Track 5: Adaptive Trial Design
(Complex Clinical Trial Design)

Clinical utility of phase 3 adaptive platform trials: Pandemics and peacetime

Prof David Lye

Director, Infectious Disease Research and Training Office,
National Centre for Infectious Disease (NCID)
Deputy Executive Director, Programme for Research in Epidemic Preparedness and Response (PREPARE)
Professor, Lee Kong Chian School of Medicine, NTU &
NUS Yong Loo Lin School of Medicine

Adaptive platform trials

- REMAP-CAP
- SNAP
- UK RECOVERY
- NIH ACTT 1-4
- NIH ACTIV 1-6

US NIH ACTT trials

Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

N Engl J Med 2020;383:1813-26.

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

A.C. Kalil, T.F. Patterson, A.K. Mehta, K.M. Tomashek, C.R. Wolfe, V. Ghazaryan, V.C. Marconi, G.M. Ruiz-Palacios, L. Hsieh, S. Kline, V. Tapson, N.M. Iovine, M.K. Jain, D.A. Sweeney, H.M. El Sahly, A.R. Branche, J. Regalado Pineda, D.C. Lye, U. Sandkovsky, A.F. Luetkemeyer, S.H. Cohen, R.W. Finberg, P.E.H. Jackson, B. Taiwo, C.I. Paules, H. Arguinchona, N. Erdmann, N. Ahuja, M. Frank, M. Oh, E.-S. Kim, S.Y. Tan, R.A. Mularski, H. Nielsen, P.O. Ponce, B.S. Taylor, L.A. Larson, N.G. Rouphael, Y. Saklawi, V.D. Cantos, E.R. Ko, J.J. Engemann, A.N. Amin, M. Watanabe, J. Billings, M.-C. Elie, R.T. Davey, T.H. Burgess, J. Ferreira, M. Green, M. Makowski, A. Cardoso, S. de Bono, T. Bonnett, M. Proschan, G.A. Deye, W. Dempsey, S.U. Nayak, L.E. Dodd, and J.H. Beigel, for the ACTT-2 Study Group Members*

N Engl J Med 2021;384:795-807.

Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-bind, randomised, placebo-controlled, phase 3 trial

*Andre C Kalil, Aneesh K Mehta, Thomas F Patterson, Nathaniel Erdmann, Carlos A Gomez, Mamta K Jain, Cameron R Wolfe, Guillermo M Ruiz-Palacios, Susan Kline, Justino Regalado Pineda, Anne F Luetkemeyer, Michelle S Harkins, Patrick E H Jackson, Nicole M Iovine, Victor F Tapson, Myoung-don Oh, Jennifer A Whitaker, Richard A Mularski, Catharine I Paules, Dilek Ince, Jin Takasaki, Daniel A Sweeney, Uriel Sandkovsky, David L Wyles, Elizabeth Hohmann, Kevin A Grimes, Robert Grossberg, Maryrose Laguio-Vila, Allison A Lambert, Diego Lopez de Castilla, Eu Suk Kim, LuAnn Larson, Claire R Wan, Jessica J Traenkner, Philip O Ponce, Jan E Patterson, Paul A Goepfert, Theresa A Sofarelli, Satish Mocherla, Emily R Ko, Alfredo Ponce de Leon, Sarah B Doernberg, Robert L Atmar, Ryan C Maves, Fernando Dangond, Jennifer Ferreira, Michelle Green, Mat Makowski, Tyler Bonnett, Tatiana Beresnev, Varduhi Ghazaryan, Walla Dempsey, Seema U Nayak, Lori Dodd, Kay M Tomashek, John H Beigel, on behalf of the ACTT-3 study group members**

Lancet Respir Med 2021; 9: 1365-76

Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a randomised, double-blind, double placebo-controlled trial

*Cameron R Wolfe, Kay M Tomashek, Thomas F Patterson, Carlos A Gomez, Vincent C Marconi, Mamta K Jain, Otto O Yang, Catharine I Paules, Guillermo M Ruiz Palacios, Robert Grossberg, Michelle S Harkins, Richard A Mularski, Nathaniel Erdmann, Uriel Sandkovsky, Eyad Almasri, Justino Regalado Pineda, Alexandra W Dretler, Diego Lopez de Castilla, Angela R Branche, Pauline K Park, Aneesh K Mehta, William R Short, Susan L F McLellan, Susan Kline, Nicole M Iovine, Hana M El Sahly, Sarah B Doernberg, Myoung-don Oh, Nikhil Huprikar, Elizabeth Hohmann, Colleen F Kelley, Mark Holodniy, Eu Suk Kim, Daniel A Sweeney, Robert W Finberg, Kevin A Grimes, Ryan C Maves, Emily R Ko, John J Engemann, Barbara S Taylor, Philip O Ponce, LuAnn Larson, Dante Paolo Melendez, Allan M Seibert, Nadine G Rouphael, Joslyn Strebe, Jesse L Clark, Kathleen G Julian, Alfredo Ponce de Leon, Anabela Cardoso, Stephanie de Bono, Robert L Atmar, Anuradha Ganesan, Jennifer L Ferreira, Michelle Green, Mat Makowski, Tyler Bonnett, Tatiana Beresnev, Varduhi Ghazaryan, Walla Dempsey, Seema U Nayak, Lori E Dodd, John H Beigel, Andre C Kalil, for the ACTT-4 Study Group**

Lancet Respir Med 2022

Published Online
May 23, 2022

ACTT trial milestones

Milestone/Metric	Total (if applicable)	ACTT-1	ACTT-2	ACTT-3	ACTT-4
#of sites that enrolled	93	66	67	63	67
Countries	10	10	8	5	5
Number Enrolled	4,074	1,062	1,033	969	1,010
Protocol finalized		18-Feb-2020	1-May-2020	15-Jul-2020	10-Nov-2020
First Subject Enrolled		21-Feb-2020	8-May-2020	5-Aug-2020	1-Dec-2020
Last randomization		20Aug2020	1-Jul-2020	11-Nov-2020	13-Apr-2021
Enrollment period (days)		59	54	98	133
FSFV to LSLV (days)	avg = 118.5d	90	84	138	168

Platform Trials — Beware the Noncomparable Control Group

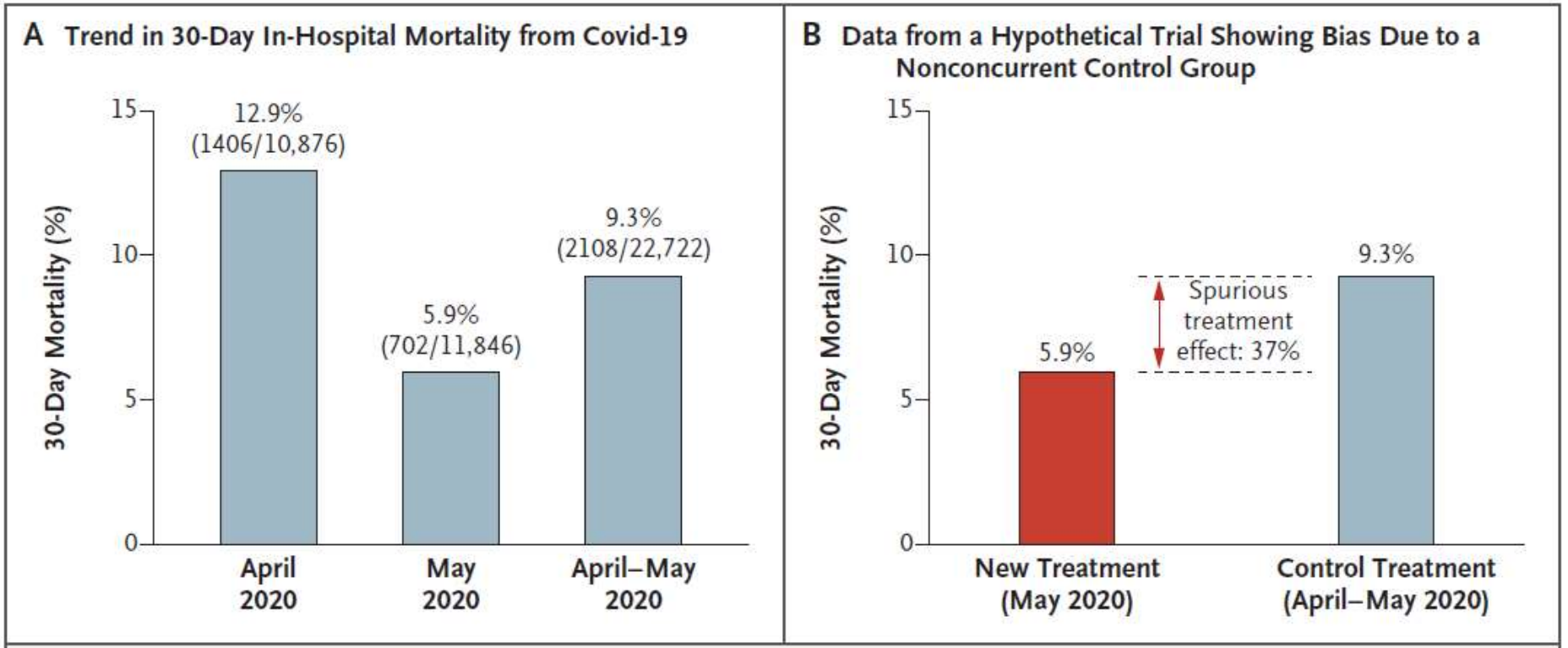


Figure 1. Hypothetical Example of How Nonconcurrent Randomization Could Bias the Results of a Trial.

Panel A shows the 30-day in-hospital mortality from Covid-19 in April 2020 (12.9% [SE, 0.3]), in May 2020 (5.9% [SE, 0.2]), and over both months (9.3 [SE, 0.2]) (data are from eFig. 2B in Asch et al.[2]). Panel B shows the data from a hypothetical trial for an ineffective new agent used in May 2020 as compared with a control treatment used in April and May 2020. The data show that mortality was lower by 37% with the ineffective new agent than with the control treatment.

Temporal Improvements in COVID-19 Outcomes for Hospitalized Adults: A Post Hoc Observational Study of Remdesivir Group Participants in the Adaptive COVID-19 Treatment Trial

Gail E. Potter, PhD; Tyler Bonnett, MS; Kevin Rubenstein, MS; David A. Lindholm, MD; Rekha R. Rapaka, MD, PhD; Sarah B. Doernberg, MD, MAS; David C. Lye, MBBS; Richard A. Mularski, MD, MSHS, MCR; Noreen A. Hynes, MD, MPH; Susan Kline, MD, MPH; Catharine I. Paules, MD; Cameron R. Wolfe, MBBS, MPH; Maria G. Frank, MD; Nadine G. Rouphael, MD, MSc; Gregory A. Deye, MD; Daniel A. Sweeney, MD; Rhonda E. Colombo, MD, MHS; Richard T. Davey, Jr., MD; Aneesh K. Mehta, MD; Jennifer A. Whitaker, MD, MS; Jose G. Castro, MD; Alpesh N. Amin, MD, MBA; Christopher J. Colombo, MD, MA; Corri B. Levine, PhD, MS, MPH; Mamta K. Jain, MD, MPH; Ryan C. Maves, MD; Vincent C. Marconi, MD; Robert Grossberg, MD; Sameh Hozayen, MD, MSc; Timothy H. Burgess, MD, MPH; Robert L. Atmar, MD; Anuradha Ganesan, MBBS, MPH; Carlos A. Gomez, MD; Constance A. Benson, MD; Diego Lopez de Castilla, MD, MPH; Neera Ahuja, MD; Sarah L. George, MD; Seema U. Nayak, MD; Stuart H. Cohen, MD; Tahaniyat Lalani, MBBS, MHS; William R. Short, MD, MPH; Nathaniel Erdmann, MD, PhD; Kay M. Tomashek, MD, MPH, DTM*; and Pablo Tebas, MD*

Ann Intern Med. doi:10.7326/M22-2116 Annals.org
For author, article, and disclosure information, see end of text.
This article was published at Annals.org on 29 November 2022.

Figure 3. Propensity score–weighted and unweighted survival curves for recovery and mortality in ACTT-1 and ACTT-2.

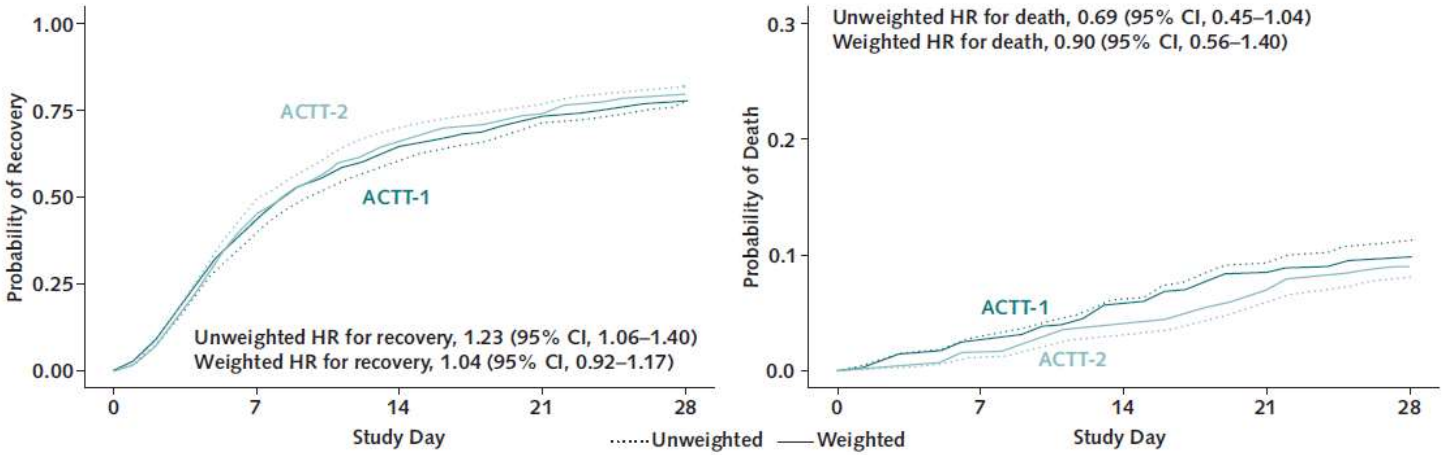
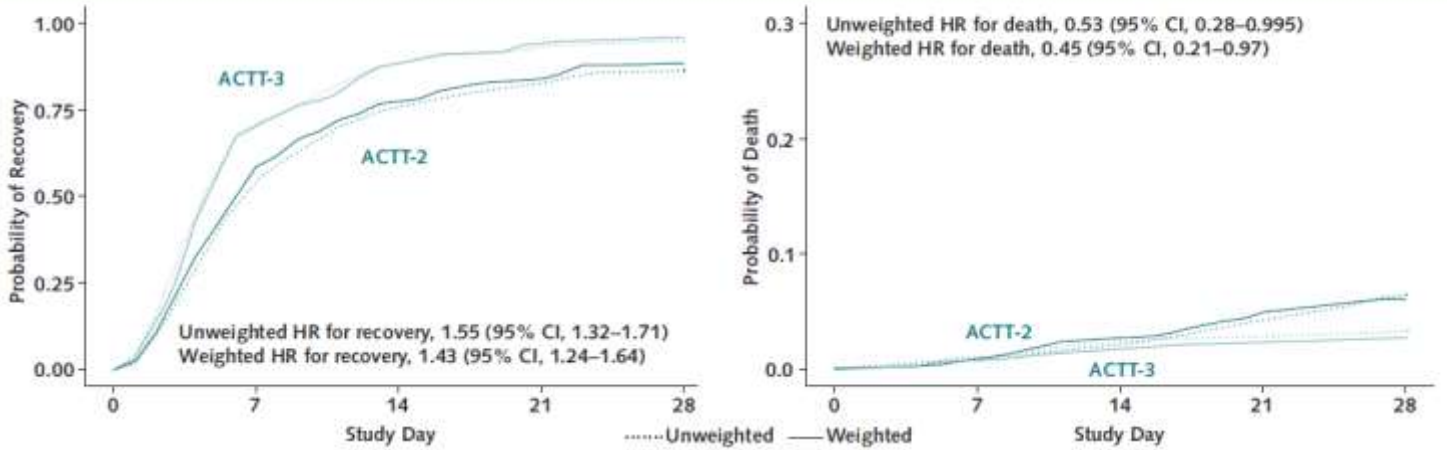


Figure 4. Propensity score–weighted and unweighted survival curves for recovery and mortality for the comparison between ACTT-2 and ACTT-3.



https://www.nih.gov/research-training/medical-research-initiatives/activ#challenge

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ACCELERATING COVID-19 THERAPEUTIC INTERVENTIONS AND VACCINES (ACTIV)

ACTIV

- Therapeutics
- Vaccines
- Surveillance
- Governance
- Publications

On this page

Overview | Challenge | Opportunity | Leadership Organizations | Organization Chart

Overview

US NIH ACTIV-3 trials

A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19

ACTIV-3/TICO LY-CoV555 Study Group*

N Engl J Med 2021;384:905-14.

Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial

ACTIV-3/Therapeutics for Inpatients with COVID-19 (TICO) Study Group†*

Lancet Infect Dis 2021

Published Online
December 23, 2021

Efficacy and Safety of Ensovibep for Adults Hospitalized With COVID-19

A Randomized Controlled Trial

ACTIV-3/TICO Study Group*

Ann Intern Med. doi:10.7326/M22-1503

Tixagevimab–cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial

ACTIV-3–Therapeutics for Inpatients with COVID-19 (TICO) Study Group†*

Lancet Respir Med 2022;
10: 972–84

ACTIV-1: Immune Modulators

- The ACTIV-1 protocol pdf evaluated the safety and efficacy of immune modulators, a class of drugs that help minimize the deleterious effects of an overactive immune response to SARS-CoV-2 infection, when given as an add-on therapy to remdesivir, an antiviral approved for treatment of COVID-19, and the standard of care. The different treatments were assessed in hospitalized adults with moderate to severe COVID-19 disease with respect to illness severity, recovery speed, mortality and hospital resource utilization.

*Cenicriviroc

Infliximab, abatacept

ACTIV-2: Outpatient Monoclonal Antibodies and Other Therapies

- The ACTIV-2 protocol pdf evaluated the safety of monoclonal antibodies and other therapies and their ability to reduce the duration of symptoms in in adults with COVID-19 who were not hospitalized and to test if the treatments could increase the proportion of participants with undetectable virus.
- The ACTIV-2 SCORPIO-HR protocol pdf is evaluating whether an antiviral can reduce the duration of symptoms in adults with COVID-19 who are not hospitalized.

*LY-COV555, SNG001, camostat, BMS-986414, BMS-986413/C135-LS and C144-LS

#BRII-196/8, AZD7442, SAB185

ACTIV-3: Inpatient Monoclonal Antibodies and Other Therapies

- The ACTIV-3 inpatient protocol pdf evaluated monoclonal antibodies and other therapies for safety and efficacy in reducing time to recovery and effects on extrapulmonary complications and respiratory dysfunction in adults hospitalized with COVID-19.
- The ACTIV-3 critical care protocol pdf determined the safety and efficacy of monoclonal antibodies and other therapies in hospitalized patients with life-threatening cases of COVID-19, including those with Acute Respiratory Distress Syndrome (ARDS), a life-threatening condition in which the lungs are severely inflamed and may be unable to maintain sufficient oxygen in the blood.

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ACTIV-4: Antithrombotics

- The ACTIV-4 outpatient protocol pdf investigated whether anticoagulants or antithrombotic therapy could reduce life-threatening cardiovascular or pulmonary complications in newly diagnosed COVID-19 patients who did not require hospital admission.
- The ACTIV-4 inpatient protocol pdf evaluated the safety and effectiveness of using varying doses of heparin, a blood thinner, to prevent or reduce the formation of blood clots and improve outcomes in adults hospitalized COVID-19.
- The ACTIV-4 convalescent protocol pdf investigated the effectiveness and safety of anticoagulants and/or antiplatelets administered to patients who had been discharged from the hospital or are convalescing in reducing thrombotic complications such as heart attack, stroke, blood clots in major veins and arteries, deep vein and pulmonary thrombosis, and death.
- The ACTIV-4 host tissue protocol pdf evaluated the safety and effectiveness of a group of novel drugs at preventing host tissue damage, including potentially life-threatening complications such as blood vessel damage, lung damage, blood clots, and heart injury, in adults hospitalized with COVID-19.

*Fostamatinib, TRV027, TXA127, SGL2 inhibitors, therapeutic heparin, P2Y12 Inhibitors, crizanlizumab

#Heparin and LMW heparin

^Apixaban, aspirin,

ACTIV-5: Big Effect Trial

- The ACTIV-5 protocol evaluated whether certain approved therapies or investigational drugs in late-stage clinical development show promise against COVID-19 in hospitalized patients.

*Lenzilumab

ACTIV-6: Outpatient Repurposed Drugs

- The ACTIV-6 protocol pdf was designed to test the effectiveness of repurposed drugs (drugs that are FDA-approved for non-COVID-19 indications and have known safety profiles) in reducing the duration and severity of symptoms associated with mild-to-moderate COVID-19; drugs that demonstrated efficacy were further evaluated for effects on clinical outcomes (hospitalization, mortality) and long-term COVID-19 symptoms.

*Ivermectin, fluvoxamine, fluticasone

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RECOVERY

RECOVERY is an international clinical trial identifying treatments that may be beneficial for people hospitalised with pneumonia.

RECOVERY started in the UK in early 2020 as the Randomised Evaluation of COVID-19 Therapy, a clinical trial testing treatments for people admitted to hospital with COVID-19 pneumonia. Since then it has identified four life-saving treatments for COVID-19, and shown that several other commonly used treatments were not effective. RECOVERY is now open at sites across Europe, Asia and Africa and in 2023 expanded to test treatments of other types of pneumonia including influenza and non-viral community-acquired pneumonia.

GLOBAL CUMULATIVE TOTALS

49127 Participants

190 Active sites

A range of promising but unproven treatments are being evaluated in RECOVERY. The treatments being tested depend on the cause of pneumonia:

For patients with pneumonia caused by influenza

- oseltamivir (an antiviral treatment)
- baloxavir (an antiviral treatment)
- corticosteroids

For patients with pneumonia caused by other organisms (often referred to as 'community-acquired pneumonia' or CAP)

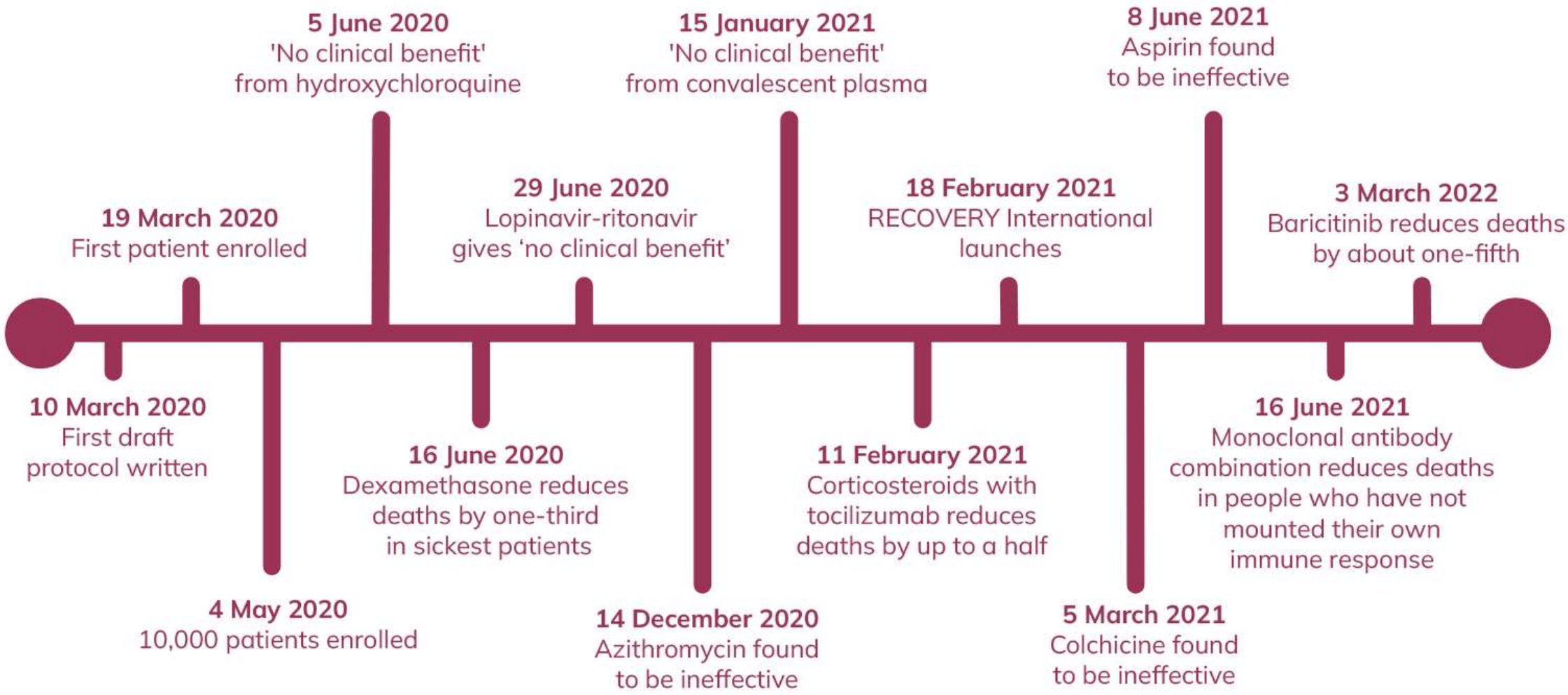
- corticosteroids

UNIVERSITY OF OXFORD

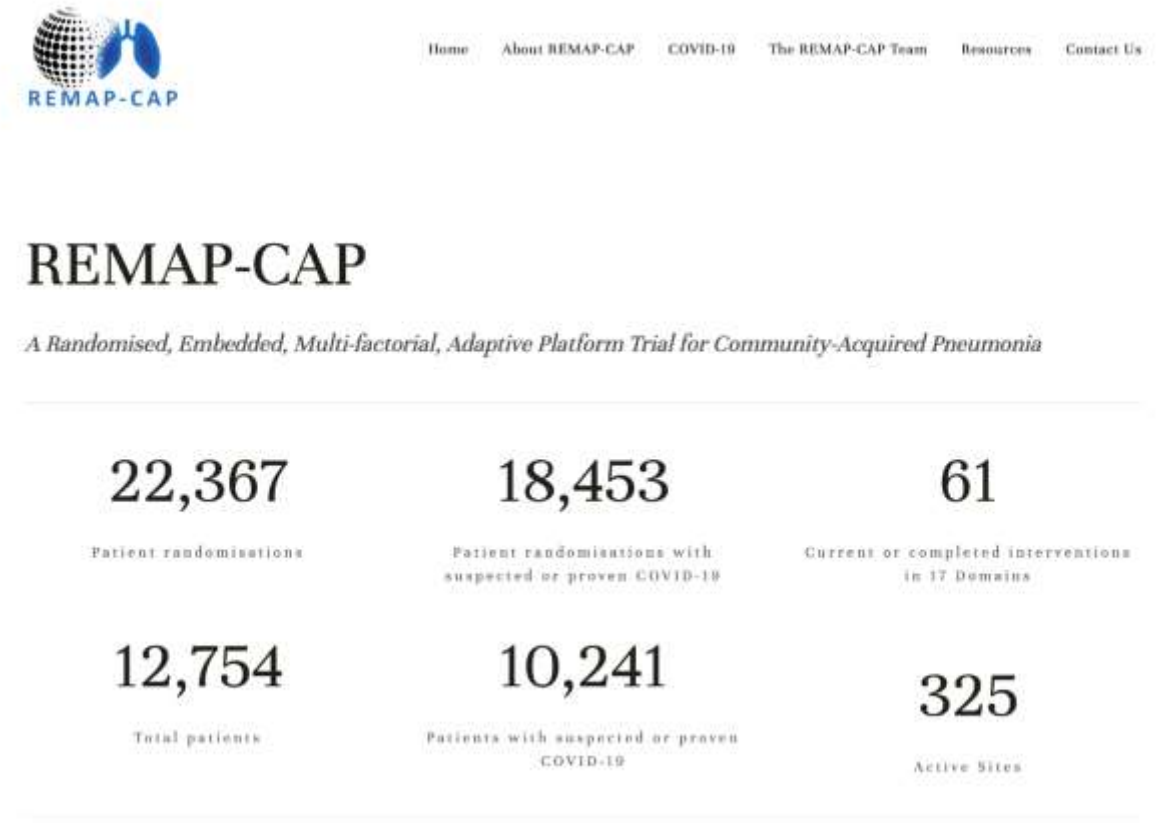
RECOVERY

Randomised Evaluation of COVID-19 Therapy

2 years on



REMAP-CAP
Randomised Embedded Multifactorial Adaptive Platform for Community-acquired Pneumonia



- Antibiotic choice
- Macrolide duration
- Corticosteroid (influenza and bacterial)
- Influenza antiviral
- Anticoagulation- low vs. intermediate dose (COVID-19)
- Ventilation
- Imatinib
- Influenza immune modulation (under construction)
- COVID-19 antiviral (under construction)

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19

The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial

The Writing Committee for the REMAP-CAP Investigators

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Convalescent Plasma on Organ Support–Free Days in Critically Ill Patients With COVID-19

A Randomized Clinical Trial

Writing Committee for the REMAP-CAP Investigators

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Antiplatelet Therapy on Survival and Organ Support–Free Days in Critically Ill Patients With COVID-19

A Randomized Clinical Trial

REMAP-CAP Writing Committee for the REMAP-CAP Investigators

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Effect of Angiotensin-Converting Enzyme Inhibitor and Angiotensin Receptor Blocker Initiation on Organ Support–Free Days in Patients Hospitalized With COVID-19

A Randomized Clinical Trial

Writing Committee for the REMAP-CAP Investigators

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Heterogeneous Treatment Effects of Therapeutic-Dose Heparin in Patients Hospitalized for COVID-19

Ewan C. Goligher, MD, PhD; Patrick R. Lawler, MD, MPH; Thomas P. Jensen, MS; Victor Talisa, PhD; Lindsay R. Berry, PhD; Elizabeth Lorenzi, PhD; Bryan J. McVerry, MD; Chung-Chou Ho Chang, PhD; Eric Leifer, PhD; Charlotte Bradbury, MD, PhD; Jeffrey Berger, MD; Beverly J. Hunt, MD, PhD; Lana A. Castellucci, MD; Lucy Z. Kornblith, MD; Anthony C. Gordon, MD; Colin McArthur, MD; Steven Webb, MD; Judith Hochman, MD; Matthew D. Neal, MD; Ryan Zarychanski, MD, MSc; Scott Berry, PhD; Derek C. Angus, MD, MPH; for the REMAP-CAP, ATTACC, and ACTIV-4a Investigators

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 26, 2021 VOL. 385 NO. 9

Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19

The REMAP-CAP, ACTIV-4a, and ATTACC Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 22, 2021 VOL. 384 NO. 16

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19

The REMAP-CAP Investigators*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19

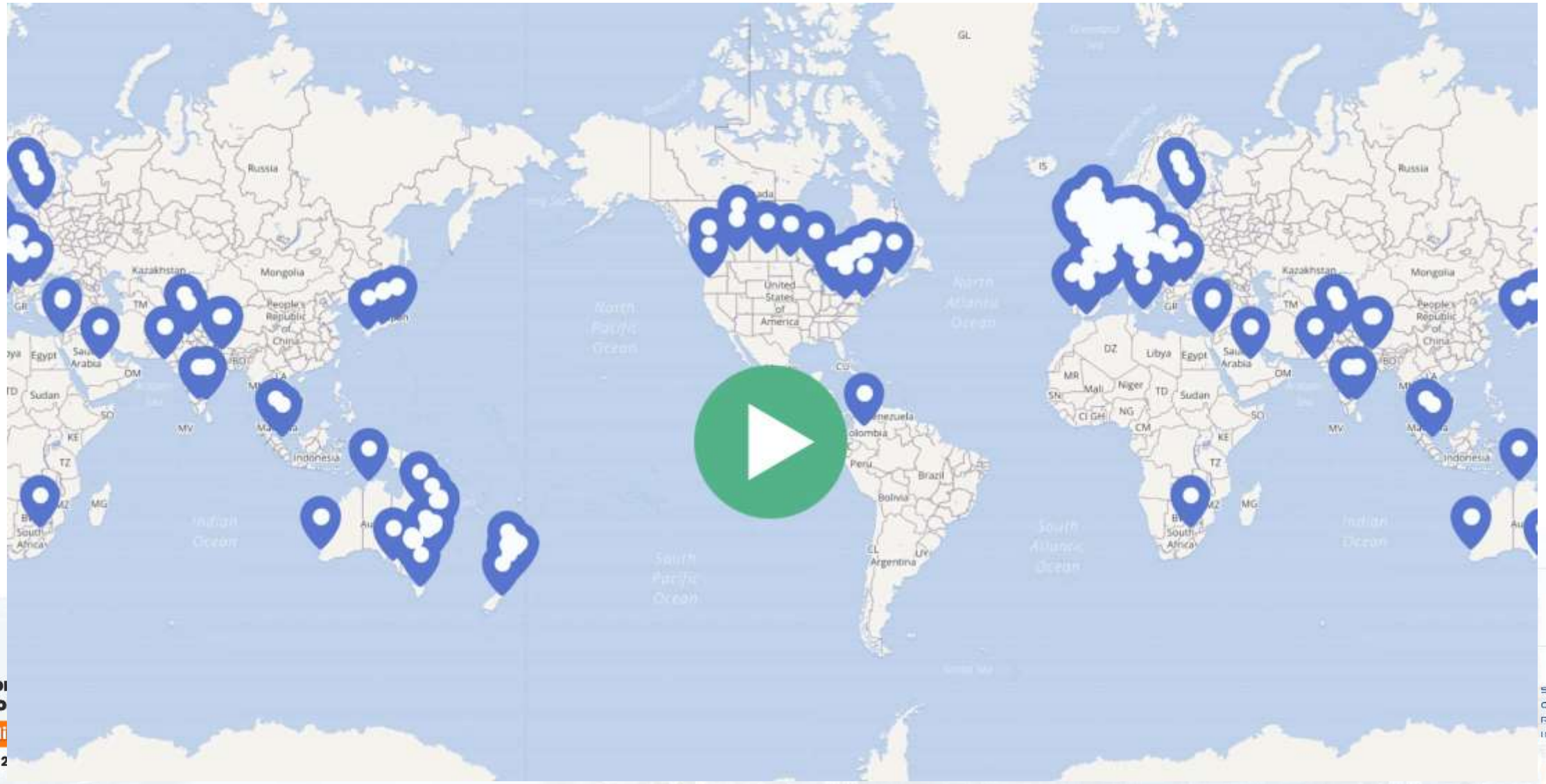
The ATTACC, ACTIV-4a, and REMAP-CAP Investigators*

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Long-term (180-Day) Outcomes in Critically Ill Patients With COVID-19 in the REMAP-CAP Randomized Clinical Trial

Writing Committee for the REMAP-CAP Investigators

More than 300 hospitals in 30 countries



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30 - 31 Jul 2

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Clinical questions in common bacteraemia

- Non-antibiotic-resistant
  - Does IV penicillin work for penicillin-sensitive *S aureus* vs SOC?
  - Does IV cefazolin work for methicillin-sensitive *S aureus* vs SOC?
  - Does early oral antibiotic work for *S aureus* bacteraemia?
  - Duration of treatment for uncomplicated *S aureus* bacteraemia?
  - Does IV cefazolin work for *E coli* and *Klebsiella* bacteraemia vs broader spectrum?
  - Does early oral antibiotic work for gram negative bacteraemia?
  - Duration of antibiotic for gram negative bacteraemia?
- Antibiotic-resistant
  - Does cefepime work for ESBL bacteraemia?
  - Does piperacillin-tazobactam or cefepime work for AmpC bacteraemia?
  - What is optimal antibiotic for XDR *Acinetobacter* bacteraemia?
  - What is optimal antibiotic for carbapenemase producing Enterobacterales bacteraemia?
  - Are combination antibiotics better than monotherapy for *Pseudomonas* bacteraemia?

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

Dafna Yahav,[1,2] Erica Franceschini,[3] Fidi Koppel,[4] Adi Turjeman,[2,5] Tanya Babich,[2,5] Roni Bitterman,[4] Ami Neuberger,[4,6] Nesrin Ghanem-Zoubi,[4] Antonella Santoro,[3] Noa Eliakim-Raz,[1,2] Barak Pertzov,[5] Tali Steinmetz,[5] Anat Stern,[4] Yaakov Dickstein,[4] Elias Maroun,[4] Hiba Zayyad,[4] Jihad Bishara,[1,2] Danny Alon,[7] Yonatan Edel,[2,8] Elad Goldberg,[9] Claudia Venturelli,[3] Cristina Mussini,[3] Leonard Leibovici,[2,5] Mical Paul[4,6]; for the Bacteremia Duration Study Group*

Clinical Infectious Diseases® 2018;XX(XX):1–8

Table 2. 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
Extended hospitalization beyond 14 d	15 (4.9)	19 (6.4)	−1.5 (−5.1 to 2.2)	.483
Distant complications	2 (0.7)	1 (0.3)	…	1.0
Relapse of bacteremia	8 (2.6)	8 (2.7)	−0.07 (−2.6 to 2.5)	.957
Suppurative complications	16 (5.2)	10 (3.4)	1.8 (−1.4 to 5.1)	.257
14-d mortality	7 (2.3)	4 (1.3)	0.95 (−1.42 to 3.44)	.288
28-d mortality	15 (4.9)	13 (4.4)	0.54 (−2.98 to 4.06)	.753
New clinically or microbiologically documented infection	70 (22.9)	68 (22.8)	0.06 (−6.6 to 6.8)	.987
Functional capacity: needs assistance/dependent in ADL or bedridden at 30 d	150 (51.4) (n = 292)	163 (57.2) (n = 285)	−5.8 (−13.9 to 2.3)	.031
Resistance development	33 (10.8)	29 (9.7)	1.0 (−3.7 to 5.9)	.690
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**
Adverse events				
Acute kidney injury	14 (4.6)	12 (4.0)	0.5 (−2.7 to 3.8)	.842
Liver function abnormalities	16 (5.2)	20 (6.7)	−1.5 (−5.3 to 2.3)	.494
Diarrhea during hospital stay	17 (5.6)	23 (7.7)	−2.2 (−6.1 to 1.8)	.285
Diarrhea until day 90[a]	49 (16)	54 (18.1)	−2.1 (−8.1 to 3.9)	.491
Rash	2 (0.7)	4 (1.4)	…	.445
Clostridium difficile infection	3 (1.0)	1 (0.3)	…	.322

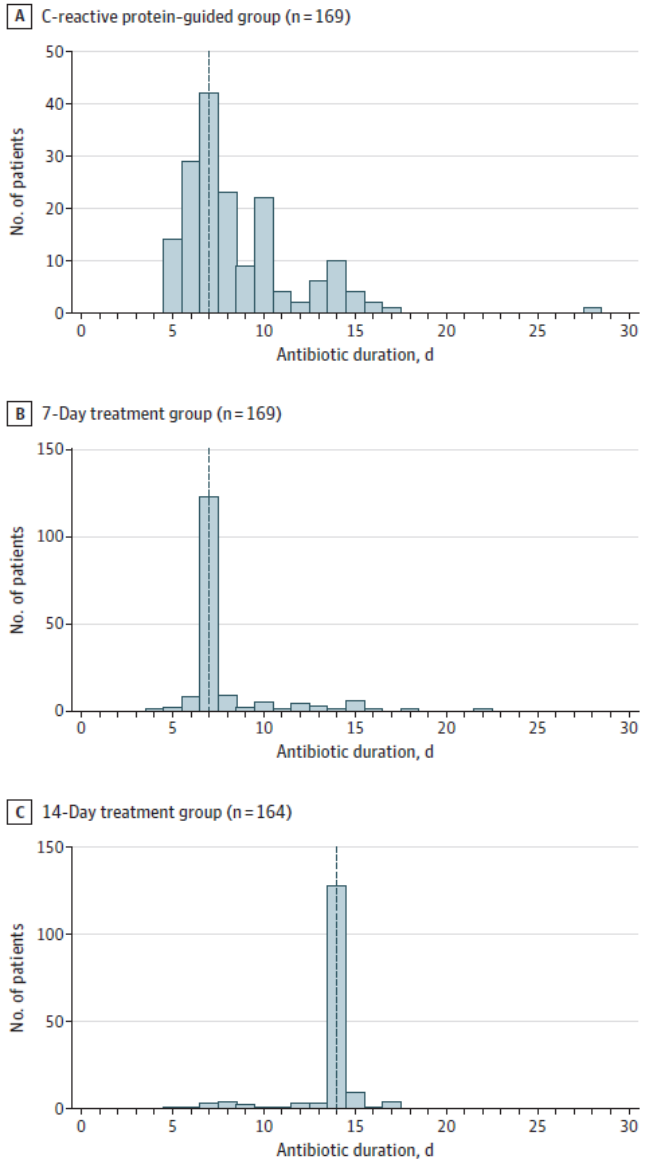
Effect of C-Reactive Protein–Guided Antibiotic Treatment Duration, 7-Day Treatment, or 14-Day Treatment on 30-Day Clinical Failure Rate in Patients With Uncomplicated Gram-Negative Bacteremia

A Randomized Clinical Trial

Elodie von Dach, PhD; Werner C. Albrich, MD; Anne-Sophie Brunel, MD; Virginie Prendki, MD; Clémence Cuvelier, MD; Domenica Flury, MD; Angèle Gayet-Ageron, MD, PhD; Benedikt Huttner, MD; Philipp Kohler, MD; Eva Lemmenmeier, MD; Shawna McCallin, PhD; Anne Rossel, MD; Stephan Harbarth, MD; Laurent Kaiser, MD; Pierre-Yves Bochud, MD; Angela Huttner, MD

JAMA. 2020;323(21):2160-2169.

Figure 2. Durations of Antibiotic Therapy in the Primary Analysis Set in a Study of the Effect of C-Reactive Protein (CRP)–Guided Antibiotic Treatment Duration, 7-Day Treatment, or 14-Day Treatment on Clinical Failure in Patients With Uncomplicated Gram-Negative Bacteremia



The dotted vertical line indicates the median antibiotic duration for that group. The patient in the CRP group who received 28 days of antibiotics was diagnosed with multiple kidney abscesses the day after randomization, so CRP was not used to guide therapy.

Table 3. Clinical Outcomes in a Study of the Effect of C-Reactive Protein (CRP)–Guided, 7-Day, or 14-Day Antibiotic Treatment Duration on Clinical Failure in Patients With Gram-Negative Bacteremia

Outcome	Antibiotic therapy duration group, No. (%)			CRP-guided vs 14 d		7 d vs 14 d	
	CRP-guided (n = 169)	7 d (n = 169)	14 d (n = 165)	Difference, % (1-sided 97.5% CI)	*P* value[a]	Difference, % (1-sided 97.5% CI)	*P* value[a]
Primary outcome							
Clinical response through day 30				−3.1 (−∞ to 1.1)	<.001	1.1 (−∞ to 6.3)	<.001
Clinical success	160 (97.6)	155 (93.4)	154 (94.5)				
Clinical failure	4 (2.4)	11 (6.6)	9 (5.5)				
Recurrent bacteremia	0	1 (9)[a]	2 (22)				
Suppurative local complication	0	2 (18)[b]	1 (11)				
Distal complication	0	0	0				
Targeted therapy restart	2 (50)	3 (27)	2 (22)				
30-d all-cause mortality[c]	2 (50)	6 (55)	4 (44)				
Missing[d]	5 (2.9)	3 (1.8)	2 (1.2)				
Secondary outcomes							
Clinical response through day 60				−1.8 (−∞ to 3.7)	<.001	2.6 (−∞ to 8.9)	.010
Clinical success	146 (94.2)	141 (89.8)	146 (92.4)				
Clinical failure	9 (5.8)	16 (10.2)	12 (7.6)				
Recurrent bacteremia	0	1 (6)[b]	2 (17)				
Suppurative local complication	0	1 (6)[b]	1 (8)				
Distal complication	0	0	0				
Targeted therapy restart	7 (78)	9 (56)	5 (42)				
30-d all-cause mortality[c]	2 (22)	6 (38)	4 (33)				
Missing[d]	9 (5.3)	7 (4.1)	3 (1.8)				
Death after day 30	5 (3.0)	5 (3.0)	4 (2.4)				
Clinical response through day 90				−3.5 (−∞ to 2.9)	<.001	0.1 (−∞ to 7.0)	.002
Clinical success	133 (93.0)	135 (89.4)	137 (89.5)				
Clinical failure	10 (7.0)	16 (10.6)	16 (10.5)				
Recurrent bacteremia	0	1 (6)[b]	2 (13)				
Suppurative local complication	0	1 (6)[b]	1 (6)				
Distal complication	0	0	0				
Targeted therapy restart	8 (80)	9 (56)	9 (56)				
30-d all-cause mortality[c]	2 (20)	6 (38)	4 (25)				
Missing[d]	15 (8.9)	10 (5.9)	7 (4.2)				
Death after day 30	11 (6.5)	8 (4.7)	5 (3.0)				

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)

JAMA. 2018;320(10):984-994.

Table 2. Primary Analysis and Subgroup Analyses

	30-d Mortality, No./Total No. (%)		Risk Difference, % (1-Sided 97.5% CI)[a]	*P* Value for Noninferiority
	Piperacillin-Tazobactam	Meropenem		
Primary analysis	23/187 (12.3)	7/191 (3.7)	8.6 (−∞ to 14.5)	.90
Per-protocol analysis	18/170 (10.6)	7/186 (3.8)	6.8 (−∞ to 12.8)	.76
Subgroup analyses[b]				*P* Value for Interaction
OECD country income				
Middle income	8/37 (21.6)	1/35 (2.9)	18.8 (−∞ to 35.0)	.31
High income	15/150 (10.0)	6/156 (3.9)	6.2 (−∞ to 12.5)	
Pitt score				
≥4	5/18 (27.8)	0/9	27.8 (−∞ to 51.3)	.99
<4	18/169 (10.7)	7/182 (3.9)	6.8 (−∞ to 12.8)	
Infecting species				
E coli	17/161 (10.6)	7/166 (4.2)	6.3 (−∞ to 12.6)	.99
K pneumoniae	6/26 (23.1)	0/25	23.1 (−∞ to 42.3)	
Infection				
HAI	18/107 (16.8)	4/107 (3.7)	13.1 (−∞ to 21.8)	.26
Non-HAI	5/80 (6.3)	3/84 (3.6)	2.7 (−∞ to 10.7)	
Appropriate empirical antibiotic therapy				
Appropriate	18/126 (14.3)	5/127 (3.9)	10.3 (−∞ to 18.0)	.70
Inappropriate	5/61 (8.2)	2/64 (3.1)	5.1 (−∞ to 15.2)	
UT vs non-UT source				
UT	7/102 (6.9)	4/128 (3.1)	3.7 (−∞ to 10.7)	.44
Non-UT	16/85 (18.8)	3/63 (4.8)	14.1 (−∞ to 24.5)	
Immune compromise[c]				
Present	10/51 (19.6)	1/40 (2.5)	17.1 (−∞ to 30.5)	.27
Absent	13/136 (9.6)	6/151 (4.0)	5.6 (−∞ to 12.2)	

Association Between Minimum Inhibitory Concentration, Beta-lactamase Genes and Mortality for Patients Treated With Piperacillin/Tazobactam or Meropenem From the MERINO Study

A. Henderson,[1,2] D. L. Paterson,[1] M. D. Chatfield,[1] P. A. Tambyah,[3] D. C. Lye,[4,5,6] P. P. De,[7] R. T. P. Lin,[7] K. L. Chew,[8] M. Yin,[3] T. H. Lee,[4,5,6] M. Yilmaz,[9] R. Cakmak,[9] T. H. Alenazi,[10] Y. M. Arabi,[10] M. Falcone,[11] M. Bassetti,[12] E. Righi,[13,14] B. A. Rogers,[15,16] S. S. Kanj,[17] H. Bhally,[18] J. Iredell,[19,20] M. Mendelson,[21] T. H. Boyles,[21] D. F. M. Looke,[2,22] N. J. Runnegar,[2,22] S. Miyakis,[23,24,25] G. Walls,[26] M. A. I. Khamis,[27] A. Zikri,[27] A. Crowe,[28,29] P. R. Ingram,[30,31,32] N. Daneman,[33] P. Griffin,[22,34,35] E. Athan,[36] L. Roberts,[37] S. A. Beatson,[37] A. Y. Peleg,[38,39] K. Cottrell,[1] M. J. Bauer,[1] E. Tan,[1] K. Chaw,[40,41,42] G. R. Nimmo,[43] T. Harris-Brown,[1] and P. N. A. Harris[1,43]; For the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

Clinical Infectious Diseases® 2021;73(11):e3842–50

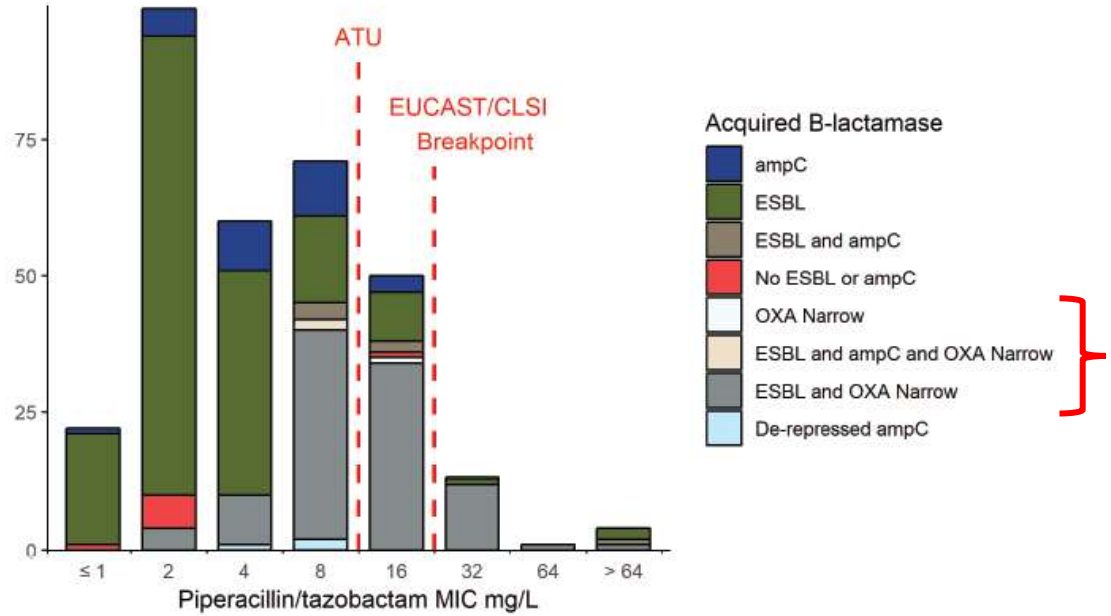


Figure 2. Piperacillin/Tazobactam resistome. Abbreviations: ATU, area of technical uncertainty; CLSI, Clinical and Laboratory Standards Institute; ESBL, extended spectrum β-lactamase; MIC, minimum inhibitory concentration.

Change in CLSI breakpoints

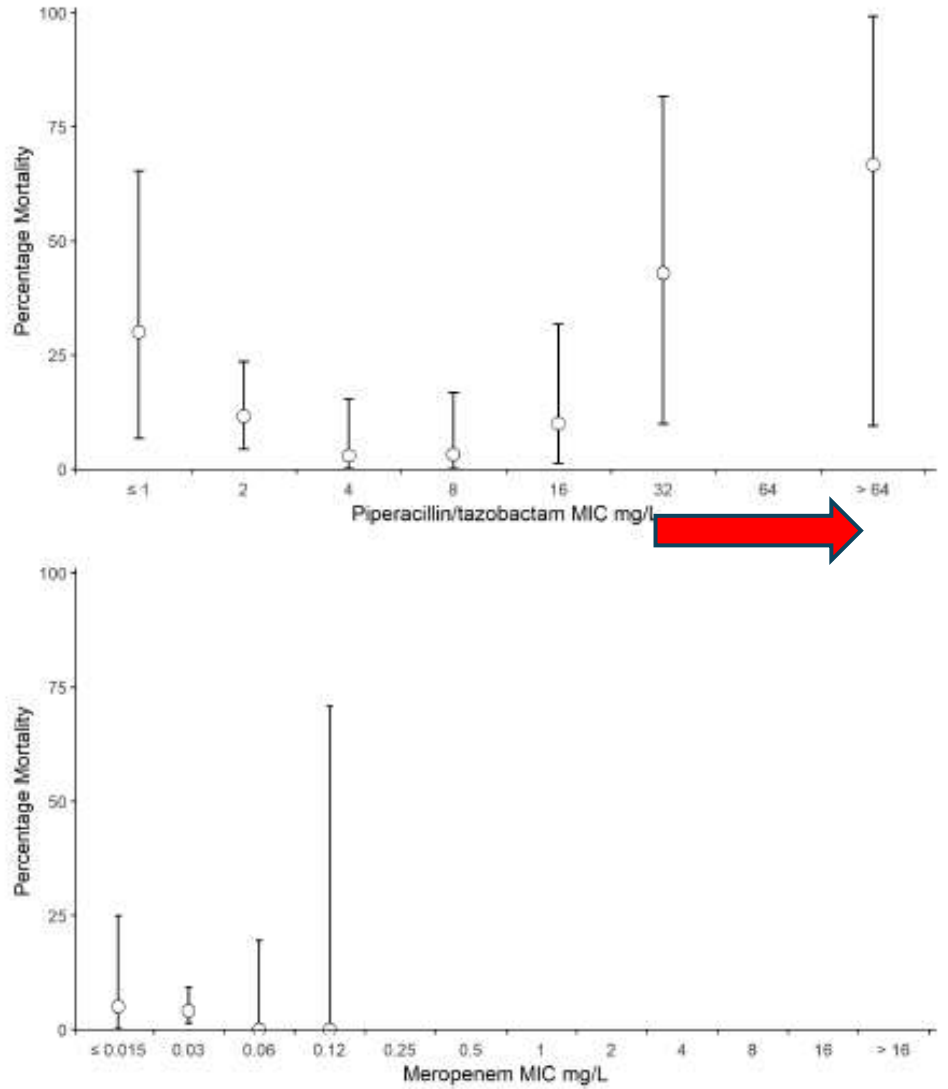


Figure 3. *A*, Percent mortality piperacillin/tazobactam. *B*, Percent mortality meropenem. Abbreviation: MIC, minimum inhibitory concentration.

Piperacillin–tazobactam versus meropenem for treatment of bloodstream infections caused by third-generation cephalosporin-resistant Enterobacteriaceae: a study protocol for a non-inferiority open-label randomised controlled trial (PeterPen)

Roni Bitterman ,[1,2] Fidi Koppel,[1] Cristina Mussini,[3] Yuval Geffen,[4] Michal Chowers,[5,6] Galia Rahav,[7,8] Lior Nesher,[9,10] Ronen Ben-Ami,[6,11] Adi Turjeman,[6,12] Maayan Huberman Samuel,[12] Matthew P Cheng,[13] Todd C Lee,[13] Leonard Leibovici,[6,12] Dafna Yahav,[6,14] Mical Paul[1,2]

BMJ Open 2021;**11**:e040210.

While the MERINO trial was the first RCT comparing PTZ with meropenem for ESBL bacteremia, allowing estimation of effects without selection bias, there are several reasons justifying further RCTs. The threefold difference in mortality between arms is striking, and such a mortality difference was never observed previously in a randomised comparison between antibiotics. Such results warrant confirmation given the profound practice implications. Several factors in the trial design favoured non-inferiority, including the recruitment of patients with mild sepsis (Median Pitt Score one at randomisation, with 40.7% of patients having resolved signs of infection at randomisation), relatively short duration of the intervention (median 6 days out of the median 13 days of treatment for the bacteremia) and 'contamination' of drug exposure between the two groups, due to use of the comparator for empirical treatment and stepdown therapy after the minimal duration of the intervention of 4 days. Considering these, the large difference in mortality observed between groups is even more surprising.

Several factors in the MERINO trial design are notable, primarily the underlying assumptions that informed the non-inferiority sample size calculation. In MERINO, the sample size calculation assumed 14% mortality for meropenem and 10% mortality for PTZ with a 5% non-inferiority margin. This was not included in the initial manuscript but later appeared as an erratum.[12] The a priori assumption that mortality would be 4% lower for PTZ allows for a smaller total sample size but is so reliant on an assumption that is not supported by the observational evidence. Removing that assumption and assuming that PTZ mortality would also be 14% (with the same one-sided alpha 2.5%, 80% power and 10% loss to follow-up) yield a sample size of 1683. Therefore, the MERINO trial as conducted was terminated after recruiting 22.5% of the sample size required under a more realistic estimate of PTZ mortality. An underpowered non-inferiority trial is at high risk of concluding 'could not demonstrate non-inferiority'.

microdilution (BMD) in a central laboratory and found that 17.8% and 6.4% were resistant to PTZ by European Committee on Antimicrobial Susceptibility Testing (EUCAST) and Clinical and Laboratory Standards Institute (CLSI) criteria, respectively.[18] Also blaOXA-1 genes were highly prevalent (67%) in the MERINO trial.[11] This may explain the high failure rate seen with PTZ, as co-carriage of OXA-1 and CTX-M-15 (the most common ESBL gene in the MERINO trial) is associated with PTZ MICs as high as 8–16 µg/mL.[20] These MICs, although still susceptible, have a much higher chance (up to 20%) for inadequate PTZ pharmacokinetics when using the dosing strategies employed in MERINO.[21]

SINGAPORE CLINICAL RESEARCH INSTITUTE

Meropenem Versus Piperacillin-Tazobactam for Definitive Treatment of Bloodstream Infections Caused by AmpC β-Lactamase–Producing *Enterobacter* spp, *Citrobacter freundii*, *Morganella morganii*, *Providencia* spp, or *Serratia marcescens*: A Pilot Multicenter Randomized Controlled Trial (MERINO-2)

Adam G. Stewart,[1,2] David L. Paterson,[1,2] Barnaby Young,[3,4,5] David C. Lye,[3,4,5,6] Joshua S. Davis,[7,8] Kellie Schneider,[7] Mesut Yilmaz,[9] Rumeysa Dinleyici,[9] Naomi Runnegar,[10] Andrew Henderson,[1,10] Sophia Archuleta,[6,11] Shirin Kalimuddin,[12,13] Brian M. Forde,[1,14,15] Mark D. Chatfield,[1] Michelle J. Bauer,[1] Jeffrey Lipman,[1,16,17] Tiffany Harris-Brown,[1] and Patrick N. A. Harris[1,18]; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

Open Forum Infectious Diseases®2021

Table 3. Primary Analysis and Subgroup Analysis

Analysis	Primary Outcome, No./Total No. (%)		Risk Difference, % (2-Sided 95% CI)	*P* Value
	PTZ	Meropenem		
Primary analysis	11/38 (29)	7/34 (21)	8.4 (–11 to 28)	.41
Per-protocol analysis	8/32 (25)	6/32 (19)	6.2 (–14 to 26)	.55
Subcomponents of the primary outcome				
Death	0/38 (0)	2/34 (6%)	5.9 (–13 to 2)	.13
Clinical failure	8/38 (21)	4/34 (12)	9.3 (–8 to 26)	.29
Microbiological failure	5/38 (13)	0/34 (0)	13.2 (2 to 24)	.03
Microbiological relapse	0/38 (0)	3/34 (9)	8.8 (–18 to 1)	.06
Subgroup analyses				
Infecting species				
Enterobacter spp	5/18 (28)	1/14 (7)	20.7 (–4 to 45)	.14
Other	6/14 (43)	6/14 (43)	0.0 (–28 to 28)	1.0
Urinary tract vs non–urinary tract source				
Urinary tract	1/8 (12)	1/6 (17)	–4.2 (–42 to 33)	.83
Non–urinary tract	10/30 (33)	6/28 (21)	11.9 (–11 to 35)	.31
Infection				
Healthcare-associated	11/35 (31)	5/24 (21)	10.6 (–12 to 33)	.37
Non–health care associated	0/3 (0)	0/3 (0)	…	
Appropriate empirical antibiotic therapy				
Appropriate	10/35 (29)	7/33 (21)	7.4 (–13 to 28)	.48
Inappropriate	1/3 (33)	0/1 (0)	33.3 (–20 to 87)	.50
Immunocompromise				
Present	1/6 (17)	1/5 (20)	–3.3 (–49 to 43)	.89
Absent	10/32 (31)	6/29 (21)	–10.5 (–11 to 32)	.35
qSOFA ≥2				
Yes	2/9 (22)	2/9 (22)	0.0 (–38 to 38)	1.0
No	9/29 (31)	5/25 (20)	11.0 (–12.0 to 34)	.36
Total duration of study drug				
<5 d	6/20 (30)	2/17 (12)	18 (–7 to 43)	.18
≥5 d	5/18 (28)	5/17 (30)	–16 (–32 to 28)	.91

Abbreviations: CI, confidence interval; PZT, piperacillin-tazobactam; qSOFA, quick Sequential Organ Failure Assessment.

Switch to oral antibiotics in Gram-negative bacteraemia: a randomized, open-label, clinical trial

Ali S. Omrani [1,2,3,*], Sulieman H. Abujarir [1,2,†], Fatma Ben Abid [1,2,4,†], Shahd H. Shaar [1,†], Mesut Yilmaz [5], Adila Shaukat [1,6], Mussad S. Alsamawi [1,7], Mohamed S. Elgara [8], Mohamed Islam Alghazzawi [8], Khaled M. Shunnar [8], Ahmed Zaqout [1,2], Yasser M. Aldeeb [1,7], Wadha Alfouzan [9,10], Muna A. Almaslamani [1,2], SOAB Study Group[††]

Clinical Microbiology and Infection 30 (2024) 492–498

Primary and secondary outcomes

Outcome	Population	IV Group	Oral Group	Difference (95% CI)[a]
Treatment failure within 90 d	ITT[b]	24 (28.2%)	22 (24.7%)	−3.7% (−16.6% to 9.3%)
	mITT[c]	21 (25.6%)	18 (21.7%)	−3.7% (−16.6% to 9.2%)
90-d all-cause mortality	ITT[b]	6 (7.1%)	7 (7.9%)	0.8% (−7.0% to 8.6%)
	mITT[c]	3 (3.7%)[d]	3 (3.6%)[e]	−0.04% (−5.8% to 5.7%)
Additional antimicrobial therapy	ITT[b]	13 (15.3%)	8 (9.0%)	−6.8% (−16.1% to 2.6%)
	mITT[c]	10 (12.2%)	4 (4.8%)	−7.1% (−15.5% to 1.3%)
Microbiological relapse	ITT[b]	13 (15.3%)	10 (11.2%)	−4.1% (−14.1% to 5.9%)
	mITT[c]	10 (12.2%)	6 (7.2%)	−4.8% (−14.0% to 4.3%)
Infection-related re-admission	ITT[b]	12 (14.1%)	19 (21.3%)	7.2% (−4.0% to 18.3%)
	mITT[c]	9 (11.0%)	15 (18.1%)	7.5% (−3.1% to 18.1%)

Early oral stepdown antibiotic therapy versus continuing intravenous therapy for uncomplicated Gram-negative bacteraemia (the INVEST trial): study protocol for a multicentre, randomised controlled, open-label, phase III, non-inferiority trial

I. Russel Lee[1*], Steven Y. C. Tong[2], Joshua S. Davis[3], David L. Paterson[4], Sharifah F. Syed-Omar[5], Kwong Ran Peck[6], Doo Ryeon Chung[6], Graham S. Cooke[7], Eshele Anak Libau[1], Siti-Nabilah B. A. Rahman[8], Mihir P. Gandhi[8], Luming Shi[8], Shuwei Zheng[9], Jenna Chaung[10], Seow Yen Tan[11], Shirin Kalimuddin[12,13], Sophia Archuleta[14,15] and David C. Lye[1,15,16,17*]

Trials (2022) 23:572

Background: The incidence of Gram-negative bacteraemia is rising globally and remains a major cause of morbidity and mortality. The majority of patients with Gram-negative bacteraemia initially receive intravenous (IV) antibiotic therapy. However, it remains unclear whether patients can step down to oral antibiotics after appropriate clinical response has been observed without compromising outcomes. Compared with IV therapy, oral therapy eliminates the risk of catheter-associated adverse events, enhances patient quality of life and reduces healthcare costs. As current management of Gram-negative bacteraemia entails a duration of IV therapy with limited evidence to guide oral conversion, we aim to evaluate the clinical efficacy and economic impact of early stepdown to oral antibiotics.

Methods: This is an international, multicentre, randomised controlled, open-label, phase III, non-inferiority trial. To be eligible, adult participants must be clinically stable / non-critically ill inpatients with uncomplicated Gram-negative bacteraemia. Randomisation to the intervention or standard arms will be performed with 1:1 allocation ratio. Participants randomised to the intervention arm (within 72 h from index blood culture collection) will be immediately switched to an oral fluoroquinolone or trimethoprim-sulfamethoxazole. Participants randomised to the standard arm will continue to receive IV therapy for at least 24 h post-randomisation before clinical re-assessment and decision-making by the treating doctor. The recommended treatment duration is 7 days of active antibiotics (including empiric therapy), although treatment regimen may be longer than 7 days if clinically indicated. Primary outcome is 30-day all-cause mortality, and the key secondary outcome is health economic evaluation, including estimation of total healthcare cost as well as assessment of patient quality of life and number of quality-adjusted life years saved. Assuming a 30-day mortality of 8% in the standard and intervention arms, with 6% non-inferiority margin, the target sample size is 720 participants which provides 80% power with a one-sided 0.025 α-level after adjustment for 5% drop-out.

27 hospitals in 11 countries

THE INVE$T TRIAL

Chief Investigator:
Professor David Lye

Evaluating the clinical efficacy and economic impact of early switch to oral antibiotics compared with continuing intravenous antibiotics for uncomplicated Gram-negative bacteraemia

Italy
IRCCS San Raffaele Hospital Milan
IRCCS Policlinico di Sant'Orsola Bologna
University Hospital of Pisa
Monaldi Hospital

United Kingdom
Imperial College Healthcare NHS Trust

Spain
Hospital del Mar

Greece
University General Hospital of Patras

Turkey
Medipol Mega University Hospital

South Korea
Samsung Medical Center

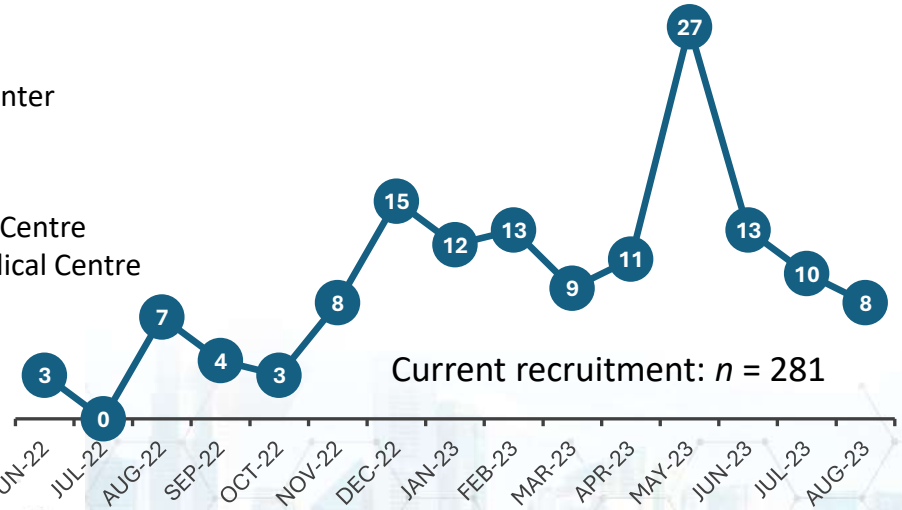
Malaysia
University Malaya Medical Centre
Universiti Kebangsaan Medical Centre
Ampang Hospital
Sungai Buloh Hospital

Lebanon
American University of Beirut Medical Centre

Israel
Rambam Hospital
Sheba Medical Centre

Singapore
Tan Tock Seng Hospital
Singapore General Hospital
National University Hospital
Changi General Hospital
Sengkang General Hospital
Ng Teng Fong General Hospital

Australia
Royal Melbourne Hospital
Royal Brisbane & Women's Hospital
Princess Alexandra Hospital
Gold Coast University Hospital



Current recruitment: *n* = 281

SINGAPORE CLINICAL RESEARCH INSTITUTE

National Centre for Infectious Diseases

Tan Tock Seng HOSPITAL

Similar randomised trials in US and Canada

05/18/2023

PUBLISHED IN HOPKINS CHILDREN'S - SPRING 2023

The amount of funding garnered by **Pranita Tamma**, director of the Pediatric Antimicrobial Stewardship Program at Johns Hopkins Children's Center, and **Sara Cosgrove**, director of the Johns Hopkins Hospital Antimicrobial Stewardship Program, from the Patient-Centered Outcomes Research Institute, to study how best to treat bloodstream infections caused by gram-negative bacteria, such as Escherichia coli. These potentially dangerous infections are most commonly seen in people with underlying chronic medical conditions.

"Traditionally, gram-negative bloodstream infections have been treated with intravenous [IV] antibiotics for the duration of a patient's therapy — either in the hospital or with placement of a vascular catheter to continue treatment at home or a skilled nursing facility," says Tamma. "However, because vascular catheters used to place IV lines can pose a risk of a secondary infection and other complications, and because IV therapy imposes limitations on patient mobility and quality of life, we want to see if oral antibiotic treatment — pills — given at an early stage in the process could achieve outcomes on par with those of IV antibiotics."

The five-year award will support a randomized controlled clinical trial at eight U.S. hospitals involving a study population of approximately 1,200 patients

Sunnybrook researchers have been awarded nearly $6.8M in funding from the Canadian Institutes of Health Research (CIHR) Spring 2022 Clinical Trials Fund.

The Clinical Trials Fund is designed to enhance Canada's clinical trials ecosystem from discovery to implementation, determining which new drugs, treatments, and therapies are safe and effective for the population. In total, CIHR's latest round of funding includes one clinical trials consortium, seven training platforms, and 22 research projects for a total investment of more than $130M.

Congratulations to the three Sunnybrook-led projects.

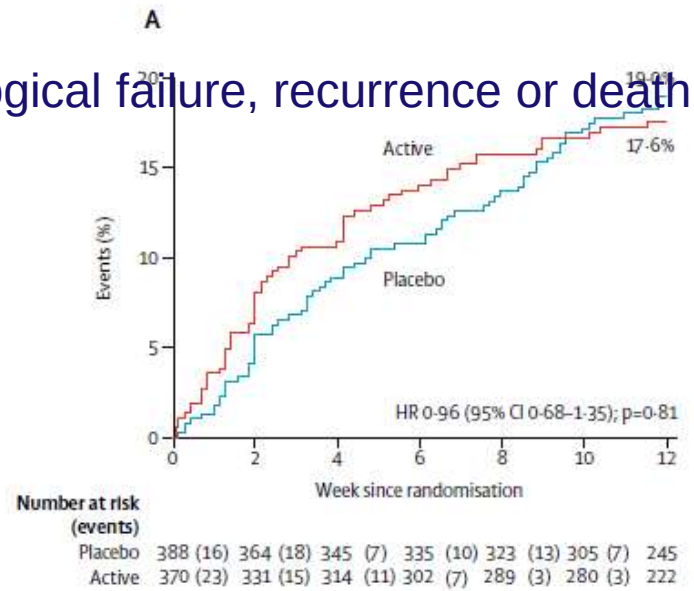
Project: BALANCE+: A Platform Trial for Gram Negative Bloodstream Infections
Principal Investigator: Dr. Nick Daneman
Sunnybrook co-principal Investigator: Dr. Rob Fowler
Funding: $2,919,785

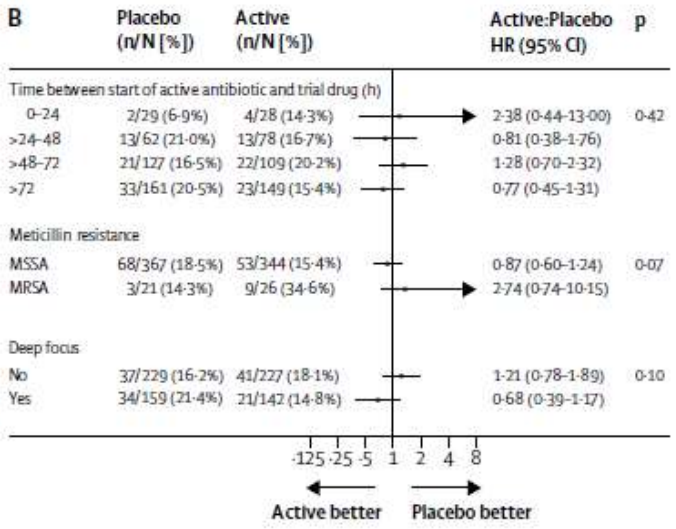
Project overview: »

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

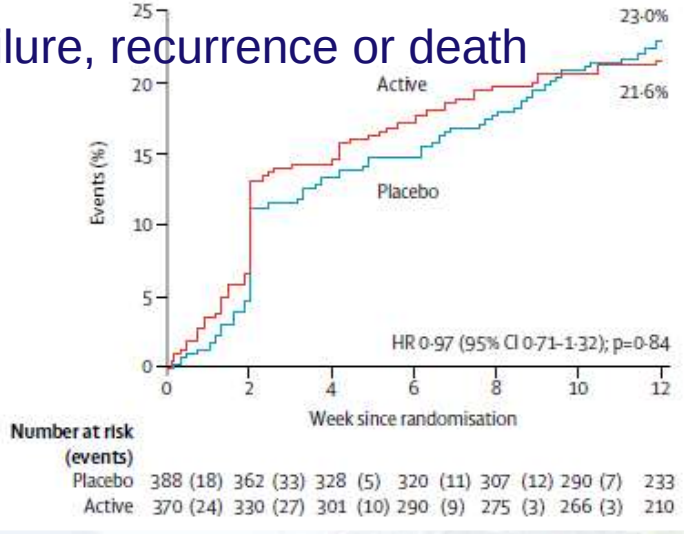
Lancet 2018; 391: 668–78

Bacteriological failure, recurrence or death

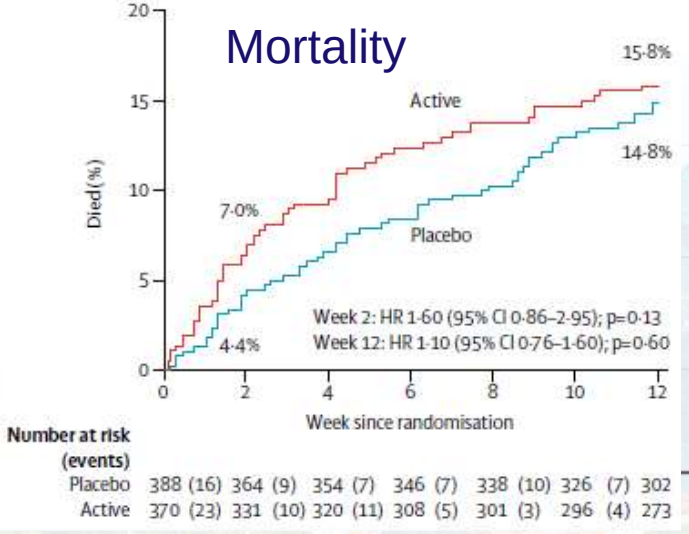




Clinical failure, recurrence or death



Mortality



Cloxacillin plus fosfomycin versus cloxacillin alone for methicillin-susceptible *Staphylococcus aureus* bacteremia: a randomized trial

nature medicine
Received: 27 April 2023
Accepted: 25 August 2023
Published online: 02 October 2023

Table 2 | Primary and secondary endpoints in the intention-to-treat and per-protocol populations

Intention-to-treat population	Cloxacillin plus fosfomycin (*n*=104)	Cloxacillin alone (*n*=110)	Risk difference % (95% CI)	*P* value*
Primary endpoint				
Treatment success at day 7	83 (79.8%)	82 (74.5%)	5.3 (−5.95–16.48)	0.360
Secondary endpoints				
All-cause mortality at day 7	4 (3.8%)	1 (0.9%)	2.9 (−2.1–7.97)	0.333
All-cause mortality at end of therapy[a]	10 (9.6%)	14 (12.7%)	−3.1 (−11.53–5.31)	0.453
All-cause mortality at TOC[b]	10 (9.6%)	17 (15.5%)	−5.9 (−14.66–2.98)	0.196
Persistent bacteremia at day 3[c] *	4/95 (4.2%)	18/102 (17.6%)	−13.4 (−22.88–−3.99)	0.006
Persistent bacteremia at day 7[d]	2/90 (2.2%)	4/97 (4.1%)	−1.9 (−7.97–4.16)	0.748
Microbiological treatment failure at 14 days[e]	0 (%)	0 (%)	–	–
Relapsing bacteremia at TOC[f]	0/93 (0%)	1/102 (1%)	−0.9 (−3.87–1.91)	1
Complicated bacteremia at TOC[g]	21/95 (22.1%)	35/105 (33.3%)	−11.2 (−23.51–1.06)	0.077
Emergence of fosfomycin-resistant strains at TOC	0 (0%)	0 (0%)	–	–
Length of intensive care unit stay, median (IQR), days	8.0 (3.0–17.0)	4.0 (3.25–8.50)	–	0.355
Duration of intravenous antibiotic treatment, median (IQR), days	14.0 (11.0–22.0)	15.5 (11.0–26.0)	–	0.245
Serious adverse events leading to discontinuation of therapy[h]	11 (10.6%)	9 (8.2%)	2.40 (−5.43–10.22)	0.547

Table 3 | Adverse events in the intention-to-treat population

	Cloxacillin plus fosfomycin (*n*=104)	Cloxacillin alone (*n*=110)	Risk difference % (95% CI)	*P* value*
Any serious adverse event at TOC	42 (40.4%)	48 (43.6%)	−3.22 (−17.41–10.91)	0.732
Main adverse events at TOC[a]				
Hypokalemia (<3 mmol L^{-1})	18 (17.31%)	11 (10%)	7.31 (−2.81–17.42)	0.173
Hypocalcemia (<2.0 mmol L^{-1}) *	15 (14.42%)	5 (4.55%)	9.92 (1.15–18.61)	0.018
Acute heart failure	6 (5.77%)	6 (5.45%)	0.27 (−6.17–6.8)	1.000
Gastrointestinal disorders	7 (6.73%)	6 (5.45%)	1.23 (−7.58–6.39)	0.917

Efficacy and safety of an early oral switch in low-risk *Staphylococcus aureus* bloodstream infection (SABATO): an international, open-label, parallel-group, randomised, controlled, non-inferiority trial

Achim J Kaasch, Luis Eduardo López-Cortés, Jesús Rodríguez-Baño, José Miguel Cisneros, M Dolores Navarro, Gerd Fätkenheuer, Norma Jung, Siegbert Rieg, Raphaël Lepeule, Laetitia Coutte, Louis Bernard, Adrien Lemaignen, Katrin Kösters, Colin R MacKenzie, Alex Soriano, Stefan Hagel, Bruno Fantin, Matthieu Lafaurie, Jean-Philippe Talarmin, Aurélien Dinh, Thomas Guimard, David Boutoille, Tobias Welte, Stefan Reuter, Jan Kluytmans, Maria Luisa Martin, Emmanuel Forestier, Hartmut Stocker, Virginie Vitrat, Pierre Tattevin, Anna Rommerskirchen, Marion Noret, Anne Adams, Winfried V Kern, Martin Hellmich, Harald Seifert, for the SABATO study group*

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	Intention-to-treat population			Clinically evaluable population		
	Oral switch group (n=108)	Intravenous group (n=105)	Percentage-point difference (95% CI)	Oral switch group (n=86)	Intravenous group (n=79)	Percentage-point difference (95% CI)
Primary endpoint						
SAB-related complication within 90 days	14 (13%)	13 (12%)	0·7 (–7·8 to 9·1)	3 (4%)	4 (5%)	–2·9 (–9·6 to 3·9)
Reason primary outcome was met						
SAB-related complication	6 (6%)	8 (8%)	–2·1 (–9·7 to 5·5)	3 (4%)	4 (5%)	–1·6 (–9·0 to 5·8)
Relapsing SAB	3 (3%)	4 (4%)	–1·0 (–6·8 to 4·7)	2 (2%)	2 (3%)	–0·2 (–5·1 to 4·7)
Deep-seated infection with *S aureus*	5 (5%)	8 (8%)	–3·0 (–10·4 to 4·4)	3 (4%)	4 (5%)	–1·6 (–9·0 to 5·8)
Death attributable to SAB	2 (2%)	0	1·9 (–1·6 to 5·3)	1 (1%)	0	1·2 (–2·3 to 4·6)
Missing outcome data	8 (7%)	5 (5%)	2·7 (–4·7 to 10·0)	..	..	..
Attributability of death non-evaluable	3 (3%)	1 (1%)	1·8 (–2·7 to 6·4)	..	..	..
Secondary endpoints						
Length of hospital stay from SAB onset, days	12 (9–19)	16 (10–19)	–2 (–4 to 0); p=0·043*	11 (9–16)	15 (10–18)	–2 (–5 to 0); p=0·020*
Participants with complications of intravenous administration†						
Any complication	9 (9%); 11	17 (17%); 5	–7·9 (–17·6 to 1·9)	6 (7%); 3	13 (17%); 2	–9·5 (–20·5 to 1·5)
Chemical phlebitis	7	9	–2·1 (–10·1 to 5·9)	5	8	–4·3 (–13·8 to 5·2)
Infectious thrombophlebitis or phlebitis	0	2	–1·9 (–5·5 to 1·7)	0	2	–2·5 (–7·2 to 2·2)
Other‡	2	6	–3·9 (–9·9 to 2·2)	1	3	–2·6 (–8·6 to 3·4)
Participants with *Clostridium difficile* infection§	2 (2%); 8	2 (2%); 7	–0·1 (–3·8 to 3·6)	2 (2%); 7	1 (1%); 5	1·1 (–4·0 to 6·1)
Survival						
14 days	98·1% (1·3); 2	100·0% (0); 0	–1·9 (–4·5 to 0·7)	98·8% (1·2); 1	100·0% (0); 0	–1·2 (–3·4 to 1·1)
30 days	94·3% (2·3); 6	96·0% (2·0); 4	–1·7 (–7·6 to 4·2)	98·8% (1·2); 1	98·7% (1·3); 1	0·1 (–3·3 to 3·5)
90 days	83·6% (3·6); 17	89·0% (3·1); 11	–5·4 (–14·8 to 4·0)	92·9% (2·8); 6	94·8% (2·5); 4	–1·9 (–9·3 to 5·5)

JAMA | Original Investigation

Effect of Vancomycin or Daptomycin With vs Without an Antistaphylococcal β-Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients With MRSA Bacteremia

A Randomized Clinical Trial

JAMA. 2020;323(6):527-537.

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Table 3. Primary and Secondary Outcomes

Outcomes	No./Total No. (%)		Risk Difference, % (95% CI)	*P* Value
	Combination Therapy	Standard Therapy		
Primary Outcome[a,b]				
Primary analysis population	59/170 (35)	68/175 (39)	−4.2 (−14.3 to 6.0)	.42
Per protocol	47/144 (33)	68/175 (39)	−6.2 (−16.7 to 4.3)	.25
Secondary Outcomes[c]				
All-cause mortality[d]				
Day 14	13/170 (8)	13/174 (7)	0.2 (−5.4 to 5.8)	.95
Day 42	25/170 (15)	19/174 (11)	3.8 (−3.3 to 10.8)	.29
Day 90	35/170 (21)	28/174 (16)	4.5 (−3.7 to 12.7)	.28
Persistent bacteremia[e]				
Day 2	50/167 (30)	61/173 (35)	−5.3 (−15.3 to 4.6)	.29
Day 5	19/166 (11)	35/172 (20)	−8.9 (−16.6 to −1.2)	.02
Microbiological relapse[a]	14/169 (8)	18/175 (10)	−2.0 (−8.1 to 4.1)	.52
Microbiological treatment failure[a]	16/170 (9)	17/175 (10)	−0.3 (−6.5 to 5.9)	.92
Acute kidney injury[f]	34/145 (23)	9/145 (6)	17.2 (9.3 to 25.2)	<.001
Duration of intravenous antibiotics, mean (SD), d	29.3 (19.5)	28.1 (17.4)		.72

The *Staphylococcus aureus* Network Adaptive Platform Trial Protocol: New Tools for an Old Foe

Steven Y. C. Tong,[1] Jocelyn Mora,[1] Asha C. Bowen,[2,3] Matthew P. Cheng,[4] Nick Daneman,[5] Anna L. Goodman,[6,7] George S. Heriot,[1] Todd C. Lee,[8] Roger J. Lewis,[9,10,11] David C. Lye,[12,13,14,15] Robert K. Mahar,[16,17] Julie Marsh,[18] Anna McGlothlin,[9] Zoe McQuilten,[19,20] Susan C. Morpeth,[21] David L. Paterson,[22] David J. Price,[1,16] Jason A. Roberts,[23,24] J. Owen Robinson,[25,26,27,28] Sebastiaan J. van Hal,[29,30] Genevieve Walls,[21] Steve A. Webb,[31] Lyn Whiteway,[32] Dafna Yahav,[33] and Joshua S. Davis[34]; for the *Staphylococcus aureus* Network Adaptive Platform (SNAP) Study Group

Clinical Infectious Diseases® 2022;75(11):2027–34

Joshua Davis

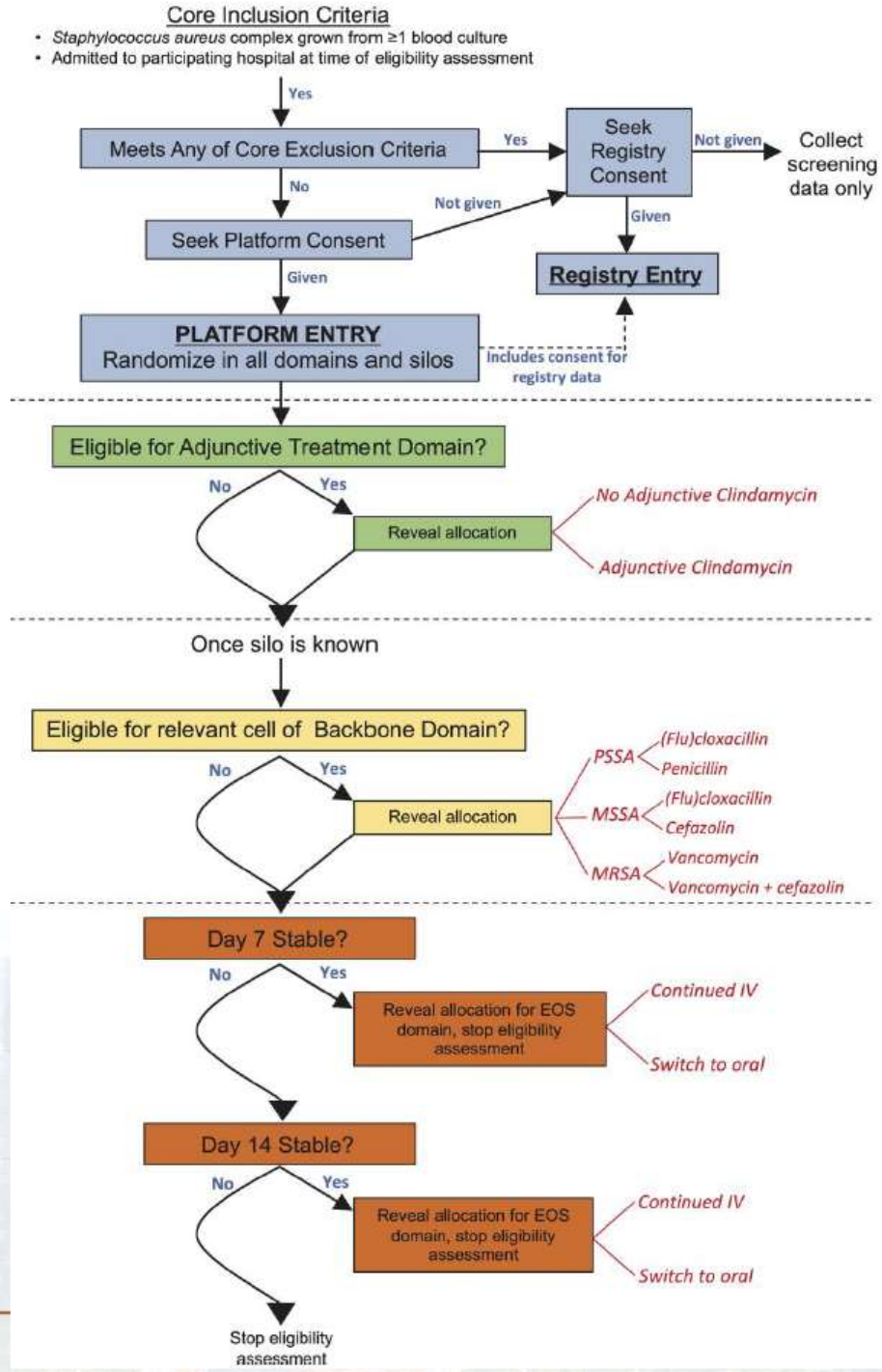
Steven Tong

Includes pregnant women and children of all ages

Aims to recruit ~ 6,000 adults and 1,000 children

PET CT domain November 2023

Primary outcome (all domains): All-cause mortality 90 days after platform entry



JOURNAL ARTICLE ACCEPTED MANUSCRIPT

Early oral antibiotic switch in *Staphylococcus aureus* bacteraemia: The *Staphylococcus aureus* Network Adaptive Platform (SNAP) Trial Early Oral Switch Protocol

Dana de Kretser, Jocelyn Mora, Max Bloomfield, Anita Campbell, Matthew P Cheng, Stephen Guy, Marjolein Hensgens, Shirin Kalimuddin, Todd C Lee, Amy Legg, Robert K Mahar, Michael Marks, Julie Marsh, Anna McGlothlin, Susan C Morpeth, Archana Sud, Jaap Ten Oever, Dafna Yahav, Steven YC Tong, Joshua S Davis, Genevieve Walls, Anna L Goodman ✉, Marc Bonten, Staphylococcus aureus Network Adaptive Platform (SNAP) Study Group members
Author Notes

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N=548

117 sites across 8 active regions

SNAP Platform
2973 participants

SNAP Registry
3351 participants

1. Australia
38 active sites

2. New Zealand
9 active sites

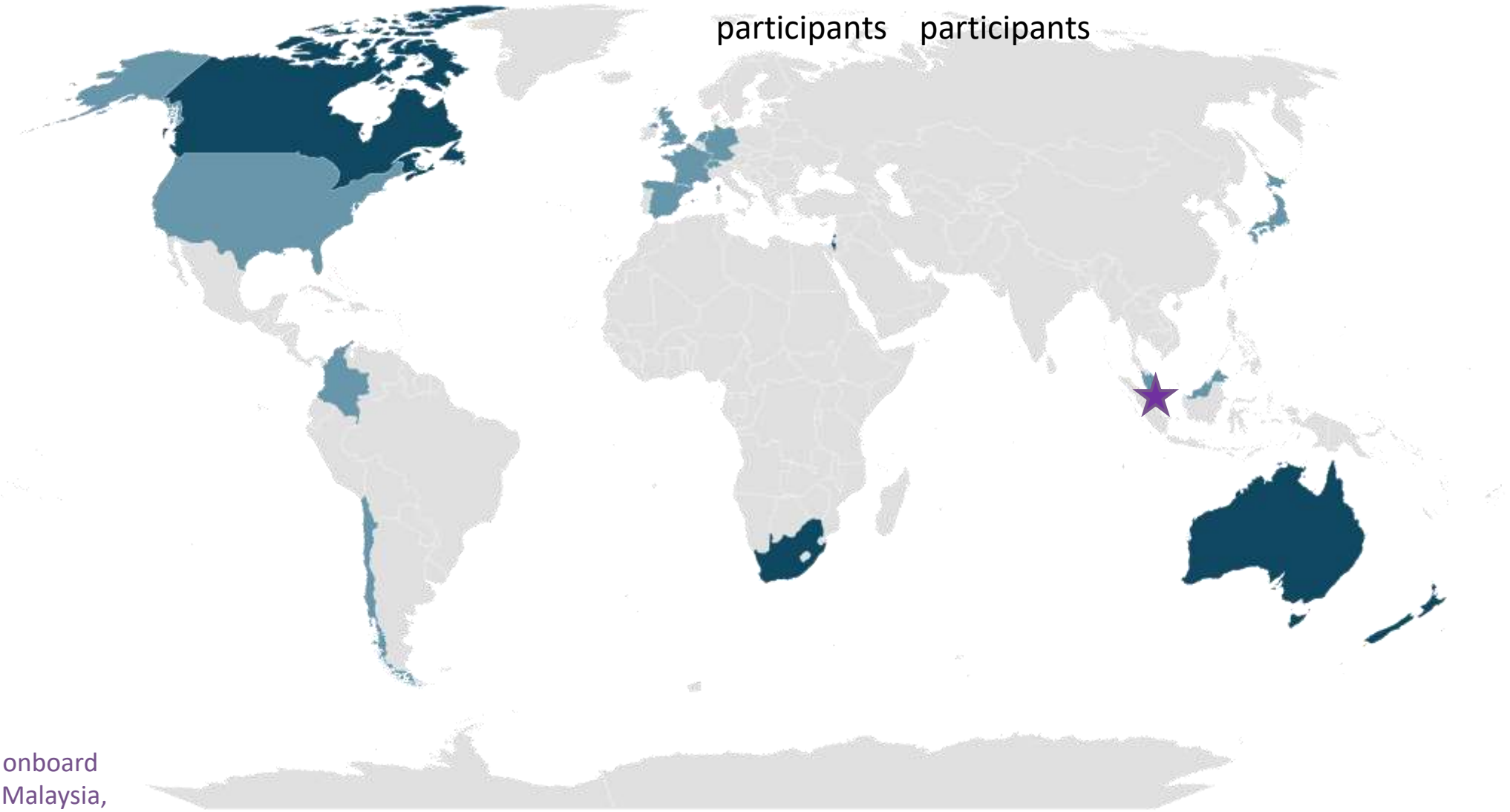
3. Canada
29 active sites

4. Singapore
2 active sites

5. Israel
3 active sites

6. South Africa
1 active site

*Other regions to come onboard include Europe, the UK, Malaysia, Japan, USA & Chile



Need for adaptive platform trials for bacteraemia

Non-antibiotic-resistant

- Does IV penicillin work for penicillin-sensitive *S aureus* vs SOC? → SNAP
- Does IV cefazolin work for methicillin-sensitive *S aureus* vs SOC? → SNAP
- Does early oral antibiotic work for *S aureus* bacteraemia? → SABATO, SNAP
- Duration of treatment for uncomplicated *S aureus* bacteraemia? → SAFE
- Does IV cefazolin work for *E coli* and *Klebsiella* bacteraemia vs broader spectrum?
- Does early oral antibiotic work for gram negative bacteraemia? → SOAB, INVEST
- Duration of antibiotic for gram negative bacteraemia? → CID 2018, JAMA 2020

Antibiotic-resistant

- Does piperacillin-tazobactam or cefepime work for ESBL bacteraemia? → partly MERINO, PeterPen
- Does piperacillin-tazobactam or cefepime work for AmpC bacteraemia? → partly MERINO2
- What is optimal antibiotic for XDR *Acinetobacter* bacteraemia?
- What is optimal antibiotic for carbapenemase producing *Enterobacterales* bacteraemia?
- Are combination antibiotics better than monotherapy for *Pseudomonas* bacteraemia?

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Thank You!

"Randomised care instead of random care"

National Centre for Infectious Diseases

Tan Tock Seng Hospital

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