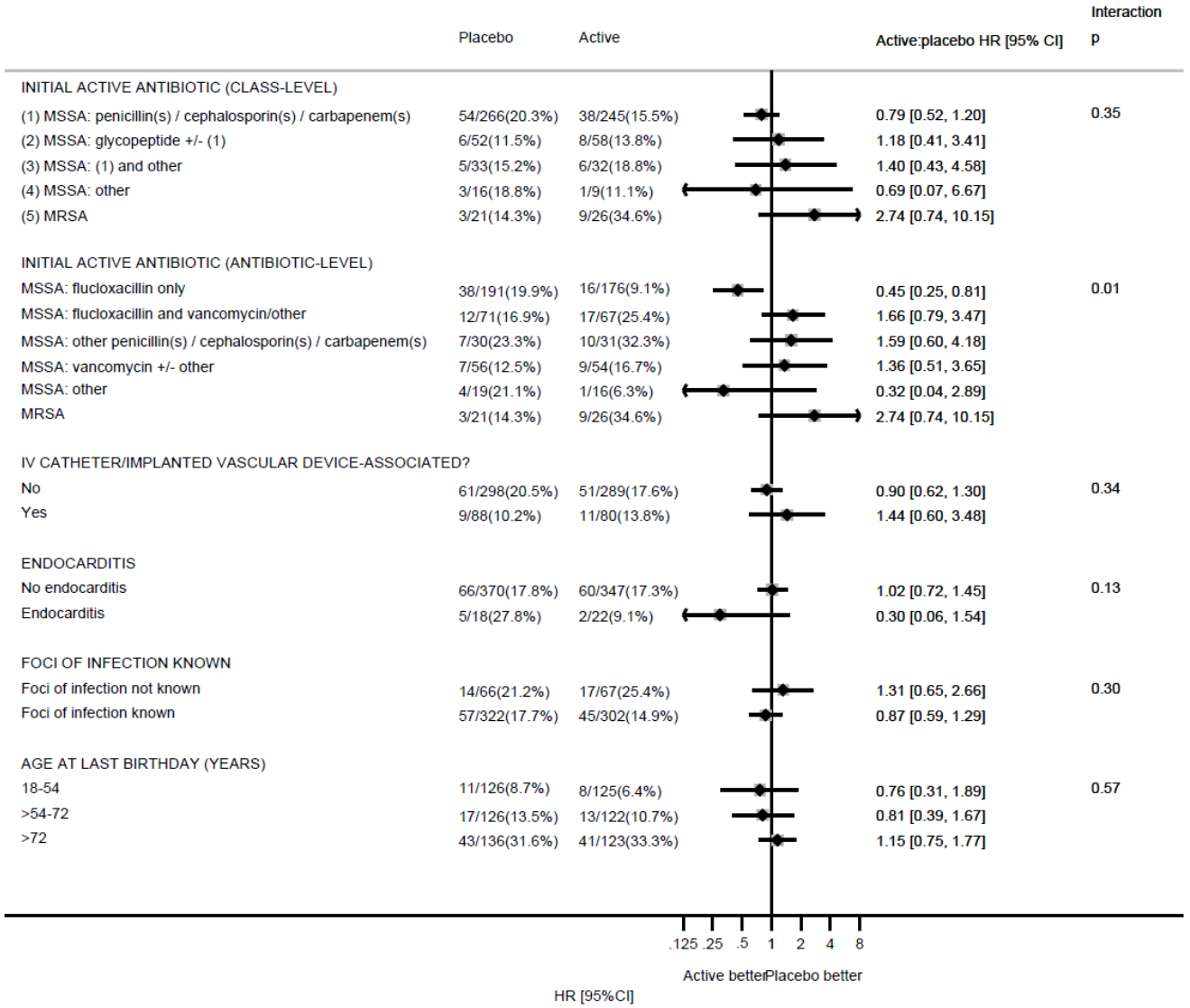

Table S5 Summary of SAEs, Grade 3/4 and antibiotic-modifying adverse events

Outcome	Placebo N=388	Rifampicin N=370	Total N=758	p*
SAEs				
Any	**94 (24.2%) 116**	**101 (27.3%) 112**	**195 (25.7%) 228**	**0.36**
Infections and infestations	39 (10.1%) 40	37 (10.0%) 38	76 (10.0%) 78	1.00
Cardiac disorders	13 (3.4%) 15	5 (1.4%) 6	18 (2.4%) 21	0.09
Vascular disorders	2 (0.5%) 2	4 (1.1%) 4	6 (0.8%) 6	0.44
Respiratory, thoracic and mediastinal disorders	12 (3.1%) 12	6 (1.6%) 6	18 (2.4%) 18	0.23
Gastrointestinal disorders	7 (1.8%) 7	10 (2.7%) 12	17 (2.2%) 19	0.47
Hepatobiliary disorders	0 (0.0%) 0	2 (0.5%) 2	2 (0.3%) 2	0.24
Skin and subcutaneous tissue disorders	1 (0.3%) 1	1 (0.3%) 1	2 (0.3%) 2	1.00
Renal and urinary disorders	4 (1.0%) 4	10 (2.7%) 10	14 (1.8%) 14	0.11
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (1.8%) 7	11 (3.0%) 12	18 (2.4%) 19	0.34
Congenital, familial and genetic disorders	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1	1.00
General disorders and administration site conditions	12 (3.1%) 12	11 (3.0%) 11	23 (3.0%) 23	1.00
Investigations	0 (0.0%) 0	1 (0.3%) 1	1 (0.1%) 1	0.49
Injury, poisoning and procedural complications	5 (1.3%) 5	3 (0.8%) 3	8 (1.1%) 8	0.73
Blood and lymphatic system disorders	1 (0.3%) 1	1 (0.3%) 1	2 (0.3%) 2	1.00
Metabolism and nutrition disorders	1 (0.3%) 1	3 (0.8%) 3	4 (0.5%) 4	0.36
Psychiatric disorders	2 (0.5%) 2	0 (0.0%) 0	2 (0.3%) 2	0.50
Nervous system disorders	5 (1.3%) 6	2 (0.5%) 2	7 (0.9%) 8	0.45
Grade 3/4 adverse events				
Any	**131 (33.8%) 193**	**129 (34.9%) 209**	**260 (34.3%) 402**	**0.76**
Infections and infestations	45 (11.6%) 53	40 (10.8%) 48	85 (11.2%) 101	0.82
Cardiac disorders	15 (3.9%) 17	6 (1.6%) 8	21 (2.8%) 25	0.08
Vascular disorders	7 (1.8%) 7	5 (1.4%) 5	12 (1.6%) 12	0.77
Respiratory, thoracic and mediastinal disorders	16 (4.1%) 17	10 (2.7%) 11	26 (3.4%) 28	0.32
Gastrointestinal disorders	21 (5.4%) 24	29 (7.8%) 40	50 (6.6%) 64	0.19
Hepatobiliary disorders	0 (0.0%) 0	3 (0.8%) 3	3 (0.4%) 3	0.12
Skin and subcutaneous tissue disorders	7 (1.8%) 7	5 (1.4%) 5	12 (1.6%) 12	0.77
Musculoskeletal and connective tissue disorders	2 (0.5%) 2	0 (0.0%) 0	2 (0.3%) 2	0.50
Renal and urinary disorders	9 (2.3%) 9	19 (5.1%) 20	28 (3.7%) 29	0.053
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (1.8%) 7	11 (3.0%) 12	18 (2.4%) 19	0.34
Reproductive system and breast disorders	0 (0.0%) 0	1 (0.3%) 1	1 (0.1%) 1	0.49
Congenital, familial and genetic disorders	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1	1.00
General disorders and administration site conditions	11 (2.8%) 11	12 (3.2%) 12	23 (3.0%) 23	0.83
Investigations	6 (1.5%) 6	11 (3.0%) 16	17 (2.2%) 22	0.22
Injury, poisoning and procedural complications	6 (1.5%) 6	5 (1.4%) 5	11 (1.5%) 11	1.00
Surgical and medical procedures	0 (0.0%) 0	1 (0.3%) 1	1 (0.1%) 1	0.49
Blood and lymphatic system disorders	3 (0.8%) 3	5 (1.4%) 6	8 (1.1%) 9	0.50
Metabolism and nutrition disorders	3 (0.8%) 3	5 (1.4%) 6	8 (1.1%) 9	0.50
Psychiatric disorders	5 (1.3%) 5	5 (1.4%) 6	10 (1.3%) 11	1.00
Nervous system disorders	11 (2.8%) 14	4 (1.1%) 4	15 (2.0%) 18	0.12
Eye disorders	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1	1.00
Antibiotic-modifying adverse events				
Any	**39 (10.1%) 52**	**63 (17.0%) 89**	**102 (13.5%) 141**	**0.006**
Infections and infestations	3 (0.8%) 3	5 (1.4%) 5	8 (1.1%) 8	0.50
Respiratory, thoracic and mediastinal disorders	2 (0.5%) 4	0 (0.0%) 0	2 (0.3%) 4	0.50
Gastrointestinal disorders	8 (2.1%) 9	24 (6.5%) 32	32 (4.2%) 41	0.003
Hepatobiliary disorders	0 (0.0%) 0	2 (0.5%) 2	2 (0.3%) 2	0.24
Skin and subcutaneous tissue disorders	7 (1.8%) 9	8 (2.2%) 9	15 (2.0%) 18	0.80
Renal and urinary disorders	1 (0.3%) 2	8 (2.2%) 10	9 (1.2%) 12	0.02
General disorders and administration site conditions	4 (1.0%) 4	13 (3.5%) 13	17 (2.2%) 17	0.03
Investigations	12 (3.1%) 13	12 (3.2%) 14	24 (3.2%) 27	1.00
Injury, poisoning and procedural complications	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1	1.00
Blood and lymphatic system disorders	1 (0.3%) 1	3 (0.8%) 3	4 (0.5%) 4	0.36
Metabolism and nutrition disorders	2 (0.5%) 3	0 (0.0%) 0	2 (0.3%) 3	0.50
Psychiatric disorders	1 (0.3%) 2	0 (0.0%) 0	1 (0.1%) 2	1.00
Nervous system disorders	1 (0.3%) 1	1 (0.3%) 1	2 (0.3%) 2	1.00

Note: Showing number of patients with one or more event (% of participants) number of events (e.g., '2 (20.0%) 3,' would indicate a total of 3 events in a total of 2 participants)
* Fisher's exact test

ET LA TOXICITÉ??

Table S5 Summary of SAEs, Grade 3/4 and antibiotic-modifying adverse events

Outcome	Placebo N=388	Rifampicin N=370	Total N=758	p*
SAEs				
Any	**94 (24.2%) 116**	**101 (27.3%) 112**	**195 (25.7%) 228**	**0.36**
Infections and infestations	39 (10.1%) 40	37 (10.0%) 38	76 (10.0%) 78	1.00
Cardiac disorders	13 (3.4%) 15	5 (1.4%) 6	18 (2.4%) 21	0.09
Vascular disorders	2 (0.5%) 2	4 (1.1%) 4	6 (0.8%) 6	0.44
Respiratory, thoracic and mediastinal disorders	12 (3.1%) 12	6 (1.6%) 6	18 (2.4%) 18	0.23
Gastrointestinal disorders	7 (1.8%) 7	10 (2.7%) 12	17 (2.2%) 19	0.47
Hepatobiliary disorders	0 (0.0%) 0	2 (0.5%) 2	2 (0.3%) 2	0.24
Skin and subcutaneous tissue disorders	1 (0.3%) 1	1 (0.3%) 1	2 (0.3%) 2	1.00
Renal and urinary disorders	4 (1.0%) 4	10 (2.7%) 10	14 (1.8%) 14	0.11
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (1.8%) 7	11 (3.0%) 12	18 (2.4%) 19	0.34
Congenital, familial and genetic disorders	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1	1.00
General disorders and administration site conditions	12 (3.1%) 12	11 (3.0%) 11	23 (3.0%) 23	1.00
Investigations	0 (0.0%) 0	1 (0.3%) 1	1 (0.1%) 1	0.49
Injury, poisoning and procedural complications	5 (1.3%) 5	3 (0.8%) 3	8 (1.1%) 8	0.73
Blood and lymphatic system disorders	1 (0.3%) 1	1 (0.3%) 1	2 (0.3%) 2	1.00
Metabolism and nutrition disorders	1 (0.3%) 1	3 (0.8%) 3	4 (0.5%) 4	0.36
Psychiatric disorders	2 (0.5%) 2	0 (0.0%) 0	2 (0.3%) 2	0.50
Nervous system disorders	5 (1.3%) 6	2 (0.5%) 2	7 (0.9%) 8	0.45
Grade 3/4 adverse events				
Any	**131 (33.8%) 193**	**129 (34.9%) 209**	**260 (34.3%) 402**	**0.76**
Infections and infestations	45 (11.6%) 53	40 (10.8%) 48	85 (11.2%) 101	0.82
Cardiac disorders	15 (3.9%) 17	6 (1.6%) 8	21 (2.8%) 25	0.08
Vascular disorders	7 (1.8%) 7	5 (1.4%) 5	12 (1.6%) 12	0.77
Respiratory, thoracic and mediastinal disorders	16 (4.1%) 17	10 (2.7%) 11	26 (3.4%) 28	0.32
Gastrointestinal disorders	21 (5.4%) 24	29 (7.8%) 40	50 (6.6%) 64	0.19
Hepatobiliary disorders	0 (0.0%) 0	3 (0.8%) 3	3 (0.4%) 3	0.12
Skin and subcutaneous tissue disorders	7 (1.8%) 7	5 (1.4%) 5	12 (1.6%) 12	0.77
Musculoskeletal and connective tissue disorders	2 (0.5%) 2	0 (0.0%) 0	2 (0.3%) 2	0.50
Renal and urinary disorders	9 (2.3%) 9	19 (5.1%) 20	28 (3.7%) 29	0.053
Neoplasms benign, malignant and unspecified	7 (1.8%) 7	11 (3.0%) 12	18 (2.4%) 19	0.34
Antibiotic-modifying adverse events				
Any	**39 (10.1%) 52**	**63 (17.0%) 89**	**102 (13.5%) 141**	**0.006**
Infections and infestations	3 (0.8%) 3	5 (1.4%) 5	8 (1.1%) 8	0.50
Respiratory, thoracic and mediastinal disorders	2 (0.5%) 4	0 (0.0%) 0	2 (0.3%) 4	0.50
Gastrointestinal disorders	8 (2.1%) 9	24 (6.5%) 32	32 (4.2%) 41	0.003
Hepatobiliary disorders	0 (0.0%) 0	2 (0.5%) 2	2 (0.3%) 2	0.24
Skin and subcutaneous tissue disorders	7 (1.8%) 9	8 (2.2%) 9	15 (2.0%) 18	0.80
Renal and urinary disorders	1 (0.3%) 2	8 (2.2%) 10	9 (1.2%) 12	0.02
General disorders and administration site conditions	4 (1.0%) 4	13 (3.5%) 13	17 (2.2%) 17	0.03
Investigations	12 (3.1%) 13	12 (3.2%) 14	24 (3.2%) 27	1.00
Injury, poisoning and procedural complications	1 (0.3%) 1	0 (0.0%) 0	1 (0.1%) 1	1.00
Blood and lymphatic system disorders	1 (0.3%) 1	3 (0.8%) 3	4 (0.5%) 4	0.36
Metabolism and nutrition disorders	2 (0.5%) 3	0 (0.0%) 0	2 (0.3%) 3	0.50
Psychiatric disorders	1 (0.3%) 2	0 (0.0%) 0	1 (0.1%) 2	1.00
Nervous system disorders	1 (0.3%) 1	1 (0.3%) 1	2 (0.3%) 2	1.00

RIFAMPICIN FOR STAPHYLOCOCCUS AUREUS BACTERAEMIA. GIVE IT ARREST

*Thomas L Holland, *Vance G Fowler Jr*
Division of Infectious Diseases and International Health,
Department of Medicine, Duke University School of Medicine

"Before ARREST, only one adequately powered randomised trial had been completed in patients with *S aureus* bacteraemia: an industry-sponsored study comparing daptomycin with standard therapy" *(leur publi DAPTO)*

"Clinicians now have additional evidence to answer two *S aureus* bacteraemia antibiotic therapy questions: daptomycin is not inferior to standard antibiotic therapy, and adjunctive rifampicin does not improve outcomes"

… "However, a daunting list of treatment-related questions remains".

- Would other antibiotic combinations fare better?
- What about monotherapy?
- How long is long enough to treat *S aureus* bacteraemia?
- Is an oral stepdown therapy for *S aureus* bacteraemia ever appropriate?

RIFAMPICIN FOR STAPHYLOCOCCUS AUREUS BACTERAEMIA. GIVE IT ARREST

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- What about monoth
- How long is long en
- Is an oral stepdown

	Intervention	Proposed sample size (N)	Outcome	Status
Investigator-initiated trials				
NIH algorithm (NCT01191840)	Algorithm-based therapy for staphylococcal bacteraemia	509	Treatment success, safety, and duration of antibiotic therapy	Enrolment completed
CAMERA-2 (NCT02365493)	Addition of a β-lactam antibiotic to standard therapy for MRSA-BSI	440	Complication-free 90-day survival	Recruiting
SABATO (NCT01792804)	Early intravenous to oral antibiotic switch in uncomplicated SAB	430	SAB-related complications at 90 days	Recruiting
Fosfomycin (NCT01898338)	Fosfomycin versus placebo, in combination with daptomycin, for MRSA bacteraemia	206	Clinical response 6 weeks after the end of therapy	Recruiting
Industry-sponsored trials				
Dalbavancin (NCT03148756)	Dalbavancin versus standard of care for therapy completion for complicated bacteraemia and endocarditis	..	Success at 12 weeks	Study terminated by sponsor
Telavancin (NCT02208063)	Telavancin versus standard of care for SAB, including right-sided endocarditis	248	Success at 8 weeks	Recruiting
Ceftobiprole (NCT03138733)	Ceftobiprole versus daptomycin for SAB, including right-sided endocarditis	390	Success at 10 weeks	Not yet recruiting
CF-301 (NCT03163446)	CF-301 (a lysin) versus placebo added to standard therapy for SAB	115	Adverse events, day 14 clinical outcome	Recruiting
SAL200 (NCT03089697)	SAL200 (a lysin) versus placebo for patients with persistent SAB	50	Safety	Recruiting

NIH=National Institutes of Health. CAMERA=combination antibiotic therapy for meticillin-resistant *S aureus* infection. MRSA=meticillin-resistant *S aureus*. BSI=bloodstream infection. SABATO=*S aureus* bacteraemia antibiotic treatment options. SAB=*S aureus* bacteraemia.

Table: **Ongoing *Staphylococcus aureus* bacteraemia trials**

COMPARING THE OUTCOMES OF ADULTS WITH ENTEROBACTERIACEAE BACTEREMIA RECEIVING SHORT-COURSE VERSUS PROLONGED-COURSE ANTIBIOTIC THERAPY IN A MULTICENTER, PROPENSITY SCORE–MATCHED COHORT

Darunee Chotiprasitsakul, Jennifer H. Han, Sara E. Cosgrove, Anthony D. Harris, Ebbing Lautenbach, Anna T. Conley, Pam Tolomeo,Jacqueleen Wise, and Pranita D. Tamma; for the Antibacterial Resistance Leadership Group

Retrospective cohort study

3 medical centers

Patients with monomicrobial Enterobacteriaceae bacteremia

in vitro active therapy

range of 6–16 days

between 2008 and 2014

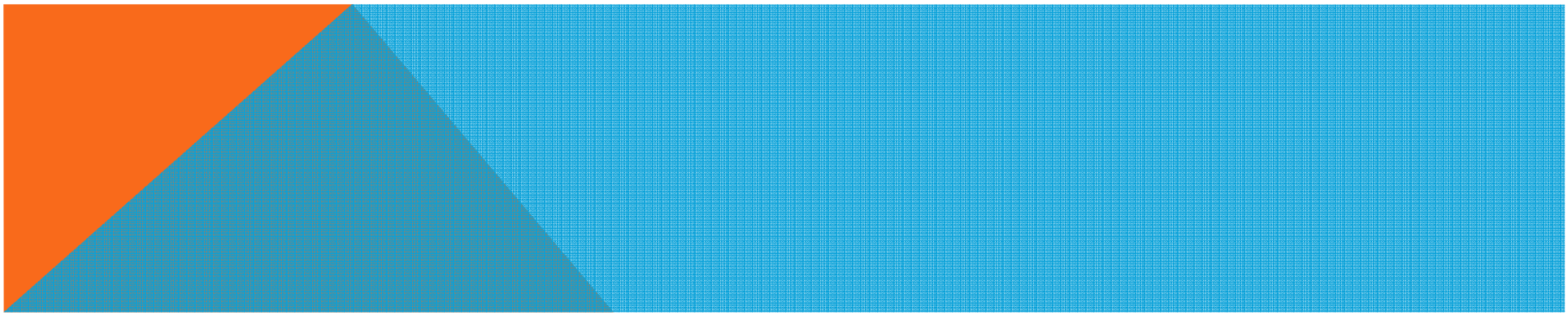
Johns Hopkins Hospital, University of Maryland Medical Center, Hospital of University of Pennsylvania

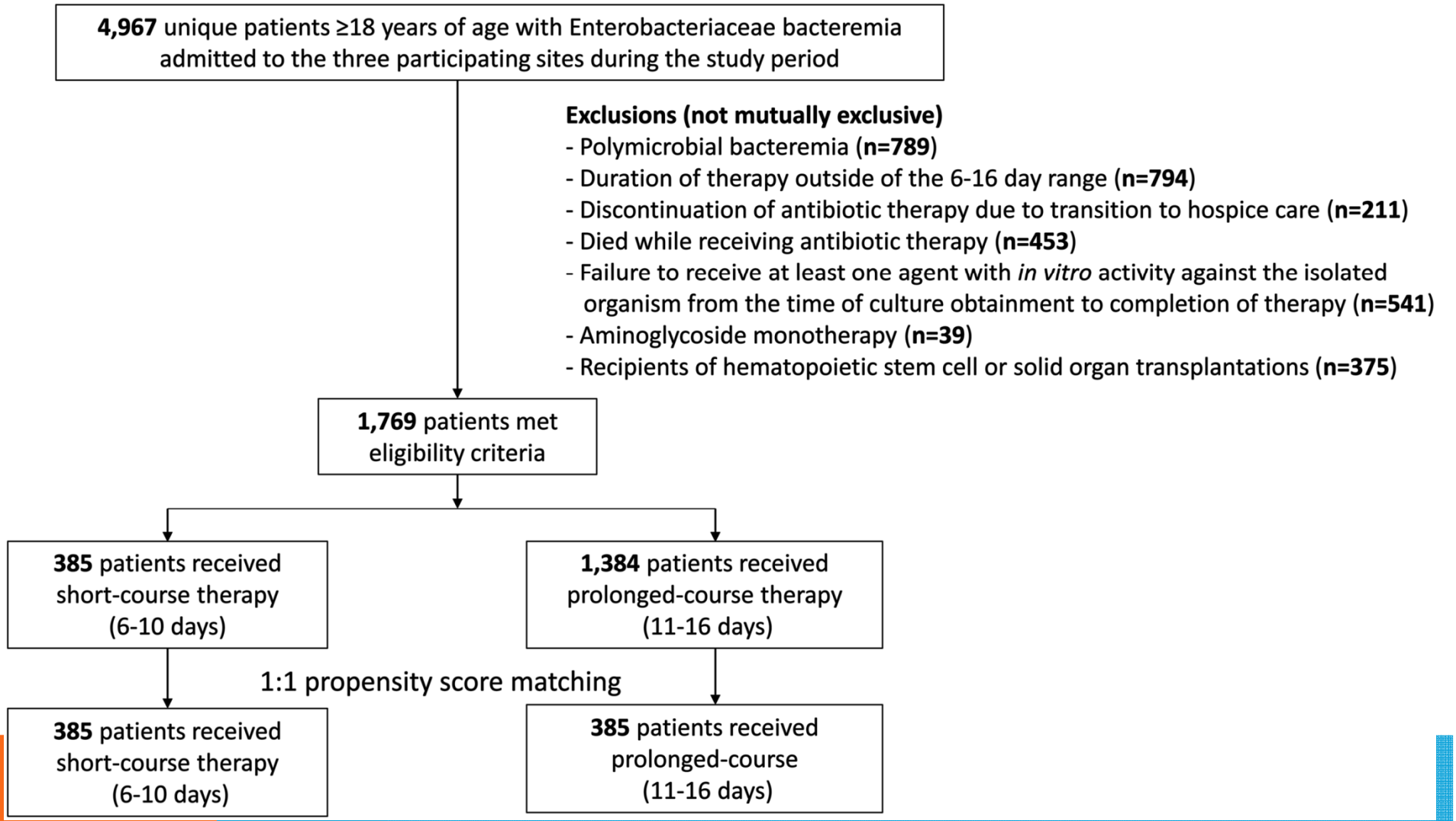
***Clinical Infectious Diseases*, Volume 66, Issue 2, 6 January 2018, Pages 172–177, https://doi.org/10.1093/cid/cix767**

METHODS

- Duration of antibiotic treatment:
- short-course (6–10 days)
- prolonged-course (11–16 days)
- Primary outcome:
- 30-day posttreatment mortality
- Secondary outcomes:
- (1) recurrent bloodstream infection with the same organism,
- (2) CDI,
- (3) emergence of multidrug-resistant gram-negative (MDRGN) colonization or infection

- **Propensity scores were generated and propensity score matching was undertaken to account for treatment decisions influenced by confounding by indication (ie, the tendency for more ill-appearing or medically complex patients who would likely be at higher risk of mortality to receive prolonged courses of antibiotic therapy).**




4,967 unique patients ≥18 years of age with Enterobacteriaceae bacteremia admitted to the three participating sites during the study period
Exclusions (not mutually exclusive)
- Polymicrobial bacteremia (n=789)
- Duration of therapy outside of the 6-16 day range (n=794)
- Discontinuation of antibiotic therapy due to transition to hospice care (n=211)
- Died while receiving antibiotic therapy (n=453)
- Failure to receive at least one agent with in vitro activity against the isolated organism from the time of culture obtainment to completion of therapy (n=541)
- Aminoglycoside monotherapy (n=39)
- Recipients of hematopoietic stem cell or solid organ transplantations (n=375)
1,769 patients met eligibility criteria
385 patients received short-course therapy (6-10 days)
1,384 patients received prolonged-course therapy (11-16 days)
1:1 propensity score matching
385 patients received short-course therapy (6-10 days)
385 patients received prolonged-course (11-16 days)

FLOW CHART

Table 3. Thirty-Day All-Cause Mortality for Hospitalized Adult Patients With Enterobacteriaceae Bacteremia in a Propensity Score–Matched Cohort

Variable	Unadjusted HR (95% CI)	*P* Value	Adjusted HR[a] (95% CI)	*P* Value
Short-course therapy (6–10 d)	1.12 (.70–1.80)	.64	1.00 (.62–1.63)	.97
Urinary source	0.36 (.19–.67)	.001	0.49 (.26–.94)	.03
Pneumonia	3.06 (1.73–5.42)	<.001	1.60 (.85–3.02)	.15
Pitt bacteremia score	1.31 (1.21–1.42)	<.001	1.29 (1.17–1.43)	<.001
ICU on day 1 of bacteremia	2.38 (1.48–3.81)	<.001	0.99 (.56–1.76)	.98
End-stage liver disease	3.58 (2.05–6.06)	<.001	4.12 (2.30–7.39)	<.001
Immunocompromised status	1.03 (.63–1.70)	.89	1.40 (.83–2.36)	.21

Abbreviations: CI, confidence interval; HR, hazard ratio; ICU, intensive care unit.

[a]Adjusted for immunocompromised status and variables with $P < .10$ in univariable analysis.

Secondary Outcomes

- **recurrent bloodstream infections with the same organism:**
- 5 (1.3%) in the short- course treatment group
- and 9 (2.3%) in the prolonged-course treatment group (OR, 1.32; 95% CI, .48–3.41).
- **CDI within 30 days of discontinuing antibiotics**
- 7 (1.8%) in the short- course treatment group
- and 6 (1.6%) in the longer-course treatment group (OR, 1.16; 95% CI, .39–3.51).
- **MDRGN resistance**
- 17 (4.4%) reports of incident in the short-course
- and 28 (7.3%) in the prolonged-course treatment groups (OR, 0.59; 95% CI, .32–1.09; *P* = .09).

ASSOCIATION OF 30-DAY MORTALITY WITH ORAL STEP-DOWN VS CONTINUED INTRAVENOUS THERAPY IN PATIENTS HOSPITALIZED WITH ENTEROBACTERIACEAE BACTEREMIA

Pranita D. Tamma, MD, MHS; Anna T. Conley, BA; Sara E. Cosgrove,MD, MS; Anthony D. Harris, MD, MPH; Ebbing Lautenbach, MD, MPH, MSCE; Joe Amoah, MD; Edina Avdic, PharmD, MBA; PamTolomeo, MPH; Jacqueleen Wise, BA; Sonia Subudhi, BA; Jennifer H. Han, MD, MSCE; for the Antibacterial Resistance Leadership Group

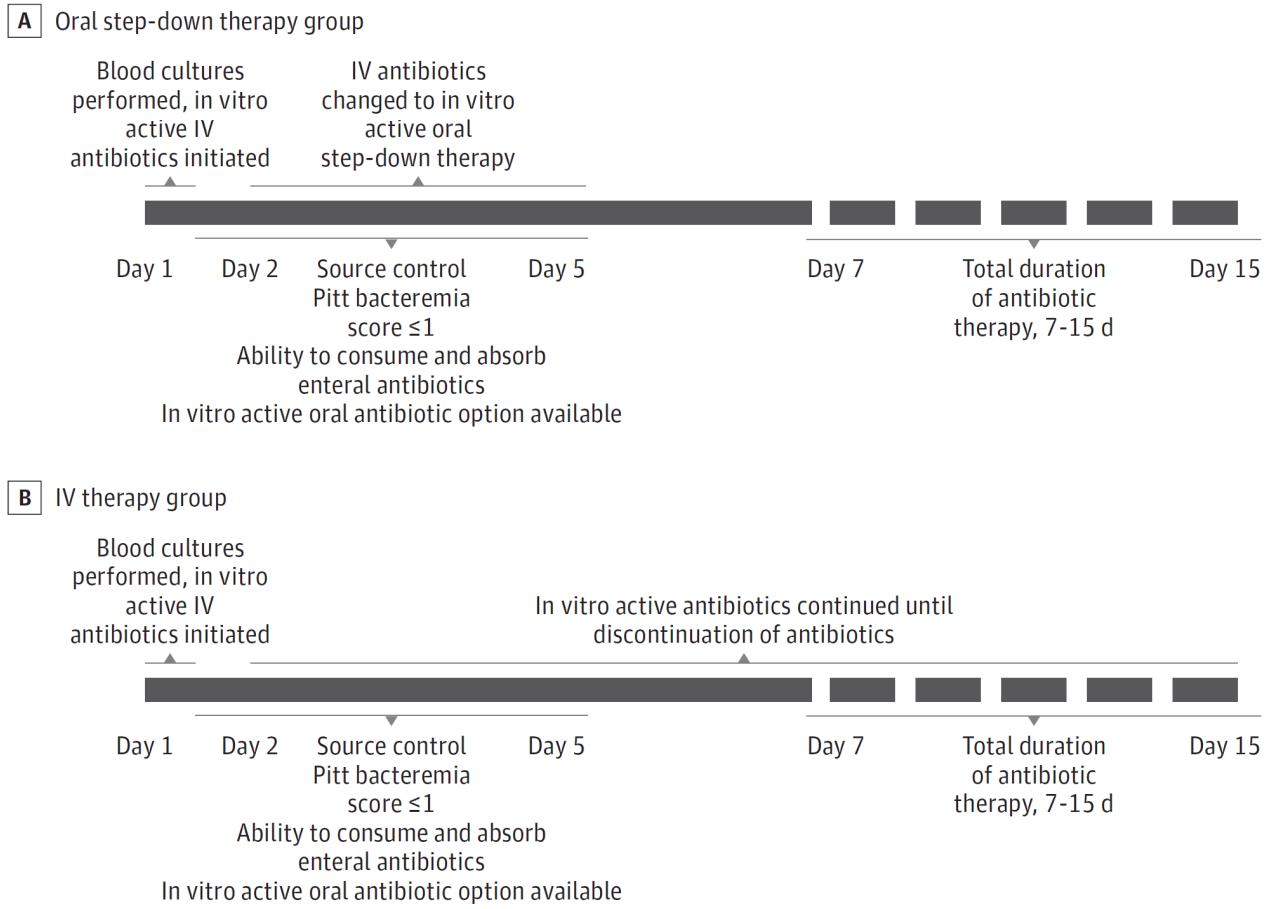
- Multicenter retrospective cohort study
- Monomicrobial Enterobacteriaceae bloodstream infections
- Exposed group (ie, those whose treatment was converted to oral therapy; hereafter referred to as the oral step-downgroup) had to be transitioned from IV to oral therapy by day 5 of therapy
- Day 1 = first day of in vitro active antibiotic therapy,
- Antibiotics had to be administered within 24 hours of the time that the first positive blood culture was collected
- Transitioning to oral therapy on day 7 or later may not be meaningful because it is possible that sufficient antibiotic therapy was already administered

The Johns Hopkins Hospital (Baltimore, Maryland) (1154 patient beds), the Hospital of the University of Pennsylvania (Philadelphia) (789 patient beds), and the University of MarylandMedical Center (Baltimore) (772 patient beds) fromJanuary 1, 2008, through December 31, 2014

JAMA Intern Med. 2019;179(3):316-323. doi:10.1001/jamainternmed.2018.6226 Published online January 22, 2019.

MÉTHODE

Figure 1. General Eligibility Criteria for the Study Sample



All patients received at least 7 days of treatment, with a range of 7 to 15 days. IV indicated intravenous.

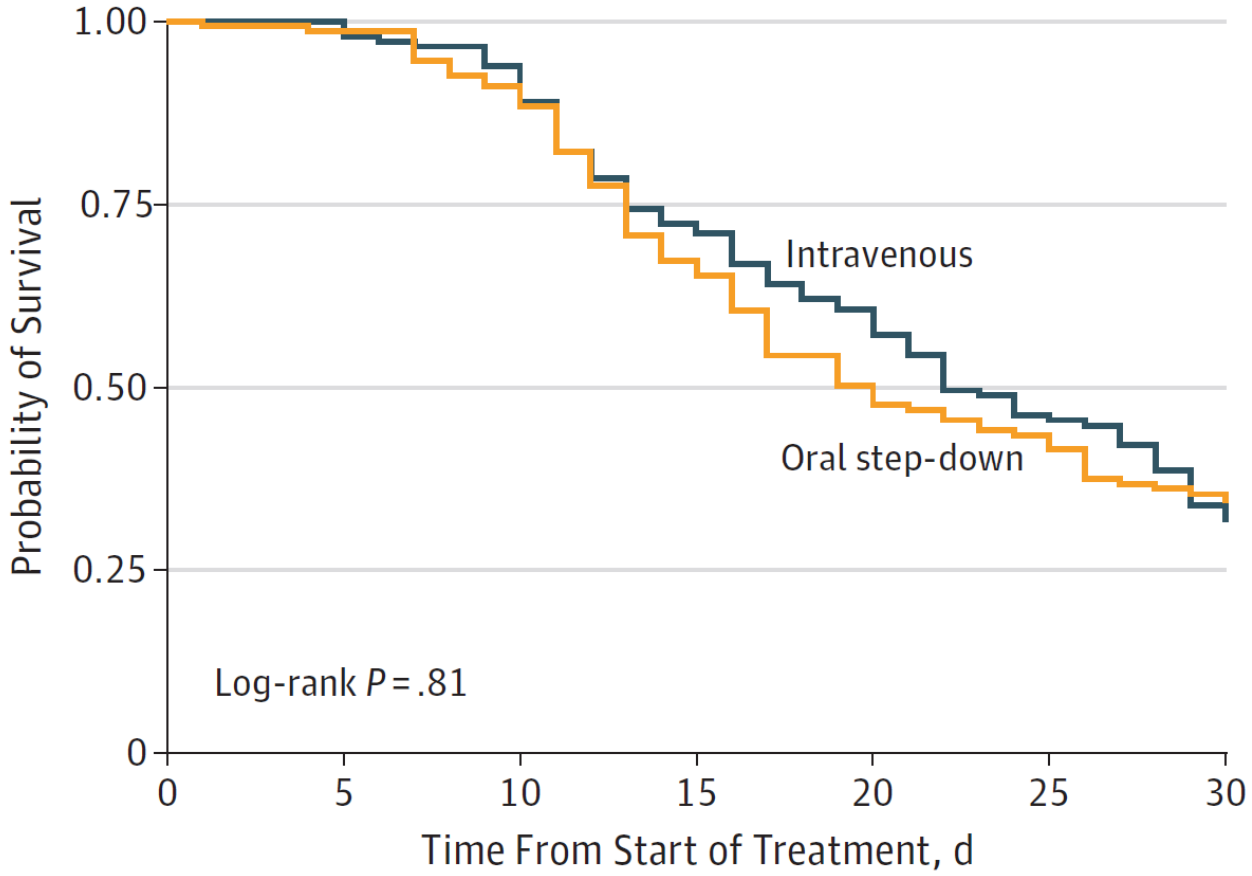
RESULTATS

- 4967 unique adult patients with Enterobacteriaceae bacteremia,
- 2161 patients met study eligibility criteria.
- The median age : 59 years (IQR, 48-69 years);
- 1185 (54.8%) were male, and 1075 (49.7%) were white.
- The oral step-down therapy group: 876 patients (40.5%),
- The IV therapy group: 1285 patients (59.5%).
- One-to-one propensity-score matching : 1478 patients, with 739 in each study arm.
- Patient characteristics were well balanced between the 2 treatment groups
- Median of 3 days (IQR, 2-4 days) of IV therapy in the oral step-down group
- and 14 days (IQR, 11-15 days) of IV therapy in the IV group.

Sources of bacteremia:

- Urinary tract (594 patients [40.2%]),
- Gastrointestinal tract (297 patients [20.1%]),
- Catheter-associated (272 patients [18.4%]),
- Biliary (210 patients [14.2%]),
- Pulmonary (58 patients [3.9%]),
- Skin and soft tissue (41 patients [2.8%]).

Figure 3. Probability of 30-Day Survival in the Propensity Score–Matched Cohort



No. at risk							
Intravenous	739	739	730	699	682	661	640
Oral step-down	739	739	726	691	666	656	642

Table 2. Antibiotic Therapy Administered to Patients Transitioned to Oral Antibiotic Therapy for Enterobacteriaceae Bacteremia

Antibiotic	Common Regimen	Bioavailability	Patients Receiving Treatment, No. (%) (n = 739)
Amoxicillin-clavulanate	500-1000 mg orally every 8-12 h	Low	38 (5.1)
Cefdinir	300 mg orally every 12 h	Low	30 (4.1)
Cefixime	200-400 mg orally every 12-24 h	Low	21 (2.8)
Cephalexin hydrochloride	500 mg orally every 6 h	Low	16 (2.2)
Cefpodoxime proxetil	200-400 mg orally every 12 h	Low	17 (2.3)
Ciprofloxacin hydrochloride	500-750 mg orally every 12 h	High	337 (45.6)
Levofloxacin	500-750 mg orally every 24 h	High	171 (23.1)
Moxifloxacin hydrochloride	400 mg orally every 24 h	High	10 (1.3)
Trimethoprim-sulfamethoxazole	160-320 mg orally every 6-12 h	High	99 (13.4)

- Of patients transitioned to a high-bioavailability agent, 518 (83.9%) received a fluoroquinolone.
- Sixty-eight (11.0%) patients in the highbioavailability group vs 15 (12.3%) patients in the lowbioavailability group died within 30 days (HR, 1.05; 95% CI, 0.67-1.66).

EFFECT OF PIPERACILLIN-TAZOBACTAM VS MEROPENEM ON 30-DAY MORTALITY FOR PATIENTS WITH *E COLI* OR *KLEBSIELLA PNEUMONIAE* BLOODSTREAM INFECTION AND CEFTRIAXONE RESISTANCE
A RANDOMIZED CLINICAL TRIAL

Can piperacillin-tazobactam be used as carbapenem-sparing therapy in patients with bloodstream infections caused by ceftriaxone-resistant *Escherichia coli* or *Klebsiella pneumoniae*?

MERINO Trial Investigators

Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

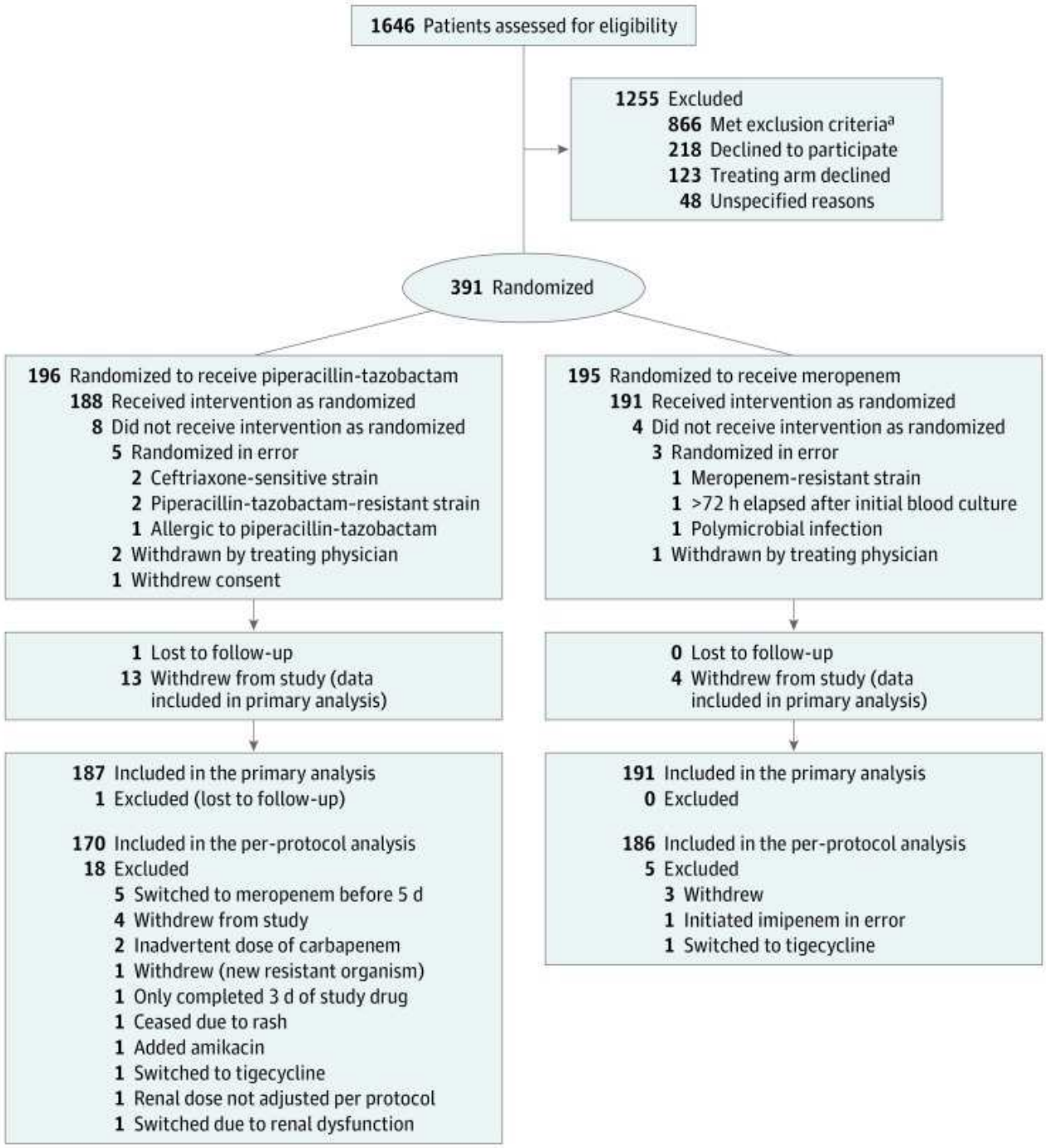
JAMA. 2018 Sep 11; 320(10): 984–94.
Published online 2018 Sep 11.
doi: 10.1001/jama.2018.12163

MÉTHODE

- **An international, multicenter, open-label, parallel group, randomized clinical trial**
- **Piperacillin-tazobactam vs meropenem**
- **Treatment of BSI caused by ceftriaxone-nonsusceptible *E coli* or *Klebsiella* spp (CMI + ESBL confirmation).**
- **Adult patients (aged ≥18 years or ≥21 years in Singapore)**
- **At least 1 positive blood culture with *E coli* or *Klebsiella* spp**
- **nonsusceptible to ceftriaxone or cefotaxime, but remained susceptible to piperacillin-tazobactam and meropenem**
- **Patients had to be randomized within 72 hours of initial positive blood culture collection.**
- **Exclusion criteria**
  - allergy to either trial drug or similar antibiotic classes,
  - no expectation of survival more than 96 hours,
  - treatment without curative intent,
  - polymicrobial bacteremia (likely skin contaminants excepted),
  - previous enrollment in the trial,
  - pregnancy or breastfeeding,
  - requirement for concomitant antibiotics with activity against gram-negative bacilli.

MÉTHODE

- **An international, multicenter, open-label, parallel group, randomized clinical trial**
- **26 hospitals in 9 countries (Australia, New Zealand, Singapore, Italy, Turkey, Lebanon, South Africa, Saudi Arabia, and Canada)**
- **from February 2014 to July 2017**
- **Patients were stratified according to**
- infecting species (*E coli* or *Klebsiella* spp; groups E or K),
- presumed source of infection (urinary tract or elsewhere),
- and severity of disease (Pitt bacteremia score ≤4 or >4).
- A high-risk stratum (E2 or K2) was defined by nonurinary source for BSI and Pitt score greater than 4
- **Meropenem, 1 g, was administered every 8 hours intravenously.**
- **Piperacillin-tazobactam, 4.5 g, was administered every 6 hours intravenously.**
- **Each dose of study drug was infused over 30 minutes.**
- **Study drug was administered for a minimum of 4 calendar days after randomization and up to 14 days,**
- **the total duration of therapy determined by the treating clinician**
- **On day 5, the primary treating team had the option to cease all antibiotics, continue the allocated agent or change to step-down therapy**



at 340 patients enrolled, a difference in the primary outcome was observed (*P* = .004). As such, the DSMB recommended **temporary suspension of the study** on July 8, 2017, pending analysis once all 391 randomized patients had completed 30-day follow-up.

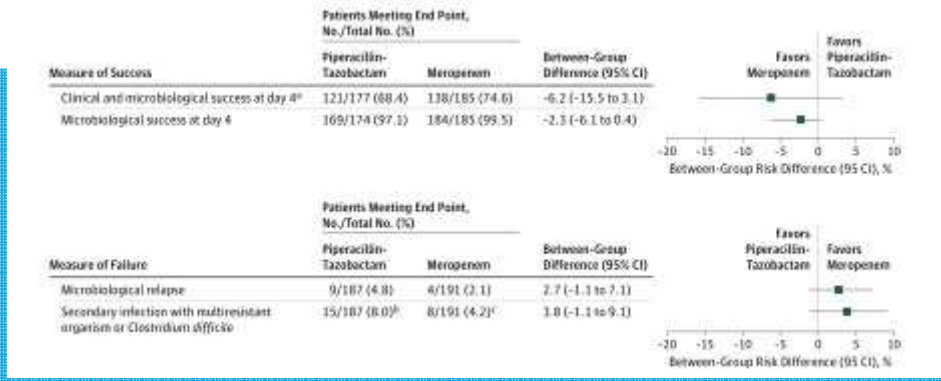
A **decision to terminate the study** on the grounds of harm and futility was made by the study management team, after discussion with site investigators, on August 10, 2017.

RÉSULTAT

- **Primary Outcome:**
- **Primary analysis population**
- 23 of 187 patients (12.3%) piperacillin-tazobactam as definitive therapy met the primary outcome of all-cause mortality at 30 days
- compared with 7 of 191 (3.7%) in the meropenem group (risk difference, 8.6% [1-sided 97.5% CI, −∞ to 14.5%]; *P* = .90 for noninferiority)
- **PP population,**
- 18 of 170 patients (10.6%) meeting the primary outcome in the piperacillin-tazobactam group
- compared with 7 of 186 (3.8%) in the meropenem group (risk difference, 6.8% [one-sided 97.5% CI, −∞ to 12.8%]; *P* = .76 for noninferiority)

- **Secondary Outcome:**

[a]Clinical and microbiological success defined as survival, negative blood cultures, temperature of 38°C or less, and peripheral white blood cell count of less than or equal to 12 000/μL (to convert to $\times 10^9$/L, multiply by 0.001).
[b]Twelve patients with meropenem- or piperacillin-tazobactam–resistant organism and 3 with *Clostridium difficile* infection.
[c]Six patients with meropenem- or piperacillin-tazobactam–resistant organism and 2 with *Clostridium difficile* infection.



IS A REPORTED PENICILLIN ALLERGY SUFFICIENT GROUNDS TO FORGO THE MULTIDIMENSIONAL ANTIMICROBIAL BENEFITS OF B-LACTAM ANTIBIOTICS?

“ we will explore the negative consequences of withholding β-lactam antibiotics in favor of other drug classes in patients with purported (but unproven) penicillin allergies, and how penicillin allergy testing can prove to be a very cost-effective element of a successful antimicrobial stewardship initiative

This article reviews the tremendous advantages offered by β-lactam therapy and makes a strong case that the debunking of false penicillin allergies through a detailed allergy history and penicillin allergy testing should be a vital component of antimicrobial stewardship practices”

George Sakoulas, Matthew Geriak, and Victor Nizet
San Diego

Clinical Infectious Diseases, Volume 68, Issue 1, 1 January 2019, Pages 157–164, https://doi.org/10.1093/cid/ciy557

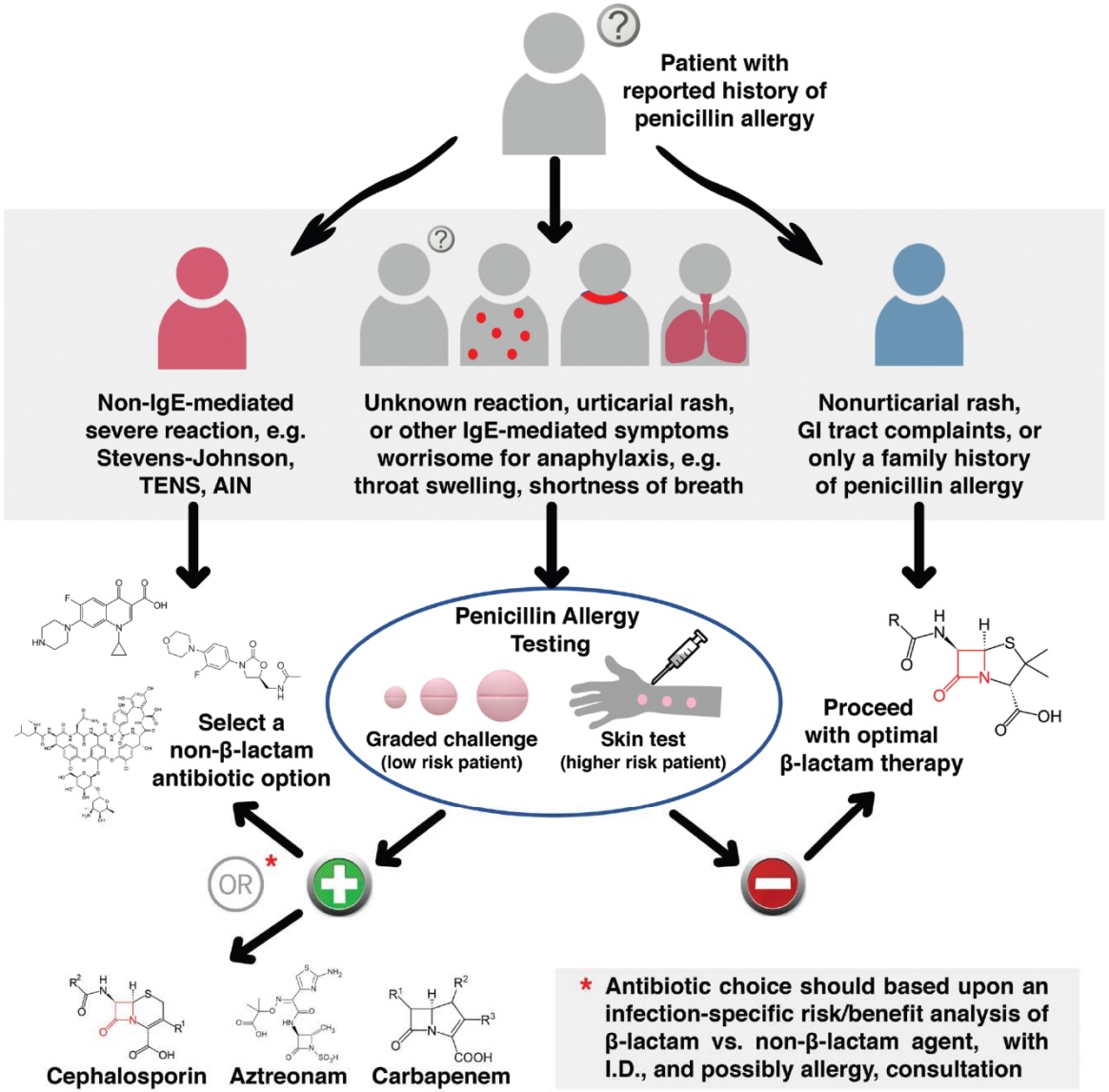


Figure 2. A proposed algorithm for approaching hospitalized patients with purported penicillin allergy, using a combination of detailed clinical history and skin testing. Abbreviations: AIN, acute interstitial nephritis; GI, gastrointestinal; ID, infectious diseases; IgE, immunoglobulin G; TENS, toxic epidermal necrolysis syndrome.

CE QUE JE GARDE EN MÉMOIRE POUR MA PRATIQUE

- **Le choix de la voie d'administration d'un antibiotique ne doit pas reposer sur le niveau d'anxiété du médecin ou des habitudes de prescription**
- **Raccourcissement de la durée de prescription des antibiothérapies pour les bactériémie à Entérobactérie**
- **Pas de risque au relais oral pour les bactériémie à Entérobactérie**
- **Pas d'utilité de la Rifampicine pour les bactériémie à *S.aureus***
- **Perte de chance avec Pipé-Tazo dans les infections à E.BLSE**

Dans l'évaluation de la balance bénéfice – risque d'une antibiothérapie: le risque est toujours une réalité, le bénéfice n'est pas toujours démontré.

Alors vigilance accrue pour les antibiotiques toxiques, les associations, les durées prolongées de traitement, et les voies d'administration invasives.