AKERSHUS UNIVERSITY HOSPITAL

Årets viktigste publikasjoner i infeksjonsmedisin

Jan-Erik Berdal
Infeksjonsmedisinsk avdeling
Ahus

Determining research priorities for clinician-initiated trials in infectious diseases

David L Paterson, on behalf of the Steering Group of the Australasian Society for Infectious Diseases Clinical Research Network*

Med J Aust 2013; 198 (5): 270-272. || doi: 10.5694/mja12.11703

Published online: 18 March 2013

1 Proposals for randomised-controlled trials ranked highest for clinical significance by infectious diseases physicians

	Mean score*	Protocol title
1	3.97	Early prosthetic joint infections managed with debridement and retention: 6 weeks of intravenous antibiotics versus 2 weeks of intravenous antibiotics and prolonged oral antibiotics
2	3.83	Native joint septic arthritis or osteomyelitis: 6 weeks of intravenous antibiotics versus 2 weeks of intravenous antibiotics and prolonged oral antibiotics
3	3.82	Uncomplicated *Staphylococcus aureus* bloodstream infections: 2 weeks of intravenous antibiotics versus 1 week of intravenous antibiotics and 1 week of oral antibiotics
4	3.74	All oral antibiotic regimen versus prolonged intravenous antibiotics for diabetic foot infection
5	3.43	Meropenem versus piperacillin–tazobactam for serious infections caused by an extended-spectrum β-lactamase producer
6	3.38	Enterococcal endocarditis: ampicillin–gentamicin versus ampicillin/ceftriaxone
7	3.30	Fosfomycin versus ertapenem for urinary tract infections caused by an extended-spectrum β-lactamase producer
8	3.26	Daptomycin versus vancomycin for methicillin-resistant *S. aureus* bloodstream infections with a minimum inhibitory concentration of vancomycin of 2 mg/L
9	3.25	Short (2-day) versus standard (5-day) intravenous treatment for cellulitis
10	3.23	14-day versus 7-day antibiotic course for bloodstream infections caused by gram-negative bacilli

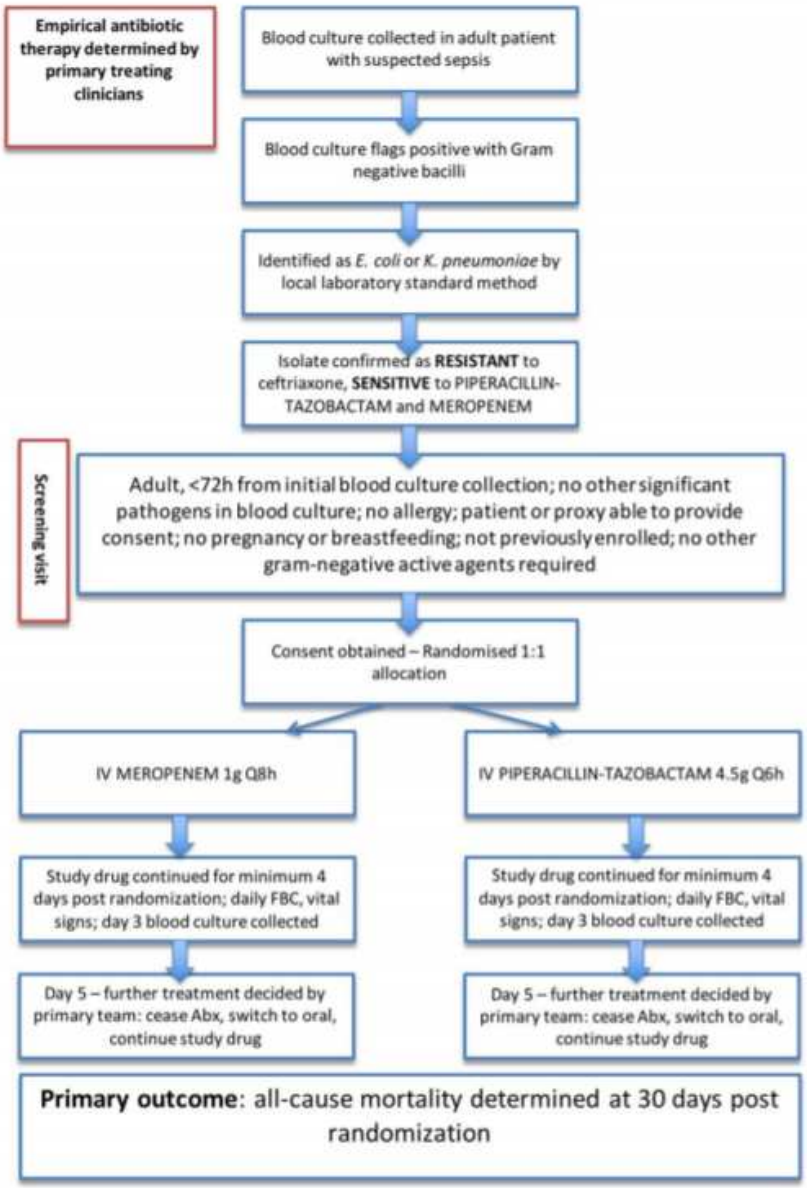
JAMA | Original Investigation

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

Patrick N. A. Harris, MBBS; Paul A. Tambyah, MD; David C. Lye, MBBS; Yin Mo, MBBS; Tau H. Lee, MBBS; Mesut Yilmaz, MD; Thamer H. Alenazi, MD; Yaseen Arabi, MD; Marco Falcone, MD; Matteo Bassetti, MD, PhD; Elda Righi, MD, PhD; Benjamin A. Rogers, MBBS, PhD; Souha Kanj, MD; Hasan Bhally, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Spiros Miyakis, MD, PhD; Genevieve Walls, MB, ChB; Mohammed Al Khamis, MD; Ahmed Zikri, PharmD; Amy Crowe, MBBS; Paul Ingram, MBBS; Nick Daneman, MD; Paul Griffin, MBBS; Eugene Athan, MBBS, MPH, PhD; Penelope Lorenc, RN; Peter Baker, PhD; Leah Roberts, BSc; Scott A. Beatson, PhD; Anton Y. Peleg, MBBS, PhD; Tiffany Harris-Brown, RN, MPH; David L. Paterson, MBBS, PhD; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

eFigure 2: Trial Workflow



Antibiotic Therapy

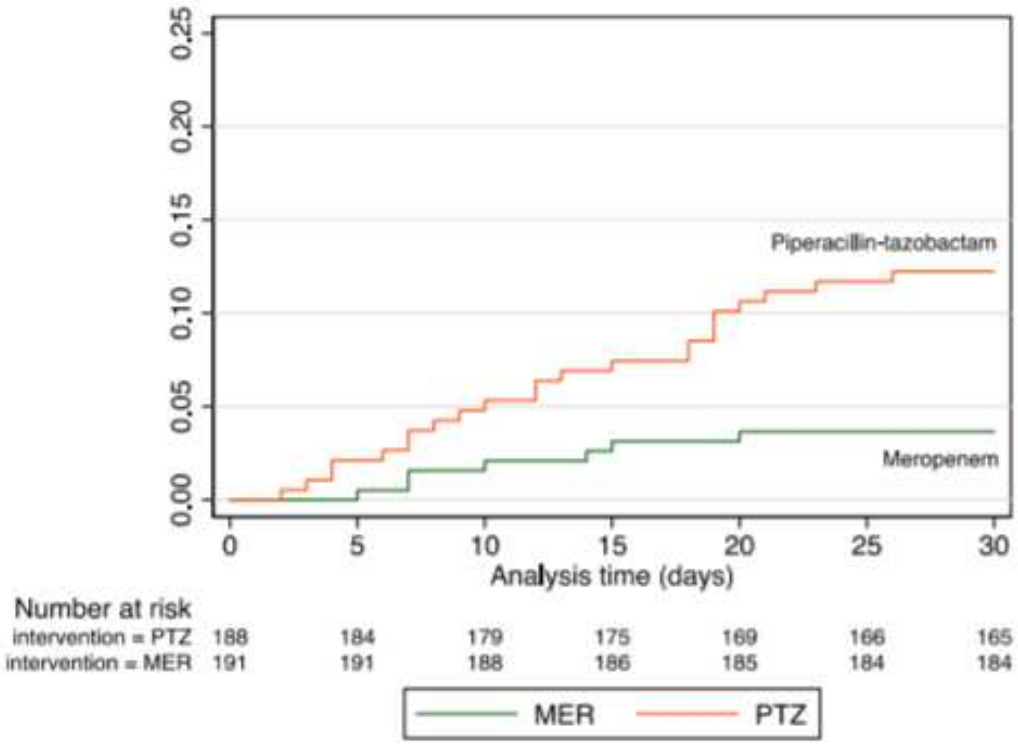
eTable 3: Details of Antibiotic Therapy

Variable	PTZ (n=188)	MER (n=191)
Total duration of study drug		
Mean days (SD)	7.3 (4.4)	7.6 (4.3)
Median days (IQR)	6 (5, 10)	6 (5, 9)
Total duration of all antibiotics		
Mean days (SD)	13.2 (6.1)	13.7 (7.6)
Median days (IQR)	13 (8,16)	13 (8, 16)
Empirical therapy		
BLBLI	39 (20.7)	50 (26.2)
Carbapenem	26 (13.8)	29 (15.2)
Other	126 (67.0)	115 (60.2)
Combination empirical therapy – no. (%)		
Yes	79 (42.0)	77 (40.3)
'Step down' therapy* – no. (%)		
Aminoglycoside	1 (0.5)	0 (0)
β-lactam/β-lactamase inhibitor	8 (4.3)	5 (2.6)
Carbapenem	38 (20.2)	39 (20.4)
Fosfomycin	2 (1.1)	1 (0.5)
Fluoroquinolone	20 (10.6)	30 (15.7)
Trimethoprim-sulfamethoxazole	7 (3.7)	13 (6.8)
Other	2 (1.1)	2 (1.0)
None	109 (58.0)	103 (53.9)
Not recorded	3 (1.6)	0 (0)
Empirical therapy congruent with randomized drug¶ - no. (%)		
Yes	39 (20.7)	29 (15.2)

*antibiotic choice once allocated trial drug ceased; ¶ includes drugs of same class; e.g. if piperacillin-tazobactam was used as empirical therapy, and the patient was randomized to piperacillin-tazobactam, this would be classified as "congruent" therapy; use of empirical ertapenem or imipenem was considered congruent with meropenem (as all are carbapenems)

Analysis of Primary and Secondary Outcomes

eFigure 4: Kaplan-Meier Failure Estimates for Primary Outcome



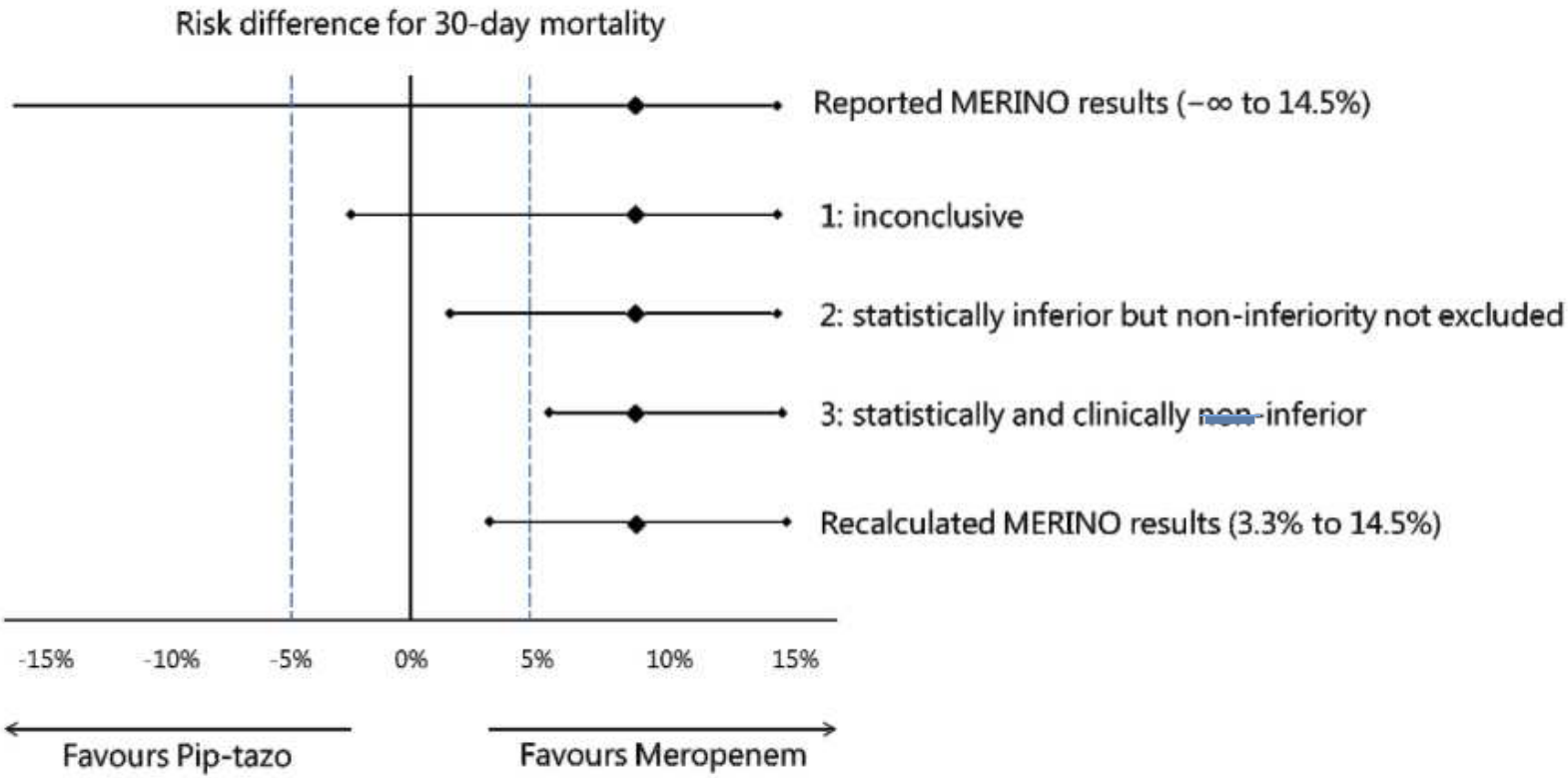
Median observation time for both meropenem (MER) and piperacillin-tazobactam (PTZ) groups = 30 days; includes primary analysis population

Mero 3,7% Pip/tazo 12,3%

Table 1. Baseline Characteristics of Patients in the Primary Analysis Population[a]

Characteristic	Pipercillin-Tazobactam (n = 188)	Meropenem (n = 191)
Organism		
Escherichia coli	162 (86.2)	166 (86.9)
Klebsiella pneumoniae	26 (13.8)	25 (13.1)
APACHE II Score, mean (SD)[c]	17.9 (6.1)	21.0 (6.9)
Charlson Comorbidity Index score, median (IQR)[d]	2.0 (1.0-4.0)	2.0 (1.0-4.0)
Pitt score, median (IQR)[e]	1.0 (0-2.0)	1.0 (0-2.0)
Immune compromise	51 (27.1)	40 (20.9)
Neutropenia	16 (8.5)	9 (4.7)

https://reflectionsipc.com/2018/09/21/an-endless-one-sided-confidence-in-pip-tazo

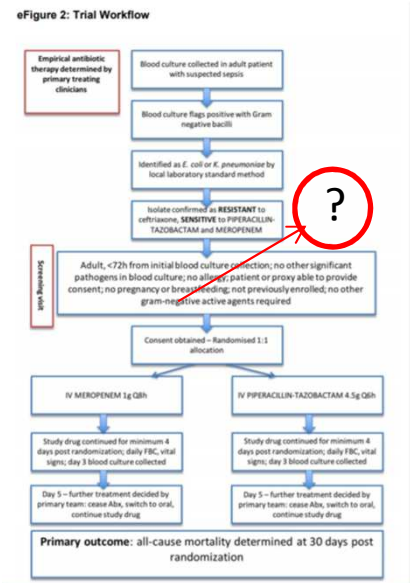


ECCMID 2019

- Muntlig meddelelse (Gunnar Skov Simonsen):

- Re-analyser/vurderinger av pip/tazo som var bedømt som følsom ble justert til resistent

- Utelukkes disse i analysene er mortalitet i pip/tazo 7-8% og non-inferiority er vist ?



BLING III: A phase III randomised controlled trial of continuous beta-lactam infusion compared with intermittent beta-lactam dosing in critically ill patients

Funding source: National Health and Medical Research Council

Interview With: Patrick Harris, BSc, MBBS, DTM&H, MRCP, FRACP, FRCPA

Whether anyone is willing to undertake a trial to identify these "lower-risk" bacteremic patients in whom a BLBLI is safe, is an interesting question. I still suspect that clinical judgement can be applied: if a patient has bacteraemia caused by an ESBL-producer, has achieved adequate source control, is not severely unwell, has few co-morbidities or other high-risk features and has improved clinically on empirical PTZ (to which the isolate has confidently been tested as susceptible – another potential variable of uncertainty), I do not believe it is mandatory that a switch to MER is required – but such subtleties are hard to define from this trial alone. However, I am fairly convinced that in patients with septic shock, immune compromise, significant co-morbidities or poor source control, a carbapenem would be a safer choice.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral versus Intravenous Antibiotics for Bone and Joint Infection

H.-K. Li, I. Rombach, R. Zambellas, A.S. Walker, M.A. McNally, B.L. Atkins, B.A. Lipsky, H.C. Hughes, D. Bose, M. Kümin, C. Scarborough, P.C. Matthews, A.J. Brent, J. Lomas, R. Gundle, M. Rogers, A. Taylor, B. Angus, I. Byren, A.R. Berendt, S. Warren, F.E. Fitzgerald, D.J.F. Mack, S. Hopkins, J. Folb, H.E. Reynolds, E. Moore, J. Marshall, N. Jenkins, C.E. Moran, A.F. Woodhouse, S. Stafford, R.A. Seaton, C. Vallance, C.J. Hemsley, K. Bisnauthsing, J.A.T. Sandoe, I. Aggarwal, S.C. Ellis, D.J. Bunn, R.K. Sutherland, G. Barlow, C. Cooper, C. Geue, N. McMeekin, A.H. Briggs, P. Sendi, E. Khatamzas, T. Wangrangsimakul, T.H.N. Wong, L.K. Barrett, A. Alvand, C.F. Old, J. Bostock, J. Paul, G. Cooke, G.E. Thwaites, P. Bejon, and M. Scarborough, for the OVIVA Trial Collaborators*

EDITOR'S CHOICE

The History of Antibiotic Treatment of Osteomyelitis

Nicolás W Cortés-Penfield, Prathit A Kulkarni

Open Forum Infectious Diseases, Volume 6, Issue 5, May 2019, ofz181,
https://doi.org/10.1093/ofid/ofz181
Published: 08 April 2019 **Article history** ▾

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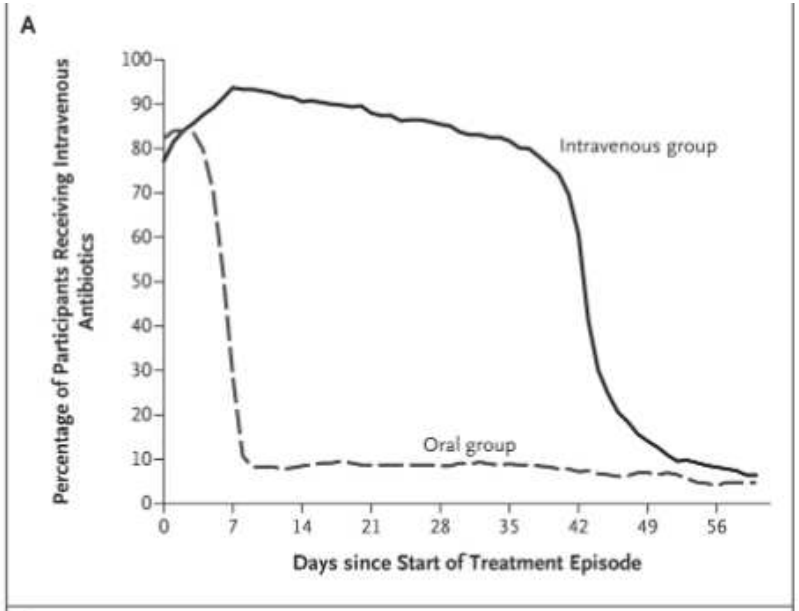
This trial was deliberately inclusive: there was no selection according to infecting organism, surgical procedure, or anatomic site. Although the resulting trial population was heterogeneous, the advantages of generalizability outweigh the disadvantages of heterogeneity. A more selective recruitment strategy, such as inclusion of only primary arthroplasty infections with *Staphylococcus aureus*, would have made the trial prohibitively long and would have limited the utility of the results. The trial hypothesis was based on the pharmacokinetic principle that appropriately selected oral agents provide adequate antibiotic concentrations at the site of infection. This principle is unlikely to have been differentially affected by, for example, the anatomic site, presence of metalwork, or extent of surgical débridement. However, selection of the appropriate oral agents necessarily relied on a clear understanding of the relevant pharmacologic variables and close liaison between surgical and infectious-disease specialists.


A
Percentage of Participants Receiving Intravenous Antibiotics
100
90
80
70
60
50
40
30
20
10
0
Intravenous group
Oral group
0
7
14
21
28
35
42
49
56
Days since Start of Treatment Episode

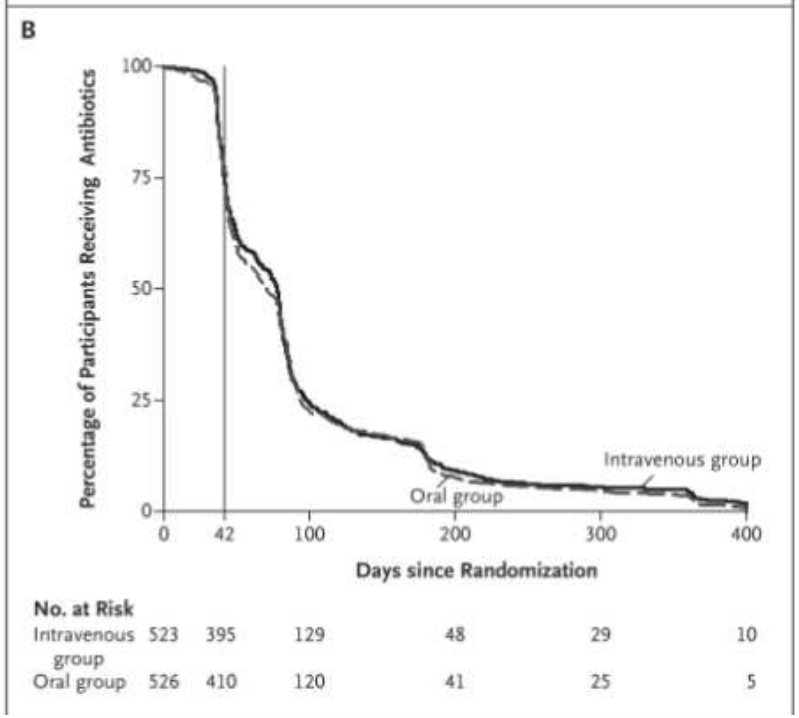

B
Percentage of Participants Receiving Antibiotics
100
75
50
25
0
Intravenous group
Oral group
0
42
100
200
300
400
Days since Randomization
No. at Risk
Intravenous group 523 395 129 48 29 10
Oral group 526 410 120 41 25 5

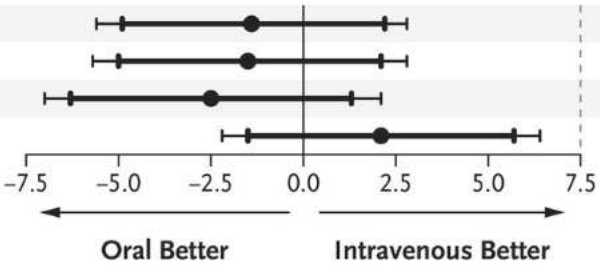
Table S10: Overview of actual antibiotics (excluding rifampicin), as defined by agents used for more than one week during the initial six-week treatment period

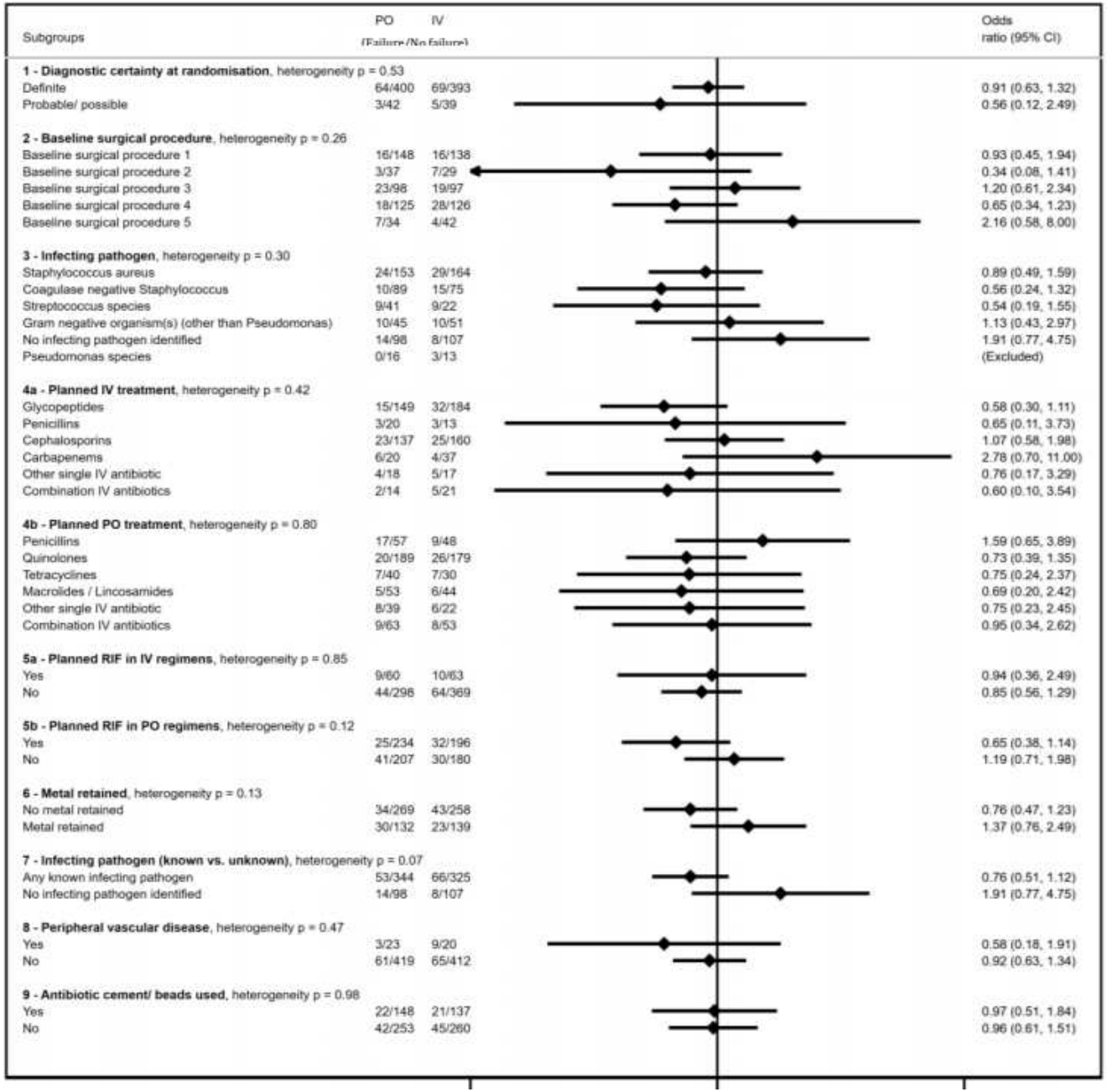
	Participants randomized to IV Antibiotic* (N = 521)	Participants randomized to PO Antibiotic* (N = 523)	Total* (N = 1044)
Glycopeptides[a] (IV)	214 (41.1%)	22 (4.2%)	236 (22.6%)
Penicillins (IV)	38 (7.3%)	11 (2.1%)	49 (4.7%)
Cephalosporins (IV)	173 (33.2%)	8 (1.5%)	181 (17.3%)
Carbapenems (IV)	41 (7.9%)	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*

Subgroup	Oral Group	Intravenous Group	Risk Difference (90% CI; 95% CI)
	patients with treatment failure/ total no. of participants		
Intention-to-treat population	70.0/527	77.3/527	−1.4 (−4.9 to 2.2; −5.6 to 2.9)
Modified intention-to-treat population	67/509	74/506	−1.5 (−5.0 to 2.1; −5.7 to 2.8)
Per-protocol population	61/466	69/443	−2.5 (−6.3 to 1.3; −7.0 to 2.1)
Worst-case sensitivity analysis	85/527	74/527	2.1 (−1.5 to 5.7; −2.2 to 6.4)




Subgroups
PO
IV
(Failure/No failure)
Odds ratio (95% CI)
1 - Diagnostic certainty at randomisation, heterogeneity p = 0.53
Definite 64/400 69/393 0.91 (0.63, 1.32)
Probable/ possible 3/42 5/39 0.56 (0.12, 2.49)
2 - Baseline surgical procedure, heterogeneity p = 0.26
Baseline surgical procedure 1 16/148 16/138 0.93 (0.45, 1.94)
Baseline surgical procedure 2 3/37 7/29 0.34 (0.08, 1.41)
Baseline surgical procedure 3 23/98 19/97 1.20 (0.61, 2.34)
Baseline surgical procedure 4 18/125 28/126 0.65 (0.34, 1.23)
Baseline surgical procedure 5 7/34 4/42 2.16 (0.58, 8.00)
3 - Infecting pathogen, heterogeneity p = 0.30
Staphylococcus aureus 24/153 29/164 0.89 (0.49, 1.59)
Coagulase negative Staphylococcus 10/89 15/75 0.56 (0.24, 1.32)
Streptococcus species 9/41 9/22 0.54 (0.19, 1.55)
Gram negative organism(s) (other than Pseudomonas) 10/45 10/51 1.13 (0.43, 2.97)
No infecting pathogen identified 14/98 8/107 1.91 (0.77, 4.75)
Pseudomonas species 0/16 3/13 (Excluded)
4a - Planned IV treatment, heterogeneity p = 0.42
Glycopeptides 15/149 32/184 0.58 (0.30, 1.11)
Penicillins 3/20 3/13 0.65 (0.11, 3.73)
Cephalosporins 23/137 25/160 1.07 (0.58, 1.98)
Carbapenems 6/20 4/37 2.78 (0.70, 11.00)
Other single IV antibiotic 4/18 5/17 0.76 (0.17, 3.29)
Combination IV antibiotics 2/14 5/21 0.60 (0.10, 3.54)
4b - Planned PO treatment, heterogeneity p = 0.80
Penicillins 17/57 9/48 1.59 (0.65, 3.89)
Quinolones 20/189 26/179 0.73 (0.39, 1.35)
Tetracyclines 7/40 7/30 0.75 (0.24, 2.37)
Macrolides / Lincosamides 5/53 6/44 0.69 (0.20, 2.42)
Other single IV antibiotic 8/39 6/22 0.75 (0.23, 2.45)
Combination IV antibiotics 9/63 8/53 0.95 (0.34, 2.62)
5a - Planned RIF in IV regimens, heterogeneity p = 0.85
Yes 9/60 10/63 0.94 (0.36, 2.49)
No 44/298 64/369 0.85 (0.56, 1.29)
5b - Planned RIF in PO regimens, heterogeneity p = 0.12
Yes 25/234 32/196 0.65 (0.38, 1.14)
No 41/207 30/180 1.19 (0.71, 1.98)
6 - Metal retained, heterogeneity p = 0.13
No metal retained 34/269 43/258 0.76 (0.47, 1.23)
Metal retained 30/132 23/139 1.37 (0.76, 2.49)
7 - Infecting pathogen (known vs. unknown), heterogeneity p = 0.07
Any known infecting pathogen 53/344 66/325 0.76 (0.51, 1.12)
No infecting pathogen identified 14/98 8/107 1.91 (0.77, 4.75)
8 - Peripheral vascular disease, heterogeneity p = 0.47
Yes 3/23 9/20 0.58 (0.18, 1.91)
No 61/419 65/412 0.92 (0.63, 1.34)
9 - Antibiotic cement/ beads used, heterogeneity p = 0.98
Yes 22/148 21/137 0.97 (0.51, 1.84)
No 42/253 45/260 0.96 (0.61, 1.51)

Supplementary Tables

Table S1a: Supplementary baseline information

	IV Antibiotic (N = 527)	PO Antibiotic (N = 527)	Total (N = 1054)
Clinical presentation*			
- localised pain	397 (75.3%)	403 (76.5%)	800 (75.9%)
- localised erythema	226 (42.9%)	207 (39.3%)	433 (41.1%)
- temperature > 38.0 C	62 (11.8%)	62 (11.8%)	124 (11.8%)
- discharging sinus / wound	296 (56.2%)	285 (54.1%)	581 (55.1%)
Anatomical site of infection*			
- spinal infection[a]	37 (7.0%)	35 (6.6%)	72 (6.8%)
- upper limb infection	43 (8.2%)	59 (11.2%)	102 (9.67%)
- lower limb infection[b]	436 (82.7%)	419 (79.5%)	855 (81.1%)
- other area of infection	12 (2.3%)	14 (2.7%)	26 (2.5%)
Operative details*			
- draining sinus arising from bone / prosthesis	177 (33.6%)	142 (26.9%)	319 (30.3%)
- frank pus adjacent to bone / prosthesis	179 (34.0%)	186 (35.3%)	365 (34.6%)
- intraoperative local antibiotics (cement or beads)	165 (31.3%)	179 (33.8%)	343 (32.5%)

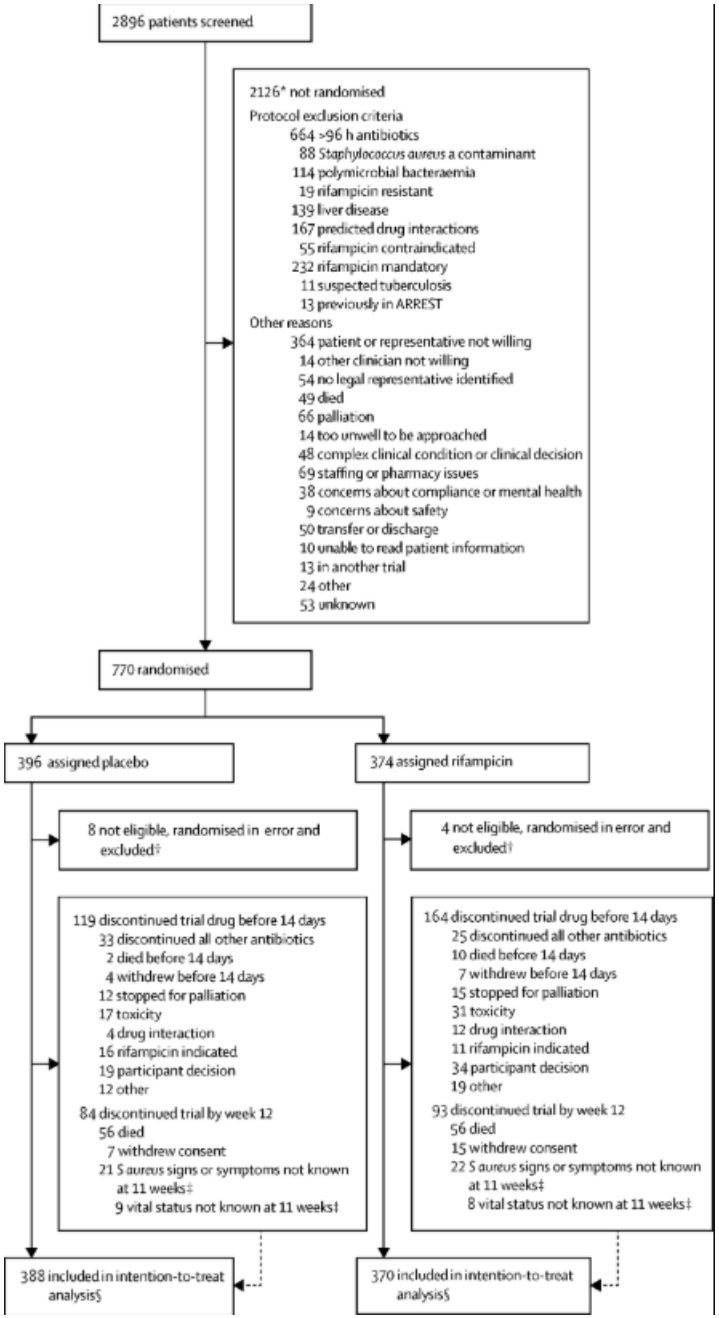
THE LANCET

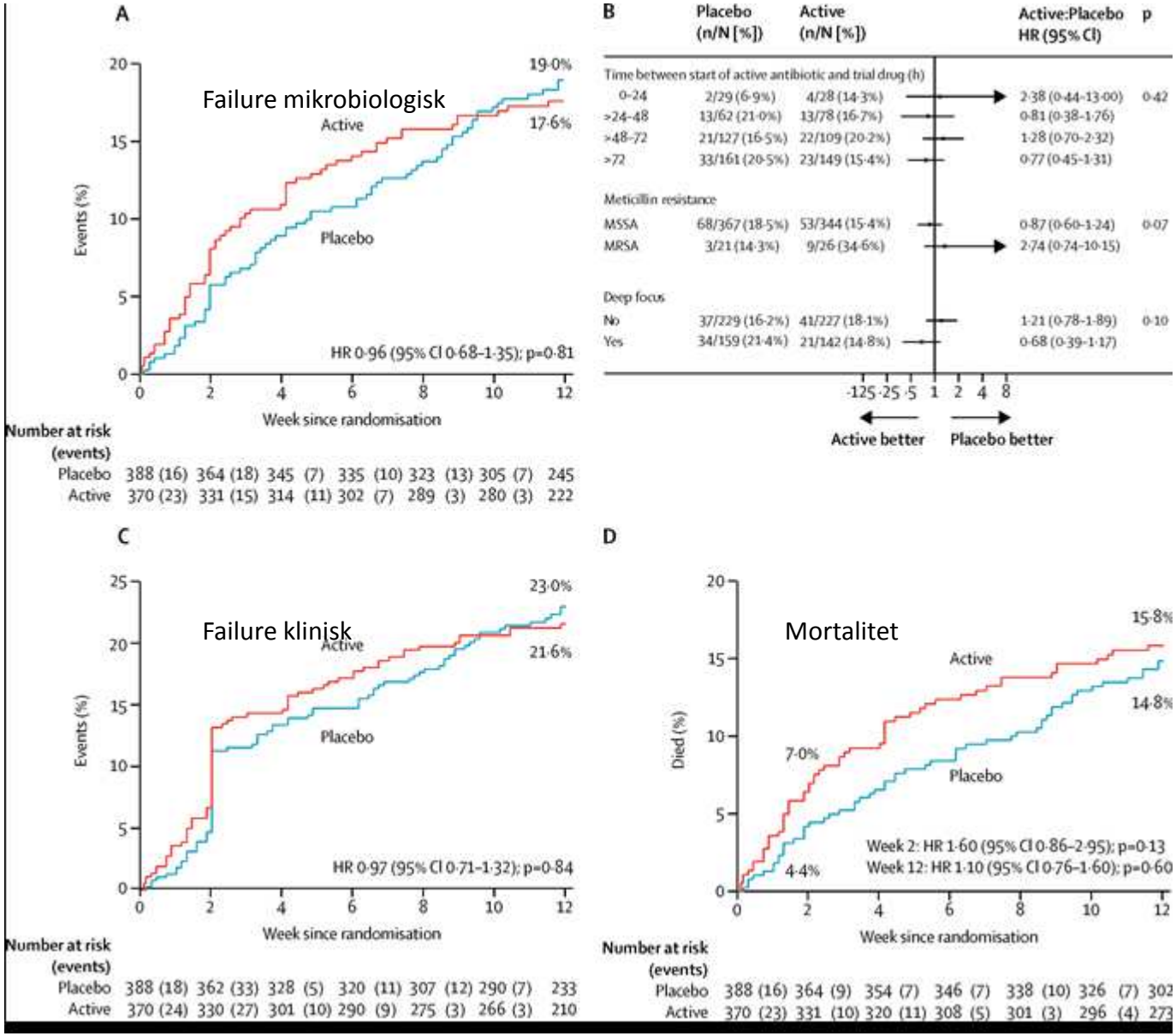
ARTICLES | VOLUME 391, ISSUE 10121, P668-678, FEBRUARY 17, 2018

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

Prof Guy E Thwaites, FRCP • Matthew Scarborough, PhD • Alexander Szubert, MSc • Emmanuel Nsutebu, FRCP • Robert Tilley, MBChB • Julia Greig, FRCP • et al. Show all authors • Show footnotes

Open Access • Published: December 14, 2017 • DOI: https://doi.org/10.1016/S0140-6736(17)32456-X •


2896 patients screened
2126* not randomised
Protocol exclusion criteria
664 >96 h antibiotics
88 Staphylococcus aureus a contaminant
114 polymicrobial bacteraemia
19 rifampicin resistant
139 liver disease
167 predicted drug interactions
55 rifampicin contraindicated
232 rifampicin mandatory
11 suspected tuberculosis
13 previously in ARREST
Other reasons
364 patient or representative not willing
14 other clinician not willing
54 no legal representative identified
49 died
66 palliation
14 too unwell to be approached
48 complex clinical condition or clinical decision
69 staffing or pharmacy issues
38 concerns about compliance or mental health
9 concerns about safety
50 transfer or discharge
10 unable to read patient information
13 in another trial
24 other
53 unknown
770 randomised
396 assigned placebo
374 assigned rifampicin
8 not eligible, randomised in error and excluded†
4 not eligible, randomised in error and excluded†
119 discontinued trial drug before 14 days
33 discontinued all other antibiotics
2 died before 14 days
4 withdrew before 14 days
12 stopped for palliation
17 toxicity
4 drug interaction
16 rifampicin indicated
19 participant decision
12 other
84 discontinued trial by week 12
56 died
7 withdrew consent
21 S aureus signs or symptoms not known at 11 weeks‡
9 vital status not known at 11 weeks‡
164 discontinued trial drug before 14 days
25 discontinued all other antibiotics
10 died before 14 days
7 withdrew before 14 days
15 stopped for palliation
31 toxicity
12 drug interaction
11 rifampicin indicated
34 participant decision
19 other
93 discontinued trial by week 12
56 died
15 withdrew consent
22 S aureus signs or symptoms not known at 11 weeks‡
8 vital status not known at 11 weeks‡
388 included in intention-to-treat analysis§
370 included in intention-to-treat analysis§


A
Failure mikrobiologisk
Active
Placebo
19·0%
17·6%
HR 0·96 (95% CI 0·68–1·35); p=0·81
Events (%)
Week since randomisation
Number at risk (events)
Placebo 388 (16) 364 (18) 345 (7) 335 (10) 323 (13) 305 (7) 245
Active 370 (23) 331 (15) 314 (11) 302 (7) 289 (3) 280 (3) 222
B
Placebo (n/N [%])
Active (n/N [%])
Active:Placebo HR (95% CI)
p
Time between start of active antibiotic and trial drug (h)
0–24 2/29 (6·9%) 4/28 (14·3%) 2·38 (0·44–13·00) 0·42
>24–48 13/62 (21·0%) 13/78 (16·7%) 0·81 (0·38–1·76)
>48–72 21/127 (16·5%) 22/109 (20·2%) 1·28 (0·70–2·32)
>72 33/161 (20·5%) 23/149 (15·4%) 0·77 (0·45–1·31)
Meticillin resistance
MSSA 68/367 (18·5%) 53/344 (15·4%) 0·87 (0·60–1·24) 0·07
MRSA 3/21 (14·3%) 9/26 (34·6%) 2·74 (0·74–10·15)
Deep focus
No 37/229 (16·2%) 41/227 (18·1%) 1·21 (0·78–1·89) 0·10
Yes 34/159 (21·4%) 21/142 (14·8%) 0·68 (0·39–1·17)
Active better
Placebo better
C
Failure klinisk
Active
Placebo
23·0%
21·6%
HR 0·97 (95% CI 0·71–1·32); p=0·84
Events (%)
Week since randomisation
Number at risk (events)
Placebo 388 (18) 362 (33) 328 (5) 320 (11) 307 (12) 290 (7) 233
Active 370 (24) 330 (27) 301 (10) 290 (9) 275 (3) 266 (3) 210
D
Mortalitet
Active
Placebo
15·8%
14·8%
7·0%
4·4%
Week 2: HR 1·60 (95% CI 0·86–2·95); p=0·13
Week 12: HR 1·10 (95% CI 0·76–1·60); p=0·60
Died (%)
Week since randomisation
Number at risk (events)
Placebo 388 (16) 364 (9) 354 (7) 346 (7) 338 (10) 326 (7) 302
Active 370 (23) 331 (10) 320 (11) 308 (5) 301 (3) 296 (4) 273

Investigation of Rifampin to Reduce Pedal Amputations for Osteomyelitis in Diabetics (VA INTREPID)

ClinicalTrials.gov Identifier: NCT03012529

29th ECCMID

Amsterdam, Netherlands
13 – 16 April 2019

The congress of ESCMID

L0014 Combination antibiotic therapy for methicillin-resistant ***Staphylococcus aureus*** bacteraemia: the CAMERA2 randomised controlled trial

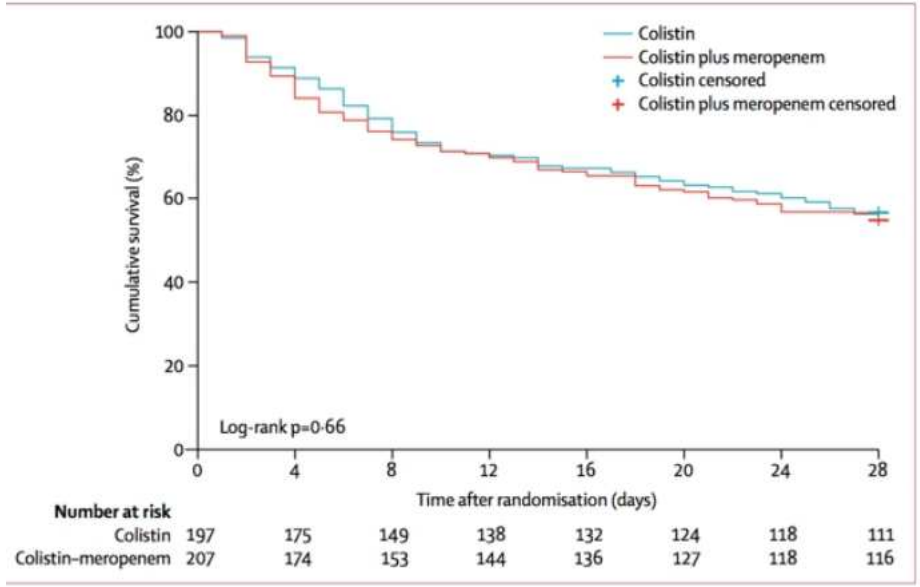
Joshua Saul Davis[1], Hong Foo[2], David Lye[3], Jane Nelson[1], Matthew O'sullivan[4], David L. Paterson[5], Mical Paul[6], Archana Sud[7], Dafna Yahav[8], Steven Y. C. Tong*[9]

"The main result was that we found no difference in the primary endpoint, which was a composite of 90-day mortality, persistent bacteremia at day 5, and microbiological failure and relapse," Steven Tong, PhD, associate professor at the Doherty Institute and the Menzies School of Research, and presenter of the CAMERA2 study, told *Contagion*® **(see video)**. "However, what we did find was that there was a markedly increased risk of acute kidney injury in the combination arm. Of patients who received combination therapy, 30% developed acute kidney injury vs 9% in the standard therapy arm."

Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial

Lancet ID 2018;18:391-400

Mical Paul, George L Daikos, Emanuele Durante-Mangoni, Dafna Yahav, Yehuda Carmeli, Yael Dishon Benattar, Anna Skiada, Roberto Andini, Noa Eliakim-Raz, Amir Nutman, Oren Zusman, Anastasia Antoniadou, Pia Clara Pafundi, Amos Adler, Yaakov Dickstein, Ioannis Pavleas, Rosa Zampino, Vered Daitch, Roni Bitterman, Hiba Zayyad, Fidi Koppel, Inbar Levi, Tanya Babich, Lena E Friberg, Johan W Mouton, Ursula Theuretzbacher, Leonard Leibovici



igure 2: Survival analysis to day 28 after randomisation

Most pts had pneumonia or bactearemia (355/406 87%) and most infections were caused by *Acinetobacter baumannii* (312/406 77%)

Combination therapy was not superior to monotherapy. The addition of meropenem to colistin did not improve clinical failure in severe *A. baumannii* infections.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2019 VOL. 380 NO. 5

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.

Fra protokollen…….

Tidsplan

Inklusionen forventes startet den 1/7 2011 og afsluttet ca. 36 måneder senere.

Projektet anmeldes til relevante myndigheder marts 2011. Databearbejdning og publikation af data forventes færdiggjort inden udgangen af 2014.

Økonomi

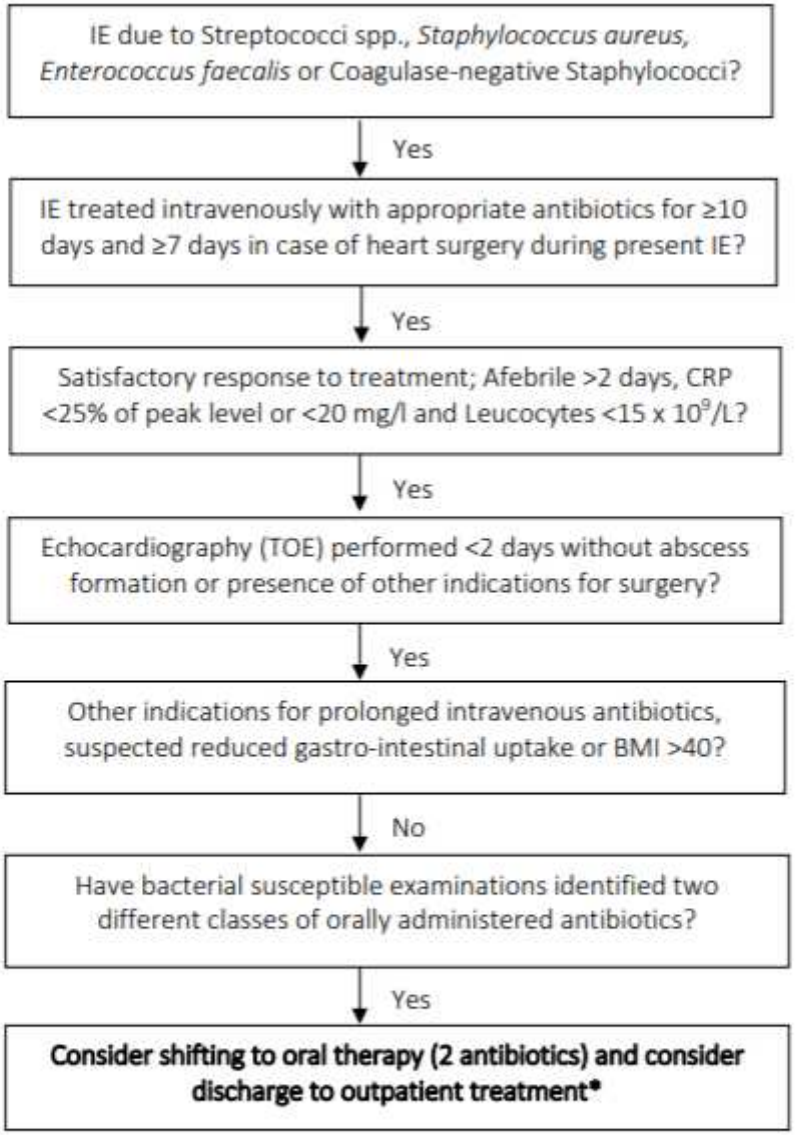
Studiets samlede budget er 6.079.796 kr. Udgifterne fordeles over 4 kalenderår (2011-2014). Det detaljerede budget fremgår af bilag 10 .

Fortvil ikke……

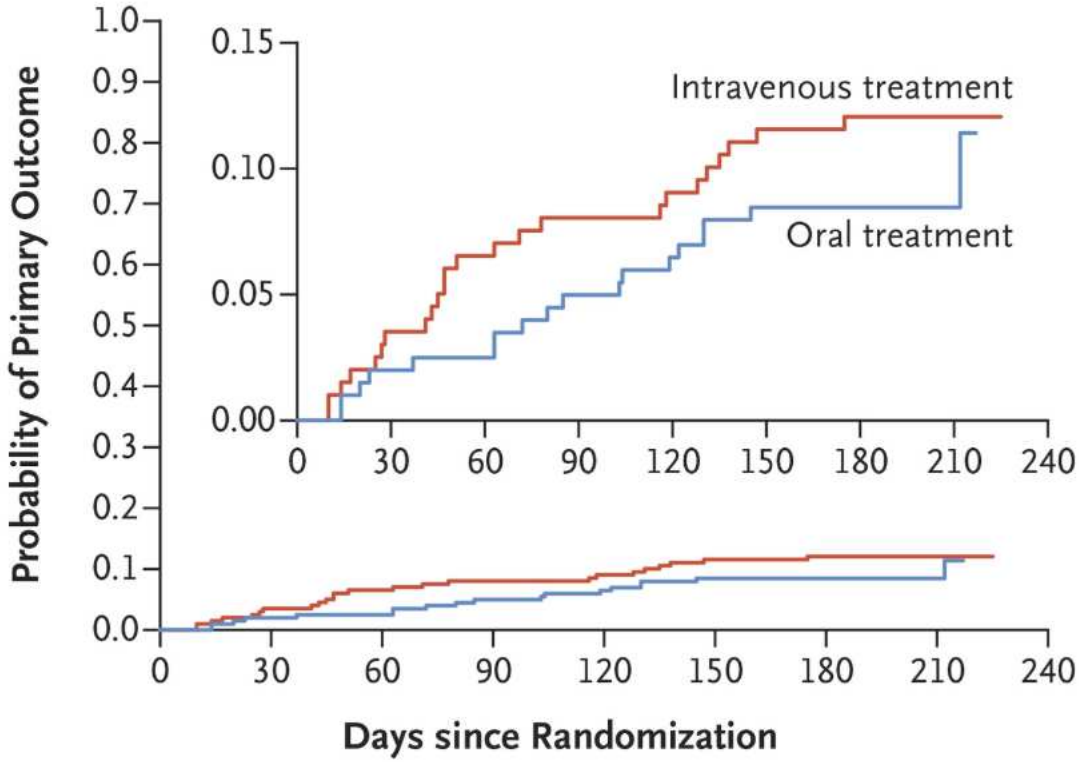
Publikationer

Der planlægges som minimum en publikation omhandlende de primære endepunkter samt en eller flere publikationer omhandlende de sekundære endepunkter.

Positive såvel som negative resultater vil blive publiceret i internationale peer-reviewede, engelsk-sprogede tidsskrifter. Såfremt dette ikke er muligt, vil de blive fremlagt andet sted (eksempelvis på en hjemmeside).



Proposal; criteria for shifting from intravenous to oral antibiotic therapy in patients with left-sided endocarditis (IE). TOE; transesophageal echocardiography. *Patients shifted to oral therapy may be discharged to outpatient treatment if OPAT criteria are met.



No. at Risk

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

Table S2
Oral regimens recommended in the POET trial

Penicillin and methicillin sensitive *Staphylococcus aureus* and coagulase-negative staphylococci:

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

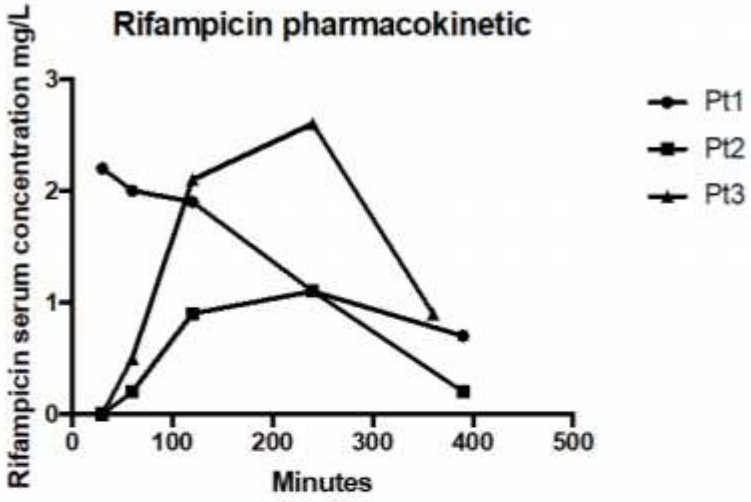
Methicillin sensitive *Staphylococcus aureus* and coagulase-negative staphylococci

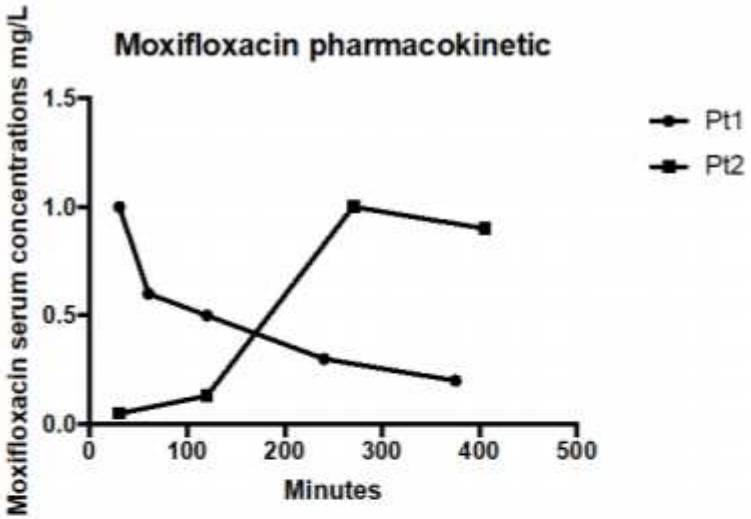
1) Dicloxacillin 1 g x 4 and fusidic acid 0.75 g x 2
2) Dicloxacillin 1 g x 4 and rifampicin 0.6 g x 2
3) Linezolid 0.6 g x 2 and fucidic acid 0.75g x 2
4) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

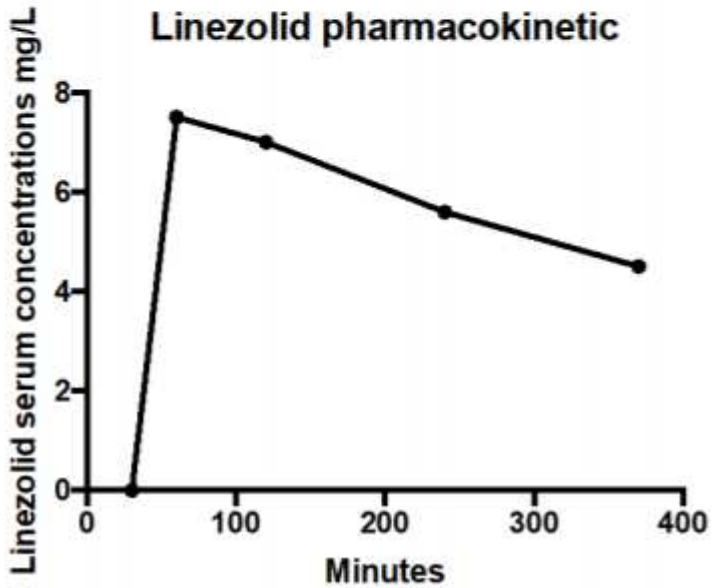
Table S3

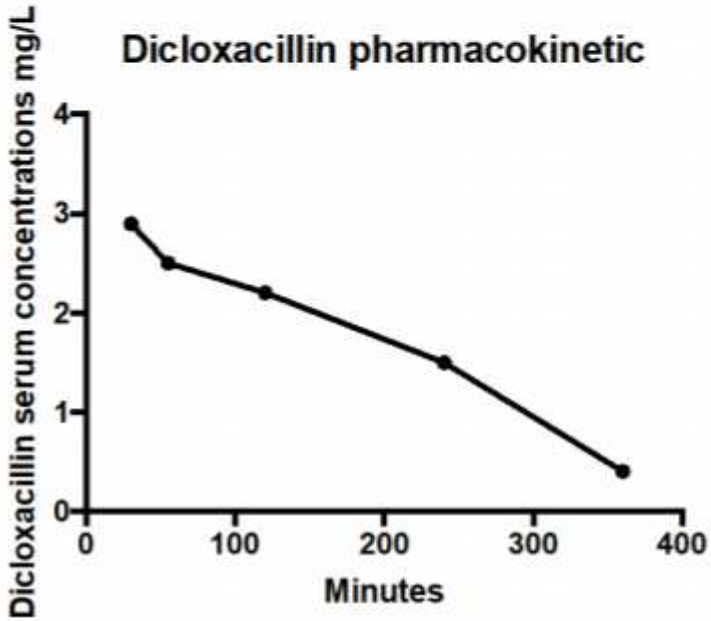
Applied cut-off levels for therapeutic plasma concentrations

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


Rifampicin pharmacokinetic
Rifampicin serum concentration mg/L
Minutes
Pt1
Pt2
Pt3


Moxifloxacin pharmacokinetic
Moxifloxacin serum concentrations mg/L
Minutes
Pt1
Pt2


Linezolid pharmacokinetic
Linezolid serum concentrations mg/L
Minutes


Dicloxacillin pharmacokinetic
Dicloxacillin serum concentrations mg/L
Minutes

EDITORIAL

Partial Oral Therapy for Osteomyelitis and Endocarditis — Is It Time?

Helen W. Boucher, M.D.

e

Metrics

January 31, 2019
N Engl J Med 2019; 380:487-489
DOI: 10.1056/NEJMe1817264

At this time, it is premature to recommend a widespread early switch to oral therapy for bone and joint infection or step down to combination oral antibiotic therapy for infective endocarditis on the left side of the heart

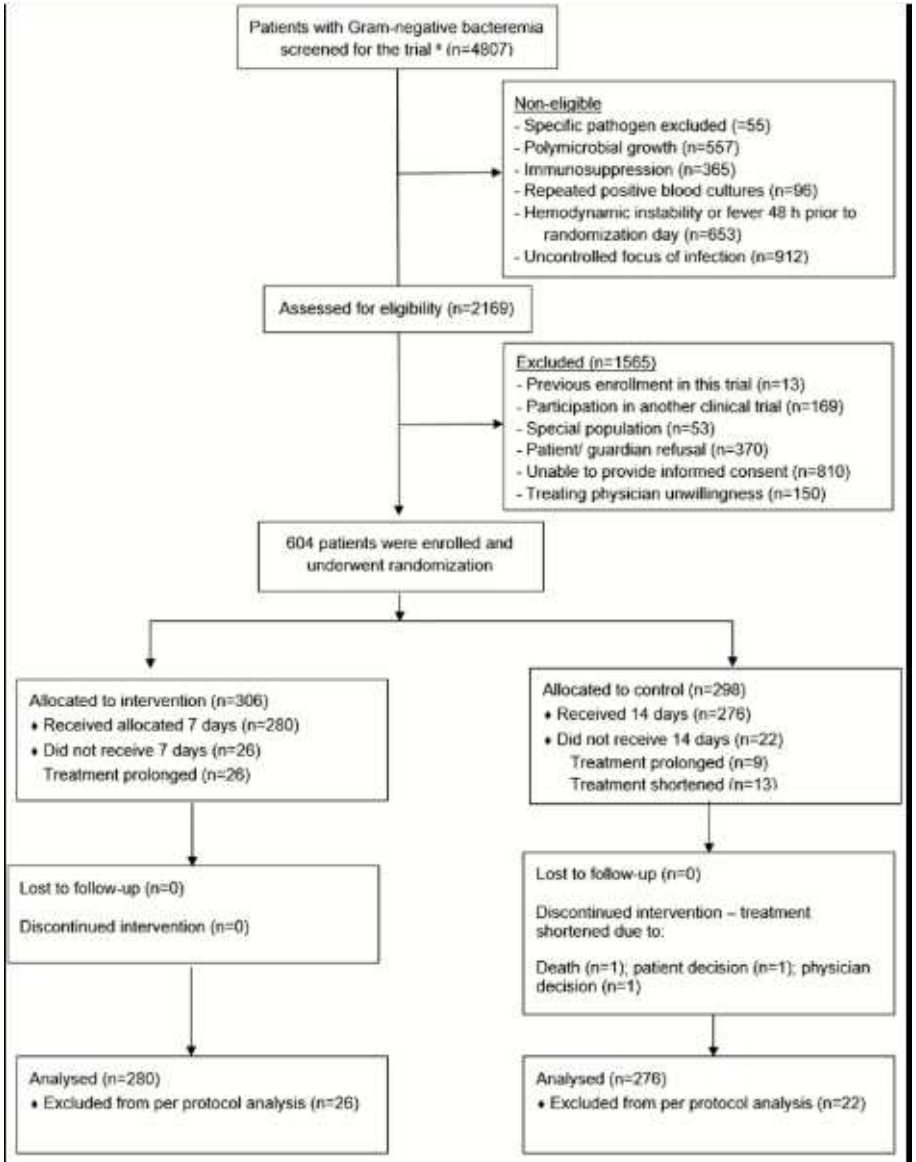
CORRECTED PROOF

Seven Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-negative Bacteremia: A Noninferiority Randomized Controlled Trial

Dafna Yahav ✉, Erica Franceschini, Fidi Koppel, Adi Turjeman, Tanya Babich, Roni Bitterman, Ami Neuberger, Nesrin Ghanem-Zoubi, Antonella Santoro, Noa Eliakim-Raz ... Show more

Clinical Infectious Diseases, ciy1054, https://doi.org/10.1093/cid/ciy1054

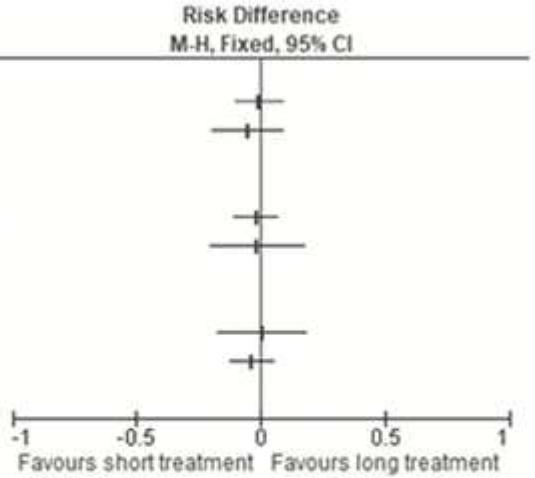
Published: 11 December 2018 **Article history** ▾



* All patients with Gram-negative bacteremia during the study period, surviving to day 7 and not discharged before recruitment

Figure 2. Primary outcome according to patient subgroups. Empirical antibiotic treatment indicates covering antibiotics ...

Subgroup	Short Events	Short Total	Long Events	Long Total	Risk Difference M-H, Fixed, 95% CI
.1 Bacteremia source					
UTI	92	212	88	199	-0.01 [-0.10, 0.09]
non-UTI	48	94	56	99	-0.06 [-0.20, 0.09]
.2 Empirical antibiotic treatment					
Covering empirical	112	260	109	242	-0.02 [-0.11, 0.07]
Non-covering empirical	28	46	35	56	-0.02 [-0.21, 0.17]
.3 Multi-drug resistance					
MDR	39	58	34	51	0.01 [-0.17, 0.18]
Non-MDR	101	248	110	247	-0.04 [-0.13, 0.05]



UTI – urinary tract infection

Empirical antibiotic treatment – covering antibiotics to the specific pathogen according to susceptibility pattern administered within 48 hours

MDR – Multidrug resistance. This subgroup includes 105 patients with an ESBL Enterobacteriaceae and 4 additional patients with another MDR bacteria (2 *Pseudomonas aeruginosa*, one *Acinetobacter baumannii* and one *Chryseobacterium meningosepticum*)

Outcomes of 7 Versus 14 Days of Antibiotic Therapy for Uncomplicated Gram-Negative Bacteremia

Outcome	Short Arm (7 d) (n = 306)	Long Arm (14 d) (n = 298)	Risk Difference (95% CI)	*P* Value
Primary outcome	140 (45.8)	144 (48.3)	−2.6 (−10.5 to 5.3)	.527
90-d all-cause mortality	36 (11.8)	32 (10.7)	1.0 (−4.0 to 6.1)	.702
Readmissions	119 (38.9)	127 (42.6)	−3.7 (−11.5 to 4.1)	.363
Time to return to baseline activity, wk (90 d)	2 (0–8.3) (n = 218)	3 (1–12) (n = 222)	…	**.010**
Total hospital days (90 d from randomization)—survivors	3 (1–9) (n = 270 alive at day 90)	3.5 (1–10) (n = 266 alive at day 90)	…	.923
Total hospital days (90 d from randomization)—all	4 (1–10)	4 (1–12)	…	.603
Duration of appropriate antibiotic therapy for bacteremia	7 (7.0–8.0)	14.0 (14.0–14.0)	…	**< .001**
Total antibiotic days from culture collection to day 90 postrandomization	10.0 (9.0–18.0) (n = 270 alive at day 90)	16.0 (15.0–22.0) (n = 266 alive at day 90)	…	**< .001**

Bacteremia Antibiotic Length Actually Needed for Clinical Effectiveness (BALANCE): study protocol for a pilot randomized controlled trial

Nick Daneman, Asgar H Rishu, Wei Xiong, Sean M Bagshaw, Deborah J Cook, Peter Dodek, Richard Hall, Anand Kumar, Francois Lamontagne, Francois Lauzier, John C Marshall, Claudio M Martin, Lauralyn McIntyre, John Muscedere, Steven Reynolds, Henry T Stelfox, Robert A Fowler and on behalf of the Canadian Critical Care Trials Group

Trials 2015 **16**:173

https://doi.org/10.1186/s13063-015-0688-z © Daneman et al.; licensee BioMed Central. 2015

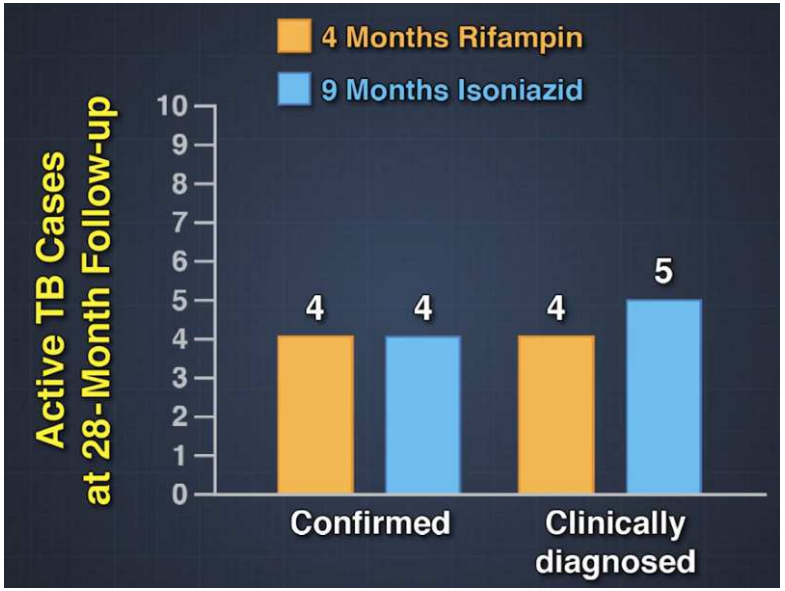
ORIGINAL ARTICLE

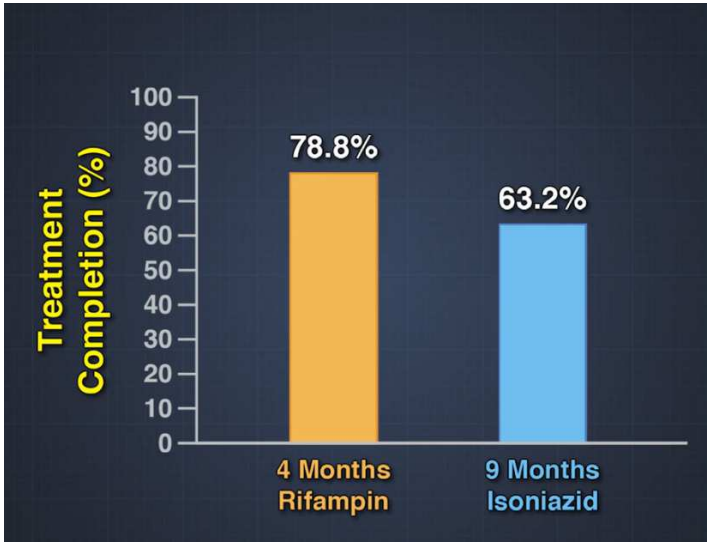
Four Months of Rifampin or Nine Months of Isoniazid for Latent Tuberculosis in Adults

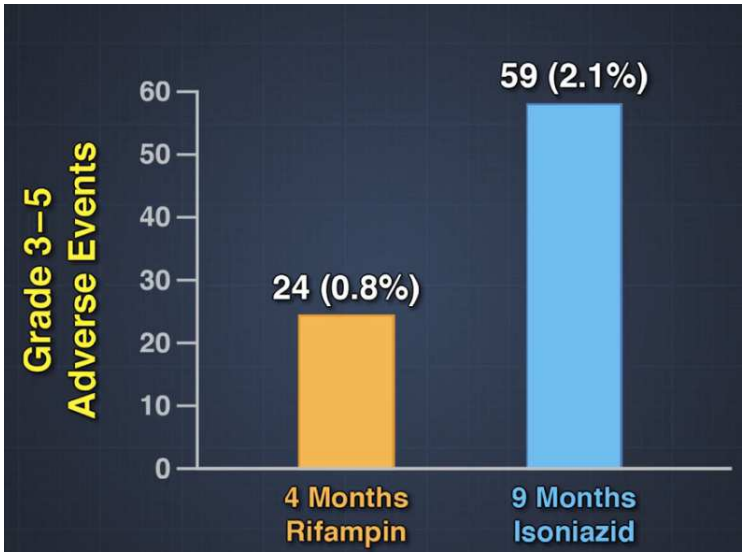
D. Menzies, M. Adjobimey, R. Ruslami, A. Trajman, O. Sow, H. Kim, J. Obeng Baah, G.B. Marks, R. Long, V. Hoeppner, K. Elwood, H. Al-Jahdali, M. Gninafon, L. Apriani, R.C. Koesoemadinata, A. Kritski, V. Rolla, B. Bah, A. Camara, I. Boakye, V.J. Cook, H. Goldberg, C. Valiquette, K. Hornby, M.-J. Dion, P.-Z. Li, P.C. Hill, K. Schwartzman, and A. Benedetti

TABELL 10.3 ANBEFALTE BEHANDLINGSREGIMER FOR FOREBYGGENDE BEHANDLING I NORGE

Medikament	Varighet av behandling	Intervall	DOT
Isoniazid med Rifampicin	3 mndr	Daglig	Ikke rutinemessig
Isoniazid med Rifapentine	3 mndr	Ukentlig	I regelen
Isoniazid	6 mndr	Daglig	Ikke rutinemessig
Rifampicin*	4 mndr	Daglig	Ikke rutinemessig


4 Months Rifampin
9 Months Isoniazid
Active TB Cases at 28-Month Follow-up
10
9
8
7
6
5
4
3
2
1
0
4
4
4
5
Confirmed
Clinically diagnosed


Treatment Completion (%)
100
90
80
70
60
50
40
30
20
10
0
78.8%
63.2%
4 Months Rifampin
9 Months Isoniazid


Grade 3–5 Adverse Events
60
50
40
30
20
10
0
24 (0.8%)
59 (2.1%)
4 Months Rifampin
9 Months Isoniazid

HIV dual therapy

Dual Therapy: Some Early Attempts That Fell Short
Maintenance Treatment

Study	Study Design: Maintenance Treatment
ACTG 343[a]	[ZDV + 3TC] vs [IDV + 3TC + ZDV]: failed
TRILEGE[b]	[ZDV + 3TC *or* ZDV + IDV] vs [ZDV + 3TC + IDV]: failed
MARCH[c]	[PI/r + 2 NRTI] vs [MVC + 2 NRTI *or* MVC + PI/r]: failed

a. Havlir DV, et al. *N Engl J Med.* 1998;339:1261-1268; b. Pialoux G, et al. *N Engl J Med.* 1998;339:1269-1276; c. Pett SL, et al. *Clin Infect Dis.* 2016;63:122-132.

Dual Therapy: Some Early Attempts That Fell Short
Initial Treatment

Study	Study Design: Initial Treatment
ACTG A5142[a]	[LPV/r + EFV] vs [EFV + 2 NRTIs] *or* [LPV/r + 2 NRTIs]: LPV/r + EFV as efficacious but not well tolerated and increased resistance during failure
SPARTAN[b]	[ATV + RAL] vs [ATV/r + TDF/FTC]: failed due to low efficacy and high resistance
NEAT[c]	[RAL + DRV/r] vs [DRV/r + TDF/FTC]: met noninferiority criterion; not efficacious in patients with VL >100,000 c/mL or CD4 cell count <200

a. Riddler SA, et al. *N Engl J Med.* 2008;358:2095-2106; b. Kozal MJ, et al. *HIV Clin Trials.* 2012;13:119-130; c. Raffi F, et al. *Lancet.* 2014;384:1942-1951.

Dual Therapy Success With PI/b + 3TC Regimens

Initial Treatment

Study	Study Design: Initial Treatment
GARDEL[a]	[LPV/r + 3TC] vs [LPV/r + 3TC *or* LPV/r + FTC + 1 NRTI]: the dual regimen had similar efficacy and better tolerability than the triple regimen through 96 weeks[b]
ANDES[c,d]	[DRV/r + 3TC] vs [DRV/r + TDF/3TC]: phase 4, the dual-therapy regimen met noninferiority criterion in 145 participants for <400 c/mL at week 24; follow-up of larger study population is ongoing

Integrase-Based 2-Drug Regimens
DTG + 3TC in Treatment-Experienced Patients

Study	Description: Maintenance Treatment
LAMIDOL[a]	Single-arm, multicenter study; 104 initiated DTG + 3TC 97% maintained VL <50 c/mL at week 40 of dual therapy, no resistance emergence
ASPIRE[b]	Phase 2, randomized, pilot study vs standard triple therapy (N = 90) No difference in success rates at week 24, no resistance emergence
TANGO*	DTG + 3TC: switch study in patients receiving TAF-containing triple therapy

SWORD og GEMINI 1og 2

THE LANCET

ARTICLES | VOLUME 391, ISSUE 10123, P839-849, MARCH 03, 2018

Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3, randomised, non-inferiority SWORD-1 and SWORD-2 studies

Josep M Llibre, MD • Chien-Ching Hung, MD • Cynthia Brinson, MD • Francesco Castelli, MD • Pierre-Marie Girard, MD • Lesley P Kahl, PhD • et al. Show all authors

Published: January 05, 2018 • DOI: https://doi.org/10.1016/S0140-6736(17)33095-7 • Check for updates

THE LANCET

ARTICLES | VOLUME 393, ISSUE 10167, P143-155, JANUARY 12, 2019

Dolutegravir plus lamivudine versus dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials

Prof Pedro Cahn, MD • Prof Juan Sierra Madero, MD • José Ramón Arribas, MD • Andrea Antinori, MD • Roberto Ortiz, MD • Amanda E Clarke, BM • et al. Show all authors

Published: November 09, 2018 • DOI: https://doi.org/10.1016/S0140-6736(18)32462-0 • Check for updates

Dolutegravir and lamivudine maintenance therapy in HIV-1 virologically suppressed patients: results of the ANRS 167 trial (LAMIDOL)

Véronique Joly ✉, Charles Burdet, Roland Landman, Marie Vigan, Charlotte Charpentier, Christine Katlama, André Cabié, Aida Benalycherif, Gilles Peytavin, Patrick Yeni ... Show more

Journal of Antimicrobial Chemotherapy, Volume 74, Issue 3, March 2019, Pages 739–745,

The End