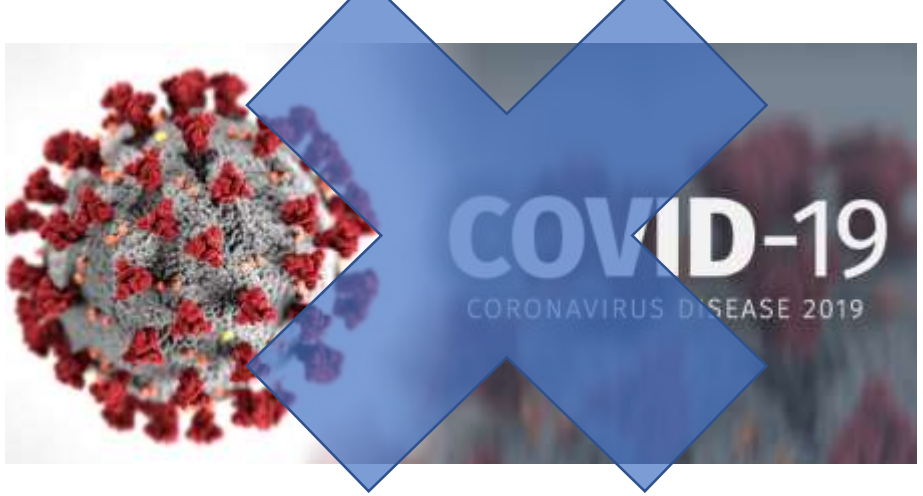


Top ID papers of 2023

NON-COVID!!

Prof Josh Davis, January 2024

THE UNIVERSITY OF NEWCASTLE AUSTRALIA

menzies school of health research

NSW GOVERNMENT Health Hunter New England Local Health District

HMRI Hunter Medical Research Institute

Criteria

- IMHO
- COVID excluded
- Published during 2023
- Deal with diagnosis or treatment of infectious diseases
- Relevant to (my) clinical practice
- Practice-changing, paradigm-shifting, or dogma-challenging.
- **In alphabetical order by first author**

Why not COVID

- www.youtube.com/watch?v=uR3LCB1scdk

Chat GPT: Write a poem about the main infectious diseases stories of 2023

Chat GPT: Write a poem about the main infectious diseases stories of 2023

In twenty-three, a world in strife, Infectious tales, the pulse of life. A virus danced, a stealthy sprite, Yet science stood, prepared for the fight.

COVID's kin, a novel strain, A global challenge, not in vain. Vaccines rolled, a shield so strong, Defying threats, they marched along.

Pandemic's echoes, still they rang, In crowded streets and silence sang. Delta waned, but new emerged, A vigilant world, its course converged.

In 2023, the world did learn, From every twist, a page did turn. Through trials faced and battles won, Resilience glowed like the morning sun.

So here's the tale of twenty-three, Of microbes, masks, and unity. Infectious stories, a chapter past, Humanity endures, steadfast

IMDb BEST OF 2023

TOP MOVIES OF 2023

1 OPPENHEIMER

2 BARBIE

3 GUARDIANS OF THE GALAXY VOL. 3

4 THE LITTLE MERMAID

5 JOHN WICK: CHAPTER 4

6 THE SUPER MARIO BROS. MOVIE

7 FIVE NIGHTS AT FREDDY'S

8 SPIDER-MAN: ACROSS THE SPIDER-VERSE

9 KILLERS OF THE FLOWER MOON

10 THE FLASH

IMDb BEST OF 2023

TOP SERIES OF 2023

1 THE LAST OF US

2 AHSOKA

3 SUCCESSION

4 BLACK MIRROR

5 THE MANDALORIAN

6 ONE PIECE

7 THE FALL OF THE HOUSE OF USHER

8 TED LASSO

9 THE BEAR

10 GEN V

Honorable Mentions

- Varghese NEJM 2023; 388: 792. Scrub typhus RCT
  - 794 patients with scrub typhus randomized to IV docyxycline, azithromycin or both for 7 days. Combo therapy was clearly superior
- Luetkemeyer NEJM 2023; 388: 1296. DoxyPEP trial
  - 501 MSM at high risk for STIs, randomised to 200mg Doxy stat after each episode of condomless sex or not. At least one STI occurred in ~10% in the doxy arm versus 30% standard of care.
- Wang NEJM 2023; 388: 1843. Leprosy PEP
  - Cluster RCT in China. 207 households (7,450 household contacts of leprosy) randomised to 1 dose rifapentine, 1 dose rifampicin or control. Rifampicin didn't work but rifapentine incidence ratio 0.16.
- De Jonge Lancet Regional Health 2023; 36:100782. PRECIOUS trial.
  - 2x2x2 Factorial RCT of CTX, Paracetamol, Metoclopramide or not after CVA. Stopped early as ran out of $$. ~1,100 randomised to CTX or not for 4 days. No benefit on anything except less UTIs.
- Omrani CMI 17/10/23; SOAB trial
  - RCT In 165 stable adults with G-ve bacteraemia, switch from IV to PO antibiotics after 3-5 days was non-inferior to continued IV (Rx failure 25.6% IV group versus 21.7% PO group).

REPORT

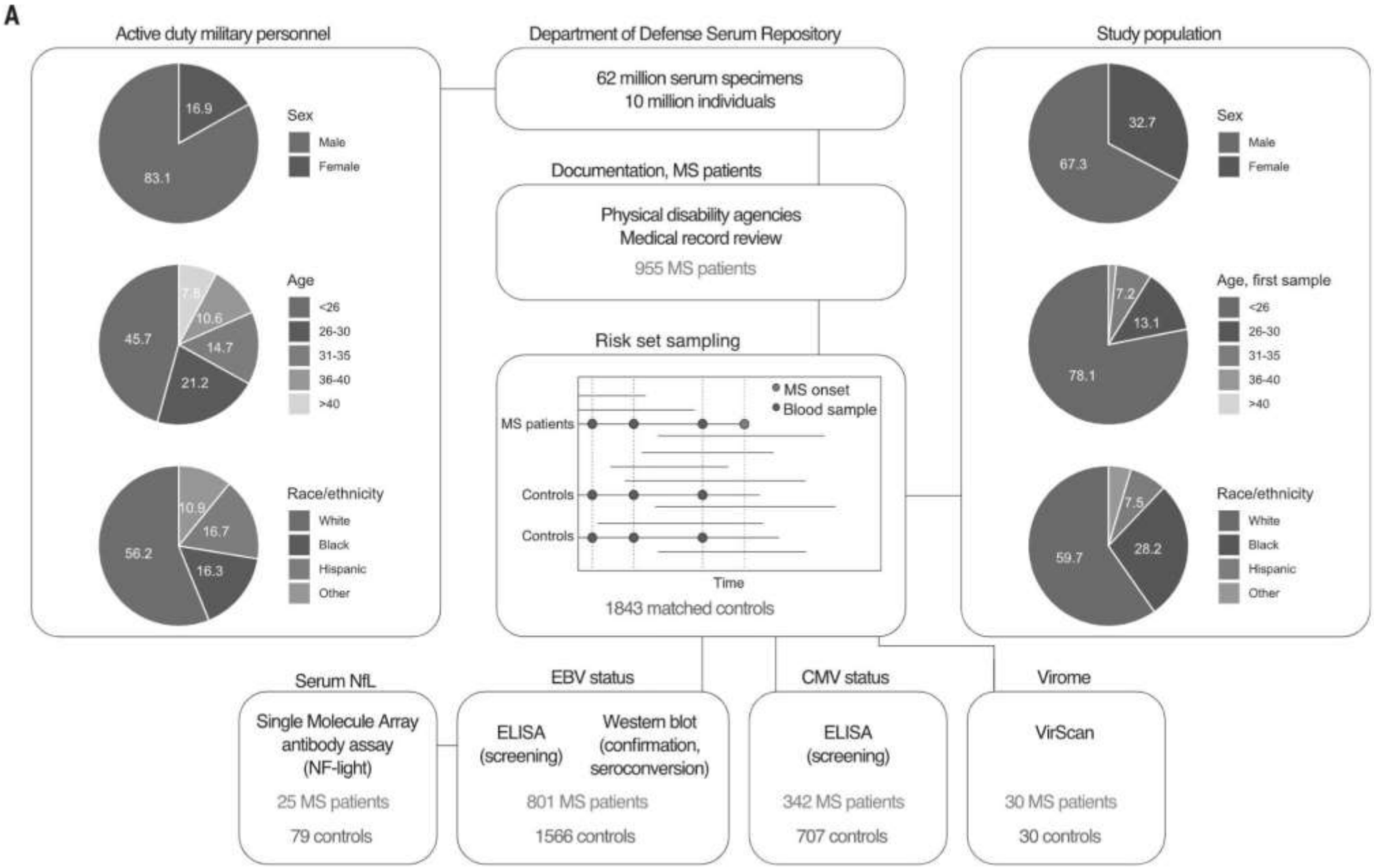
MULTIPLE SCLEROSIS

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

Kjetil Bjornevik[1]†, Marianna Cortese[1]†, Brian C. Healy[2,3,4], Jens Kuhle[5], Michael J. Mina[6,7,8], Yumei Leng[6], Stephen J. Elledge[6], David W. Niebuhr[9], Ann I. Scher[9], Kassandra L. Munger[1]‡, Alberto Ascherio[1,10,11]*‡

- WHY
  - Paradigm-shifting
- SUMMARY
  - Case-control study from a cohort of 10 million young adults in the US military
  - Used stored serum plus medical record reviews
  - 955 were diagnosed with MS plus 1,566 matched controls had blood tested for virome, serology, Neurofilament light chain
  - Risk of incident MS increased 32-fold after EBV seroconversion, but not at all after CMV seroconversion. All but 1 MS cases had preceding EBV seroconversion
  - Serum neurofilament light chain increased only after EBV seroconversion

1


A
Active duty military personnel
16.9
83.1
Sex
Male
Female
7.5
10.6
14.7
21.2
45.7
Age
<26
26-30
31-35
36-40
>40
10.9
16.7
16.3
56.2
Race/ethnicity
White
Black
Hispanic
Other
Department of Defense Serum Repository
62 million serum specimens
10 million individuals
Documentation, MS patients
Physical disability agencies
Medical record review
955 MS patients
Risk set sampling
MS onset
Blood sample
MS patients
Controls
Controls
Time
1843 matched controls
Study population
32.7
67.3
Sex
Male
Female
7.2
13.1
78.1
Age, first sample
<26
26-30
31-35
36-40
>40
7.5
28.2
59.7
Race/ethnicity
White
Black
Hispanic
Other
Serum NfL
Single Molecule Array
antibody assay
(NF-light)
25 MS patients
79 controls
EBV status
ELISA
(screening)
Western blot
(confirmation,
seroconversion)
801 MS patients
1566 controls
CMV status
ELISA
(screening)
342 MS patients
707 controls
Virome
VirScan
30 MS patients
30 controls

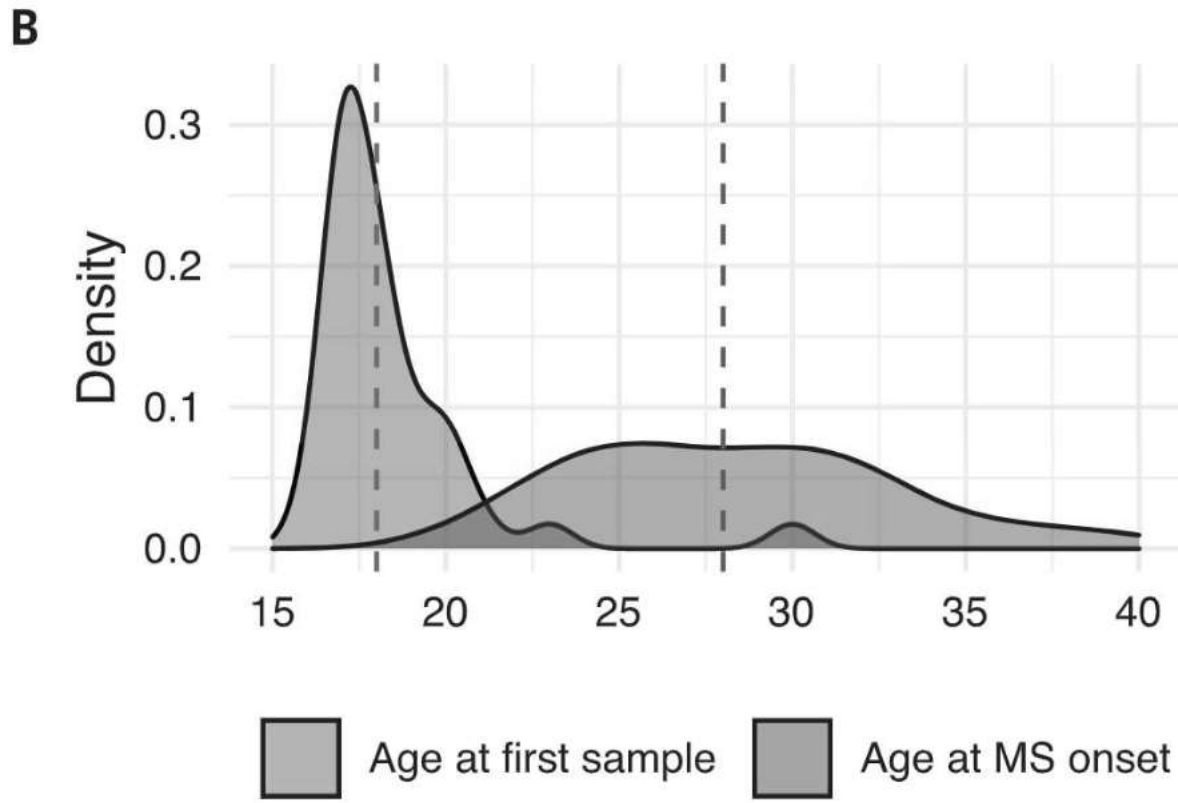
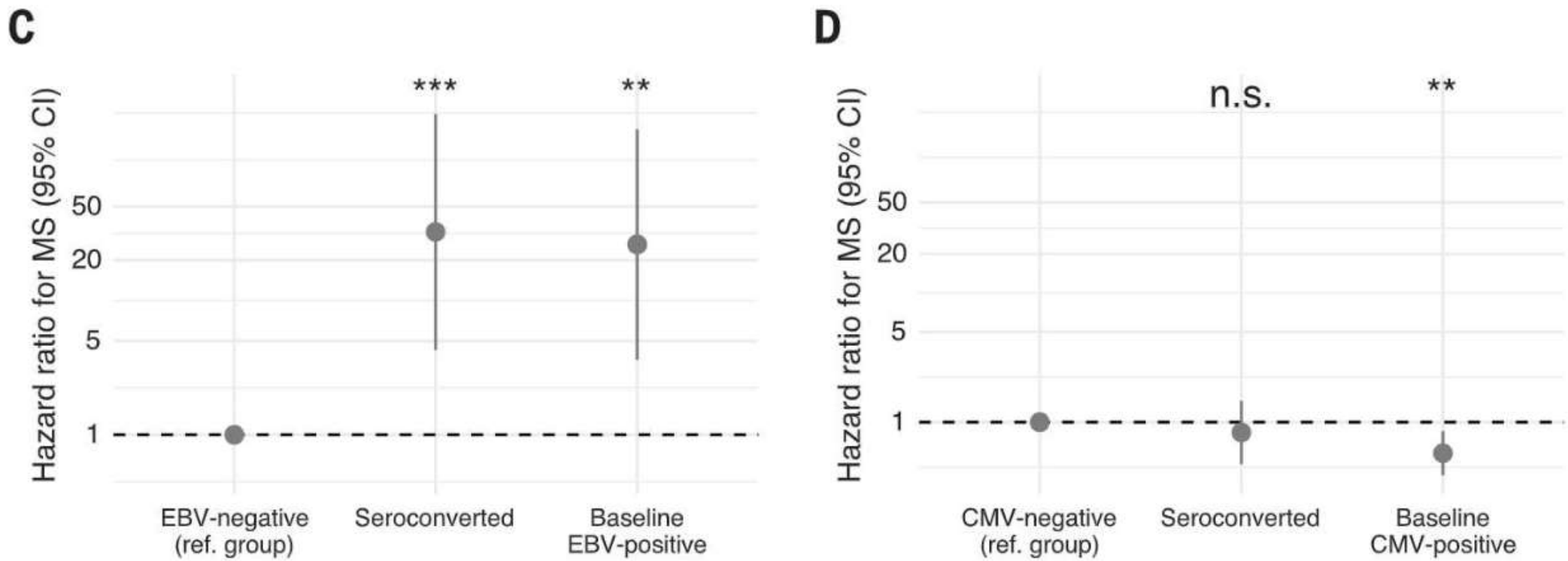


Fig. 1. Study design. (**A**) Residual serum samples from the DoDSR were obtained from 810 MS patients and 1577 matched controls. We assessed whether individuals were seropositive for EBV and CMV in up to three serum samples per person. We measured sNfL in those who were EBV-negative in the first serum sample. VirScan was used to profile the virome in a subset of MS


C
***
**
Hazard ratio for MS (95% CI)
50
20
5
1
EBV-negative
(ref. group)
Seroconverted
Baseline
EBV-positive
D
n.s.
**
Hazard ratio for MS (95% CI)
50
20
5
1
CMV-negative
(ref. group)
Seroconverted
Baseline
CMV-positive

REPORT

MULTIPLE SCLEROSIS

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

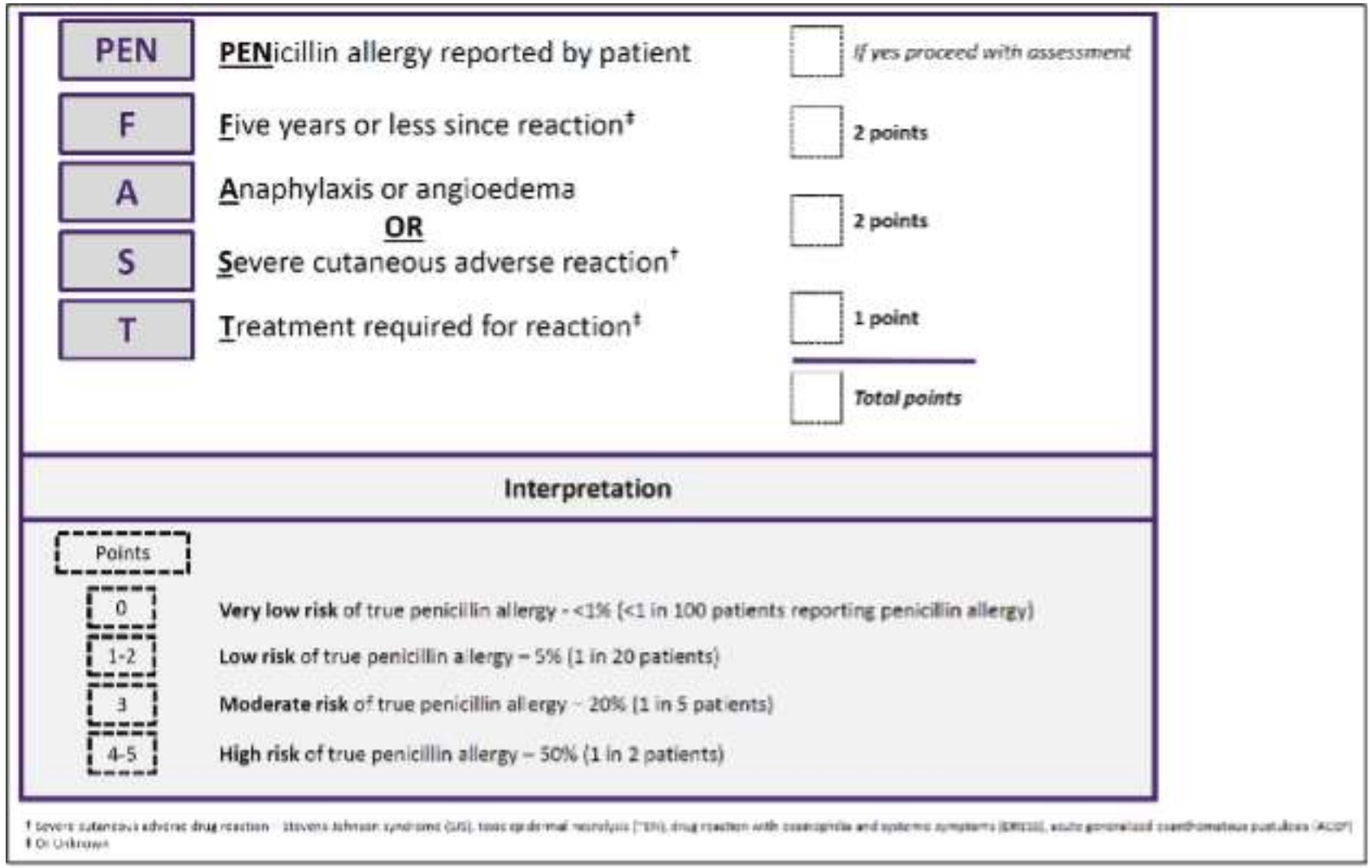
Kjetil Bjornevik[1]†, Marianna Cortese[1]†, Brian C. Healy[2,3,4], Jens Kuhle[5], Michael J. Mina[6,7,8], Yumei Leng[6], Stephen J. Elledge[6], David W. Niebuhr[9], Ann I. Scher[9], Kassandra L. Munger[1]‡, Alberto Ascherio[1,10,11]*‡

Bjornevik *et al.*, *Science* **375**, 296–301 (2022) 21 January 2022

- WHY
  - Paradigm-shifting
- IMPLICATIONS
  - EBV is the (or at least a) cause of MS
  - An EBV vaccine in childhood would likely prevent a large proportion of MS (not to mention various malignancies)
  - Antivirals (even if they were effective against EBV) would likely not have an impact as would be initiated too late/asymptomatic infection

Copaescu et al PALACE Trial. JAMA Int Med;183(9)

- WHY
  - Practice changing
- SUMMARY
  - 382 patients, 6 hospitals (Australia, US, Canada) with PENFAST score<3
  - Randomised to oral penicillin challenge or SOC (skin test then oral challenge)
  - Positive oral challenge (immune-mediated within 1 h) occurred in 1 patient (0.5%) in each group.
  - Oral challenge was with amoxycillin or penicillin V
  - Delayed rash occurred in 9 patients in DOC group and 10 in SOC group. No SAEs.


PEN
PENicillin allergy reported by patient
If yes proceed with assessment
F
Five years or less since reaction‡
2 points
A
Anaphylaxis or angioedema
OR
S
Severe cutaneous adverse reaction†
2 points
T
Treatment required for reaction‡
1 point
Total points
Interpretation
Points
0
1-2
3
4-5
Very low risk of true penicillin allergy - <1% (<1 in 100 patients reporting penicillin allergy)
Low risk of true penicillin allergy – 5% (1 in 20 patients)
Moderate risk of true penicillin allergy – 20% (1 in 5 patients)
High risk of true penicillin allergy – 50% (1 in 2 patients)

JAMA Internal Medicine

RCT: Efficacy of a Clinical Decision Rule to Enable Direct Oral Challenge in Patients With Low-Risk Penicillin Allergy

POPULATION

130 Men, 247 Women

Adults ≥18 y old with a low-risk penicillin allergy

Median age, 51 y

INTERVENTION

377 Participants analyzed

190 Control
Skin prick and intradermal penicillin testing, followed by oral challenge if skin testing results are negative

187 Intervention
Direct oral penicillin drug challenge

SETTINGS / LOCATIONS

6 Hospitals in North America and Australia

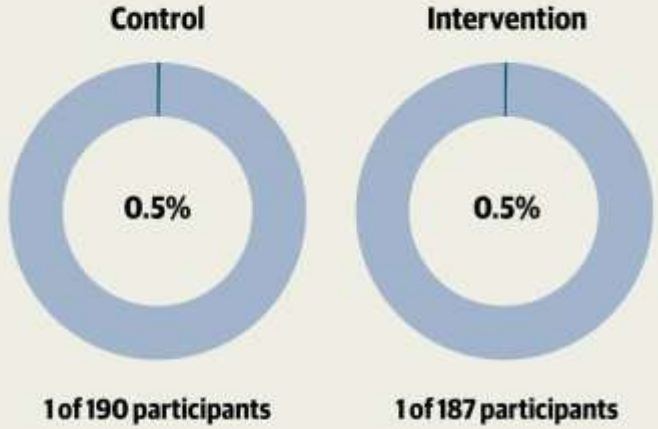
PRIMARY OUTCOME

Between-group difference in the proportion of participants with a physician-verified immune-mediated positive oral penicillin challenge (percentage points); noninferiority margin was set at 5 percentage points

FINDINGS

The intervention was found to be noninferior to the control for the primary outcome in adults with low-risk penicillin allergy

Proportion of participants with a positive oral penicillin challenge



Risk difference, 0.0084 (90% CI, −1.22 to 1.24) percentage points, which is less than the noninferiority margin

Copaescu AM, Vogrin S, James F, et al. Efficacy of a clinical decision rule to enable direct oral challenge in patients with low-risk penicillin allergy: the PALACE randomized clinical trial. *JAMA Intern Med*. Published online July 17, 2023. doi:10.1001/jamainternmed.2023.2986

Copaescu et al PALACE Trial. JAMA Int Med;183(9)

- WHY
  - Practice changing
- IMPLICATIONS
  - The PENFAST score has previously been validated on large observational datasets.
  - This strengthens the evidence with a well-designed RCT
  - Those with a penicillin allergy and a PENFAST score of < 3 should have a direct oral challenge (in hospital)
  - Not clear if can apply this to outpatients, or those with allergies to other beta-lactams.


N
0 (km) 10
0 (mi) 6

Hydrocortisone in Severe Community-Acquired Pneumonia

P.-F. Dequin, F. Meziani, J.-P. Quenot, T. Kamel, J.-D. Ricard, J. Badie, J. Reignier, N. Heming, G. Plantefève, B. Souweine, G. Voiriot, G. Colin, J.-P. Frat, J.-P. Mira, N. Barbarot, B. François, G. Louis, S. Gibot, C. Guitton, C. Giacardi, S. Hraiech, S. Vimeux, E. L'Her, H. Faure, J.-E. Herbrecht, C. Bouisse, A. Joret, N. Terzi, A. Gacouin, C. Quentin, M. Jourdain, M. Leclerc, C. Coffre, H. Bourgoin, C. Lengellé, C. Caille-Fénérol, B. Giraudeau, and A. Le Gouge, for the CRICS-TriGGERSep Network*

- WHY
  - Practice changing
- SUMMARY
  - 800 adults with severe CAP in 31 French ICUs randomised to hydrocortisone 200mg daily IV for 4 or 7 days then a taper, or placebo (total 8 versus 14 days). Day 28 mortality was 6.2% in the steroid group and 11.9% in the placebo group (p=0.006)
  - 2ry outcomes were also better (need for intubation, need to start vasopressors) in the steroid group
  - SAEs no different. Higher insulin doses needed in steroid group
  - Note study drug started within a mean

RESEARCH SUMMARY

Hydrocortisone in Severe Community-Acquired Pneumonia

Dequin P-F et al. DOI: 10.1056/NEJMoa2215145

CLINICAL PROBLEM

Glucocorticoids have powerful antiinflammatory and immunomodulatory effects that mitigate complications of pneumonia. Whether glucocorticoids can reduce mortality in patients with severe community-acquired pneumonia is uncertain.

CLINICAL TRIAL

Design: A phase 3, multicenter, double-blind, randomized, controlled trial evaluated whether early treatment with hydrocortisone could reduce mortality among adults admitted to the intensive care unit (ICU) for severe community-acquired pneumonia.

Intervention: 800 patients receiving state-of-the-art standard therapy for severe community-acquired pneumonia were assigned to receive intravenous hydrocortisone at a dose of 200 mg daily for 4 or 7 days as determined by clinical improvement, followed by tapering for a total of 8 or 14 days, or placebo administered according to the same regimen. The primary outcome was death from any cause by day 28. Secondary outcomes included death from any cause by day 90 and endotracheal intubation by day 28; safety outcomes included hospital-acquired infection and gastrointestinal bleeding.

RESULTS

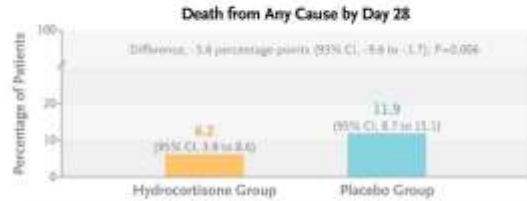
Efficacy: Among evaluable patients, the number of deaths by day 28 was significantly lower in the hydrocortisone group than in the placebo group.

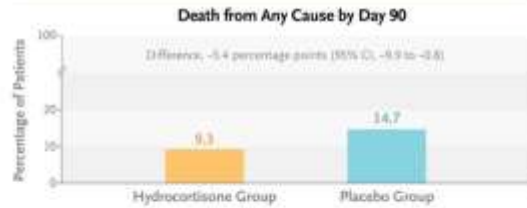
Safety: The incidence of hospital-acquired infection and of gastrointestinal bleeding was similar in the two groups. The median insulin dose during the first week of the trial was higher in the hydrocortisone group than in the placebo group.

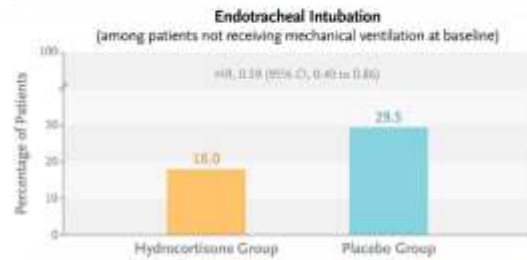
LIMITATIONS AND REMAINING QUESTIONS

- Mortality in the placebo group was lower than anticipated, which suggests that patients may have been less severely ill than expected.
- The trial did not mandate a standardized microbiologic investigation, and a pathogen was not isolated in nearly half the patients.
- A small proportion of patients were immunocompromised, so the findings should be applied with caution in this population.

Links: Full Article | NEJM Quick Take | Editorial

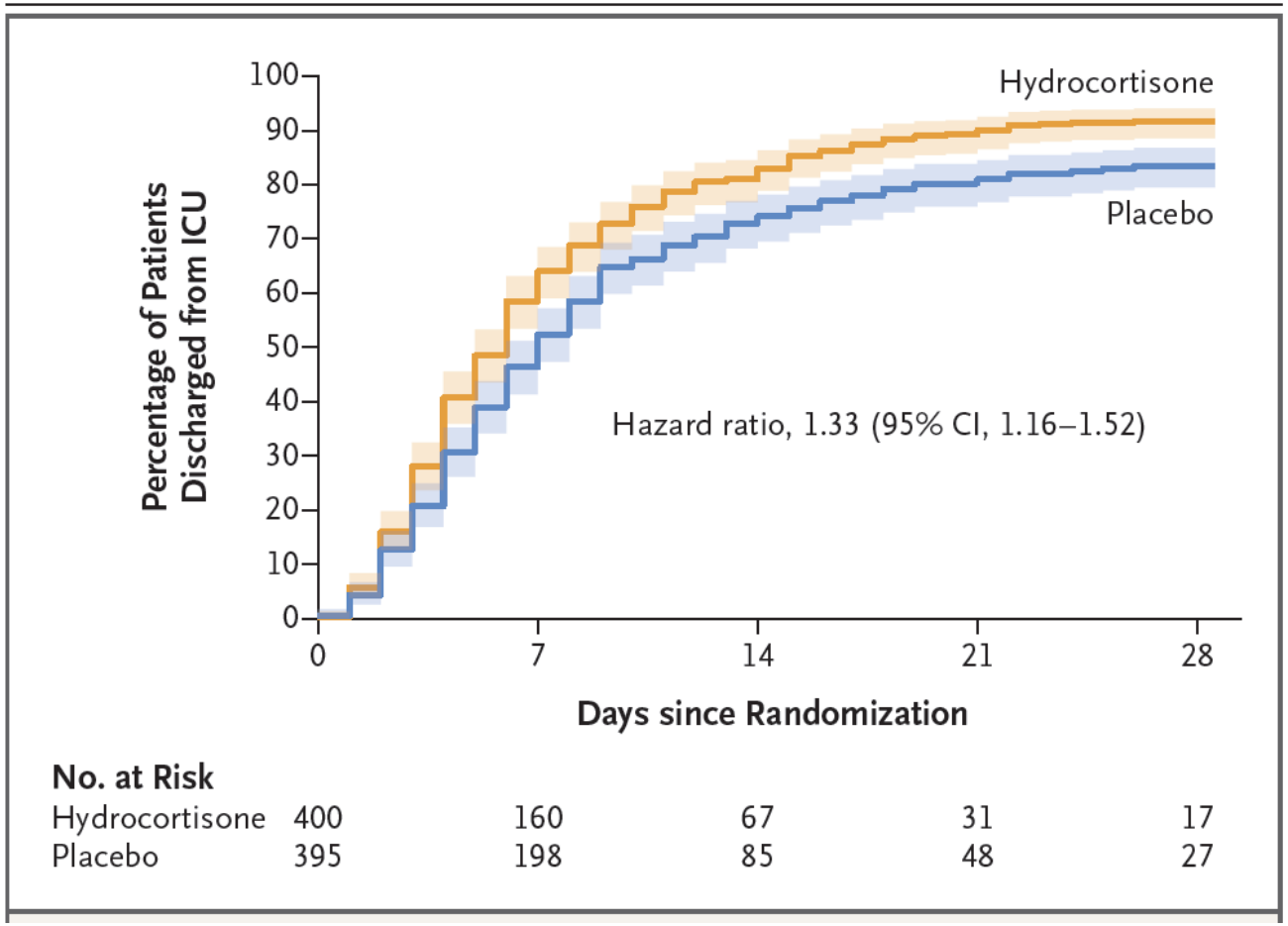


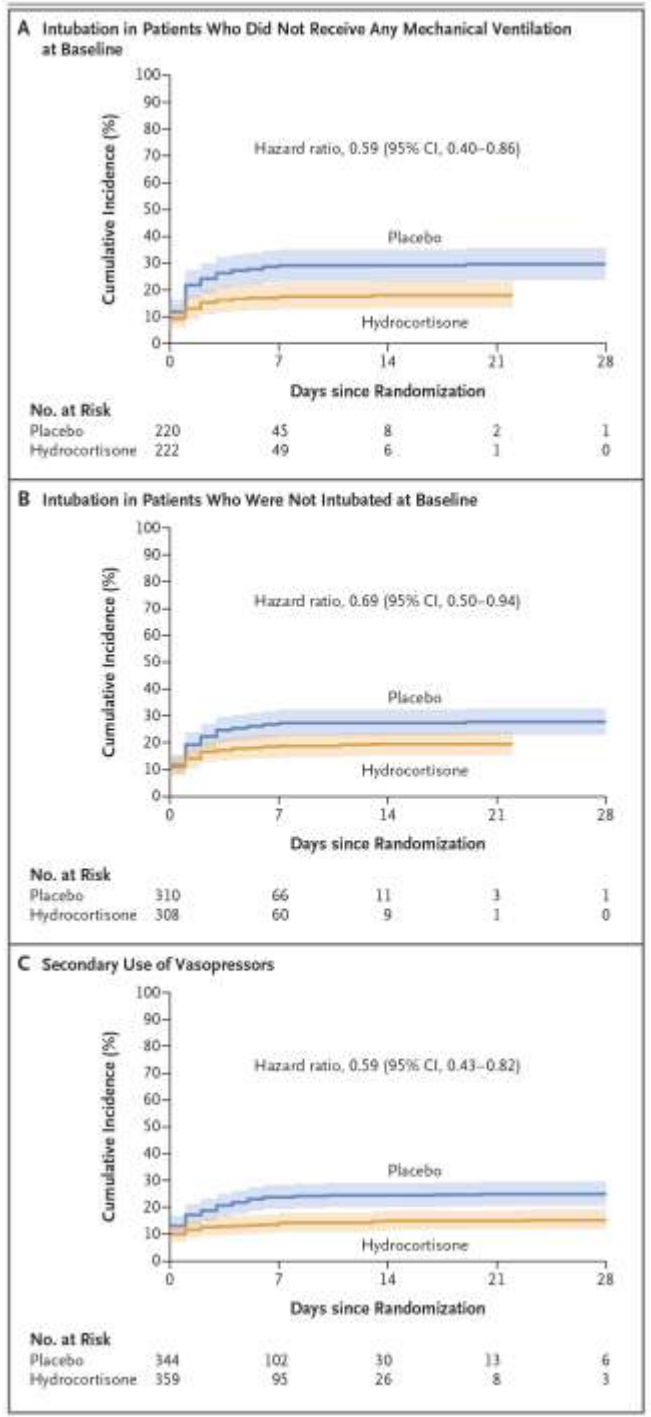




CONCLUSIONS

Among patients admitted to the ICU with severe community-acquired pneumonia, treatment with intravenous hydrocortisone was associated with a lower risk of death by day 28 than placebo.


Percentage of Patients Discharged from ICU
100
90
80
70
60
50
40
30
20
10
0
Hydrocortisone
Placebo
Hazard ratio, 1.33 (95% CI, 1.16–1.52)
0
7
14
21
28
Days since Randomization
No. at Risk
Hydrocortisone 400 160 67 31 17
Placebo 395 198 85 48 27


A Intubation in Patients Who Did Not Receive Any Mechanical Ventilation at Baseline
Cumulative Incidence (%)
Hazard ratio, 0.59 (95% CI, 0.40–0.86)
Placebo
Hydrocortisone
Days since Randomization
No. at Risk
Placebo 220 45 8 2 1
Hydrocortisone 222 49 6 1 0
B Intubation in Patients Who Were Not Intubated at Baseline
Cumulative Incidence (%)
Hazard ratio, 0.69 (95% CI, 0.50–0.94)
Placebo
Hydrocortisone
Days since Randomization
No. at Risk
Placebo 310 66 11 3 1
Hydrocortisone 308 60 9 1 0
C Secondary Use of Vasopressors
Cumulative Incidence (%)
Hazard ratio, 0.59 (95% CI, 0.43–0.82)
Placebo
Hydrocortisone
Days since Randomization
No. at Risk
Placebo 344 102 30 13 6
Hydrocortisone 359 95 26 8 3

Hydrocortisone in Severe Community-Acquired Pneumonia

P.-F. Dequin, F. Meziani, J.-P. Quenot, T. Kamel, J.-D. Ricard, J. Badie, J. Reignier, N. Heming, G. Plantefève, B. Souweine, G. Voiriot, G. Colin, J.-P. Frat, J.-P. Mira, N. Barbarot, B. François, G. Louis, S. Gibot, C. Guitton, C. Giacardi, S. Hraiech, S. Vimeux, E. L'Her, H. Faure, J.-E. Herbrecht, C. Bouisse, A. Joret, N. Terzi, A. Gacouin, C. Quentin, M. Jourdain, M. Leclerc, C. Coffre, H. Bourgoin, C. Lengellé, C. Caille-Fénérol, B. Giraudeau, and A. Le Gouge, for the CRICS-TriGGERSep Network*

- WHY
  - Practice changing
- IMPLICATIONS
  - Controversy about dosing (continuous infusion needed or not?); trial stopped early (2nd interim); 6 previous RCTs showed benefit but NOT on mortality
  - I think we should strongly consider hydrocortisone use in those with severe bacterial CAP (PSI V, HFNO>50% FiO2, or intubated)
  - REMAP-CAP steroid domain for bacterial CAP pending and important to await before definitive conclusions

2022;386:220-9.

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

- WHY
  - Practice-changing
- SUMMARY
  - 7,769 patients with HIV (145 sites in 12 countries), aged 40-75 years, low-moderate CV risk, on ART. Randomised to pitavastatin 4mg daily or placebo. Stopped early after 5 years: risk of MACE or death 4.81/1000 person-years in statin group versus 7.32 in placebo (HR 0.65, p-0.002).
  - Myalgia (2.3% versus 1.4%) and new diabetes (5.3% versus 4.0%)

RESEARCH SUMMARY

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

Grinspoon SK et al. DOI: 10.1056/NEJMoa2304146

CLINICAL PROBLEM

In persons with HIV infection, the risk of atherosclerotic cardiovascular disease is twice that in the general population. Randomized studies of primary prevention strategies in this population are needed.

CLINICAL TRIAL

Design: A phase 3, multinational, randomized, placebo-controlled trial assessed the efficacy and safety of pitavastatin for the prevention of cardiovascular events in persons with HIV infection and low-to-moderate risk of atherosclerotic cardiovascular disease.

Intervention: 7769 participants between the ages of 40 and 75 years (median screening LDL cholesterol, 108 mg/dl) receiving stable antiretroviral therapy were assigned to receive oral pitavastatin calcium (4 mg) (3888 participants) or placebo (3881 participants) daily. The primary outcome was the occurrence of a major adverse cardiovascular event — cardiovascular death, myocardial infarction, hospitalization for unstable angina, stroke, transient ischemic attack, peripheral arterial ischemia, revascularization, or death from an undetermined cause, as measured in a time-to-event analysis.

RESULTS

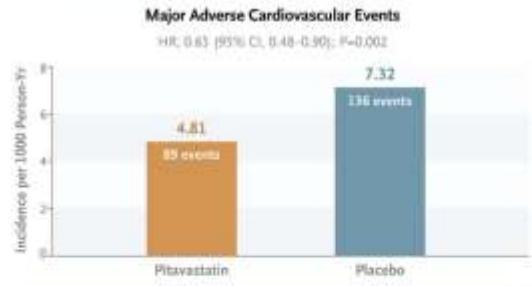
Efficacy: During a median follow-up of 5.1 years, the incidence of major adverse cardiovascular events was significantly lower in the pitavastatin group than in the placebo group.

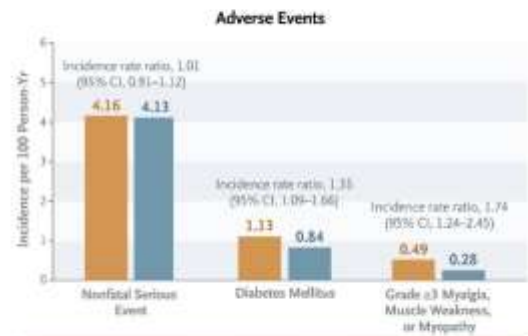
Safety: The incidence of nonfatal serious adverse events was similar in the two groups. Participants in the pitavastatin group were more likely than those in the placebo group to have newly diagnosed diabetes mellitus and grade ≥3 myalgia, muscle weakness, or myopathy.

LIMITATIONS AND REMAINING QUESTIONS

- Although other statins that do not interact with HIV medications may have similar protective effects, the results reported are specific to pitavastatin.
- Other strategies that lower LDL cholesterol may be useful in this population and need to be compared with statin therapy with respect to efficacy, safety, and cost.

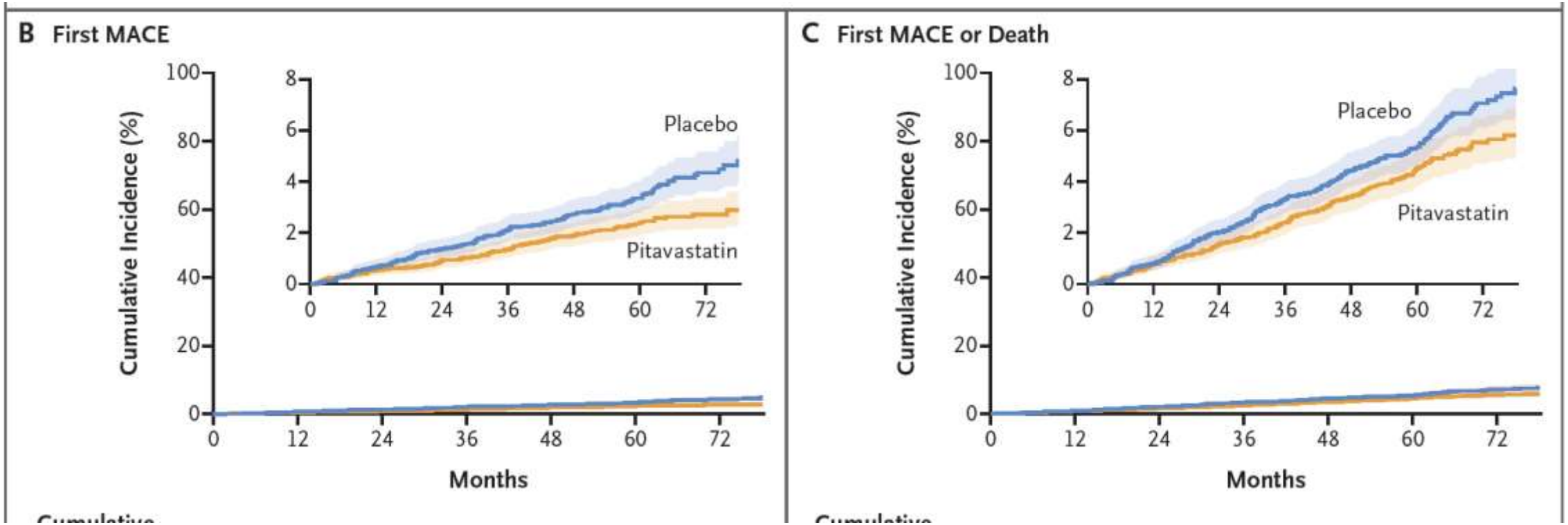
Links: Full Article | NEJM Quick Take | Editorial





CONCLUSIONS

In persons with HIV infection receiving stable antiretroviral therapy and at low-to-moderate cardiovascular risk, daily treatment with pitavastatin resulted in a significantly lower risk of major adverse cardiovascular events than placebo over approximately 5 years of follow-up.


B First MACE
Cumulative Incidence (%)
100
80
60
40
20
0
0
12
24
36
48
60
72
Months
8
6
4
2
0
Placebo
Pitavastatin
C First MACE or Death
Cumulative Incidence (%)
Placebo
Pitavastatin
Months

2022;386:220-9.

Pitavastatin to Prevent Cardiovascular Disease in HIV Infection

- WHY
  - Practice-changing
- IMPLICATIONS
  - HIV itself is a cardiovascular risk factor (hence the rationale for the trial)
  - People with HIV, aged over 40, and with >=moderate CV risk (10% 5 years) should be on a statin, regardless of LDL level (NNT ~50)
  - Those with low risk (<5%, or 5-10%) less clear (NNT 100-200, NNH ~80)
  - *Probably* other statins would also have the same effect, but this is unclear

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

T.L. Holland, S.E. Cosgrove, S.B. Doernberg, T.C. Jenkins, N.A. Turner, H.W. Boucher, O. Pavlov, I. Titov, S. Kosulnykov, B. Atanasov, I. Poromanski, M. Makhviladze, A. Anderzhanova, M.E. Stryjewski, M. Assadi Gehr, M. Engelhardt, K. Hamed, D. Ionescu, M. Jones, M. Saulay, J. Smart, H. Seifert, and V.G. Fowler, Jr., for the ERADICATE Study Group*

- WHY
  - *Potentially* Practice changing
- SUMMARY
  - 387 adults with SAB (MSSA=287/ MRSA=94) randomised to ceftobiprole 500mg QID (TDS from day 9) or daptomycin 6-10mg/kg/day (+/- aztreonam). Rx success at day 70 was 69.8% ceftobiprole versus 68.7% daptomycin – non-inferior.
  - <72 from blood draw; “complicated” bacteraemia
  - Nausea in 5.2% ceftobiprole versus 0% daptomycin; diarrhoea 4.2% vs 1.0%

RESEARCH SUMMARY

Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

Holland TL et al. DOI: 10.1056/NEJMoa2300220

CLINICAL PROBLEM

Staphylococcus aureus bacteremia is often lethal, and patients with this condition have limited antibiotic treatment options. Ceftobiprole is a cephalosporin with bactericidal activity against both methicillin-resistant *S. aureus* (MRSA) and methicillin-susceptible *S. aureus*, but its potential role in treating complicated *S. aureus* bacteremia is unclear.

CLINICAL TRIAL

Design: A phase 3, multinational, double-blind, double-dummy, randomized trial assessed whether ceftobiprole would be noninferior to daptomycin for the treatment of complicated *S. aureus* bacteremia.

Intervention: 390 adults hospitalized with complicated *S. aureus* bacteremia were assigned to receive either ceftobiprole (500 mg) intravenously every 6 hours during the first 8 days and then every 8 hours thereafter or daptomycin (6–10 mg per kilogram of body weight) intravenously every 24 hours with optional aztreonam, plus matching placebo infusions. Maximum treatment durations ranged from 28 to 42 days. The primary efficacy outcome was overall treatment success at 70 days after randomization; success was defined as survival, a reduction in symptoms, *S. aureus* bloodstream clearance, absence of new *S. aureus* bacteremia–related complications, and no receipt of other potentially effective antibiotics.

RESULTS

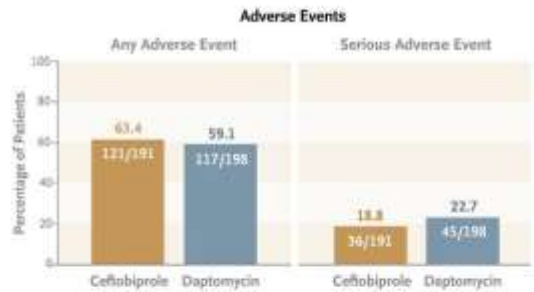
Efficacy: Among evaluable patients, ceftobiprole was found to be noninferior to daptomycin with respect to overall treatment success.

Safety: The proportion of patients with adverse events or with serious adverse events was similar in the two groups. Gastrointestinal adverse events occurred more often with ceftobiprole than with daptomycin.

LIMITATIONS AND REMAINING QUESTIONS

- Definitive conclusions could not be made about the efficacy of ceftobiprole in patients with MRSA bacteremia, who accounted for approximately one fourth of the trial patients.
- More than 95% of the patients were White.
- Daptomycin was administered primarily at the FDA-approved dose of 6 mg/kg/day, which is lower than the dose sometimes used in clinical practice.

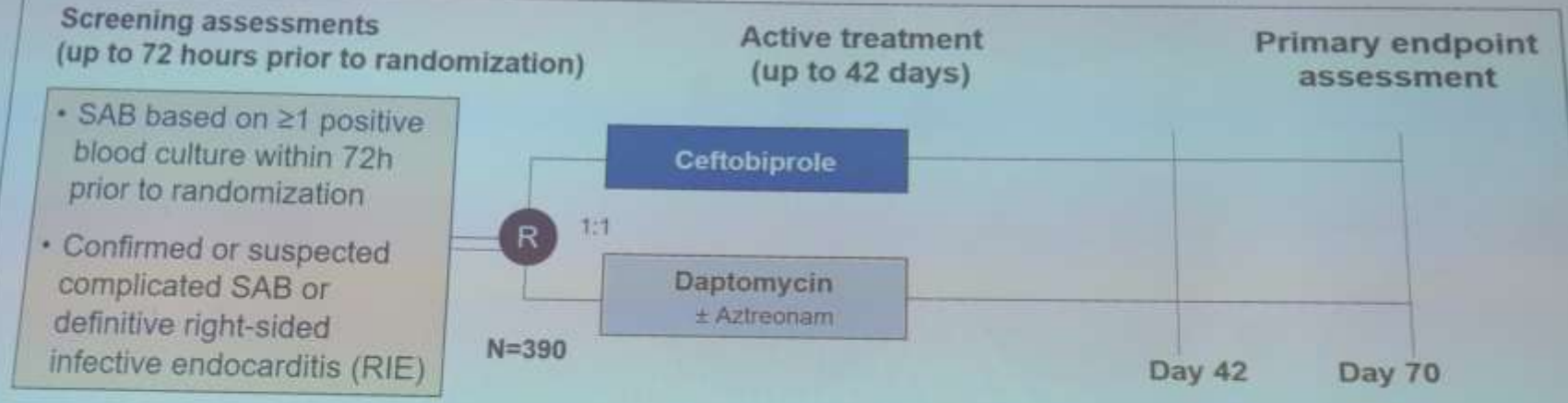
Links: Full Article | NEJM Quick Take



CONCLUSIONS

In patients with complicated *S. aureus* bacteremia, ceftobiprole was noninferior to daptomycin with respect to overall treatment success at 70 days.

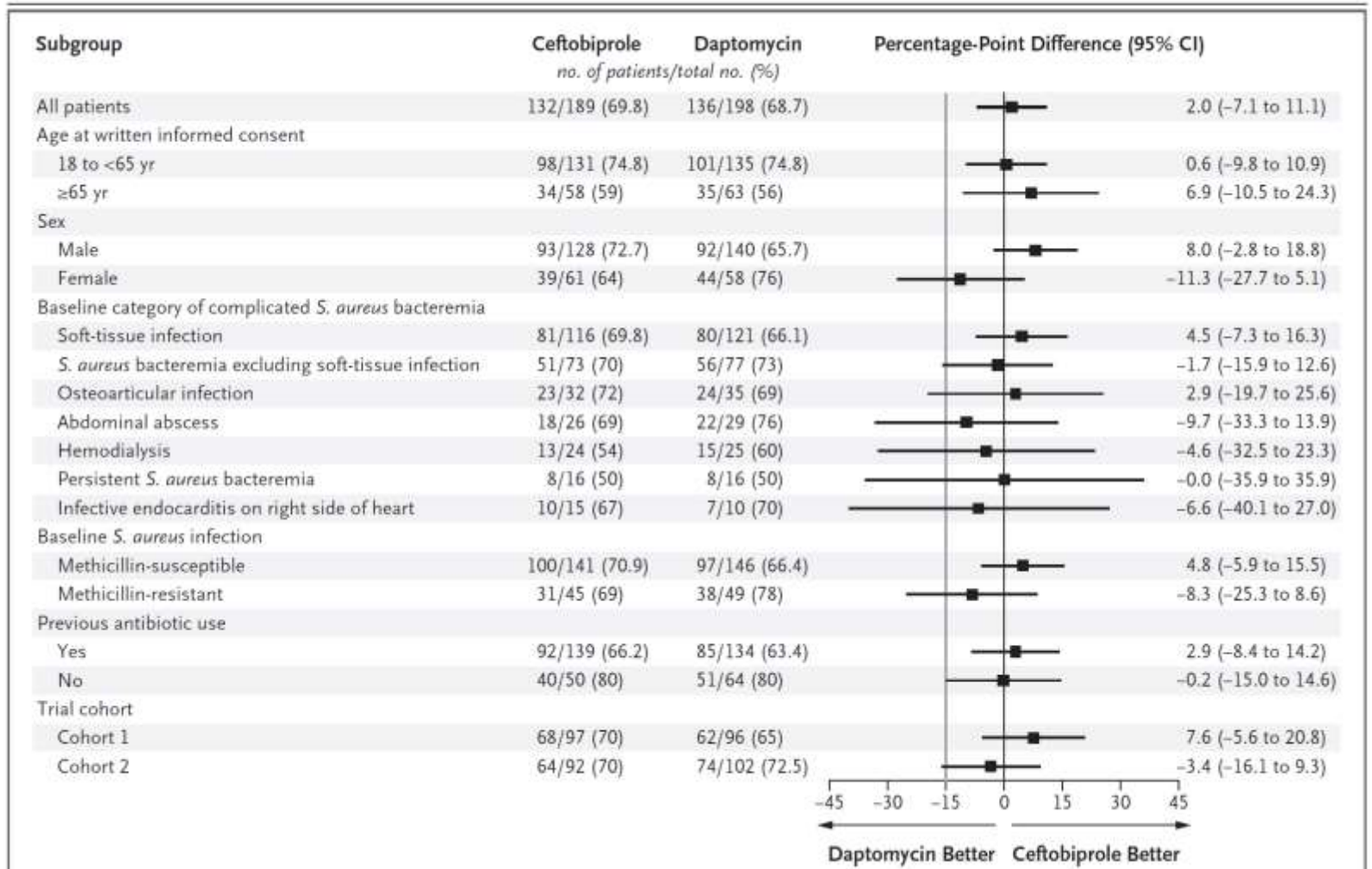
Study treatments and follow-up



- Ceftobiprole: 500 mg q6h on Days 1-8 and 500 mg q8h from Day 9 onwards
- Daptomycin: 6-10 mg/kg q24h according to institutional standards
- Optional aztreonam: 1000 mg q12h

Dose adjustments according to renal function status

Categories of complicated *S. aureus* bacteremia — no. (%)‖			
Any complicated *S. aureus* bacteremia	189 (100.0)	198 (100.0)	387 (100.0)
Soft-tissue infections**	116 (61.4)	121 (61.1)	237 (61.2)
Osteoarticular infections††	32 (16.9)	35 (17.7)	67 (17.3)
Abdominal abscesses‡‡	26 (13.8)	29 (14.6)	55 (14.2)
Hemodialysis-associated *S. aureus* bacteremia§§	24 (12.7)	25 (12.6)	49 (12.7)
Persistent *S. aureus* bacteremia¶¶	16 (8.5)	16 (8.1)	32 (8.3)
Infective endocarditis on right side of heart	15 (7.9)	10 (5.1)	25 (6.5)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

T.L. Holland, S.E. Cosgrove, S.B. Doernberg, T.C. Jenkins, N.A. Turner, H.W. Boucher, O. Pavlov, I. Titov, S. Kosulnykov, B. Atanasov, I. Poromanski, M. Makhviladze, A. Anderzhanova, M.E. Stryjewski, M. Assadi Gehr, M. Engelhardt, K. Hamed, D. Ionescu, M. Jones, M. Saulay, J. Smart, H. Seifert, and V.G. Fowler, Jr., for the ERADICATE Study Group*

- WHY
  - *Potentially* Practice changing
- IMPLICATIONS
  - Ceftobiprole will likely be FDA approved 2024 (under review – 1st new AB for SAB since Daptomycin 15y ago)
  - Design was pharma-led/registrational and thus disappointing – the area of need is MRSA not so much MSSA. I would have preferred ceftaroline (BD dosing) and only MRSA bacteraemia
  - Need head to head before recommending this over fluclox for MSSA! Still nothing shown superior to Vanco for MRSA-B

Clinical Infectious Diseases

MAJOR ARTICLE

DOI: 10.1093/cid/ciad070

Antimicrobial for 7 or 14 days for febrile urinary tract infection in men: a multicenter noninferiority double blind placebo-controlled, randomized clinical trial.

- WHY
  - Practice-changing – an exception to the rule that shorter is better
- SUMMARY
  - 240 men with febrile UTI from 27 French centres were randomised to 7 versus 14 days of antibiotic duration, double-blind, placebo controlled
  - Treatment was ofloxacin (ceftriaxone could be used days 1-3)
  - Rx success at 6 weeks was 55.7% in the 7-day group and 77.6% in the 14-day group (NOT non-inferior, risk difference -21.9%)

N° of participants with positive blood cultures - no./total participants with blood cultures performed. (%)	15/96 (15.6)	18/100 (18)
Pathogen identified - no (%)		
Escherichia coli	105 (91.3)	97 (77.6)
Klebsiella spp.	5 (4.3)	14 (11.2)
Other pathogens:	5 (4.3)	14 (11.2)

Clinical Infectious Diseases

MAJOR ARTICLE

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Antimicrobial for 7 or 14 days for febrile urinary tract infection in men: a multicenter noninferiority double blind placebo-controlled, randomized clinical trial.

- WHY
  - Practice-changing – an exception to the rule that shorter is better
- IMPLICATIONS
  - Previous RCT showed 7 days non-inferior to 14 in males with afebrile outpatient UTIs
  - Men are different from women
  - Shorter is not always better

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 9, 2023 VOL. 388 NO. 10

Treatment Strategy for Rifampin-Susceptible Tuberculosis

- WHY
  - Practice changing
- SUMMARY
  - 674 adults with Rif-S TB randomised to either standard Rx (RI24+PE8) or 3 shorter regimens. Composite 1ry outcome of death/active disease/ongoing Rx at week 96 occurred in 3.9% standard Rx, 11.4% rif-linezolid, 5.8% bedaquiline-linezolid.
  - Shorter regimens: 8 weeks of the 5 drugs +/- a further 4-8 weeks PRN
  - Average Rx duration 180 days (standard) vs 85 days (Bedaquiline)
  - Rif-Linezolid regimen was NOT non-inferior to standard, but Bedaquiline-Linezolid WAS non-inferior.

RESEARCH SUMMARY

Treatment Strategy for Rifampin-Susceptible Tuberculosis

Paton NI et al. DOI: 10.1056/NEJMoa2212537

CLINICAL PROBLEM

The global standard treatment for drug-susceptible tuberculosis is a 24-week rifampin-based regimen, but adherence can be challenging. Clinical trials have shown a high probability of cure with shorter regimens, which suggests that a 24-week regimen may not be needed.

CLINICAL TRIAL

Design: A phase 2–3, international, adaptive, randomized, open-label, noninferiority trial assessed the efficacy and safety of a strategy involving shorter initial treatment for rifampin-susceptible tuberculosis.

Intervention: 674 participants 18 to 65 years of age were randomly assigned to undergo either standard treatment with a 24-week rifampin-based regimen or a strategy involving initial treatment with an 8-week regimen, extended treatment for persistent clinical disease, monitoring after treatment, and retreatment for relapse. There were four strategy groups with different initial regimens; noninferiority was assessed in the two strategy groups with complete enrollment, which had initial regimens of high-dose rifampin–linezolid and bedaquiline–linezolid (each with isoniazid, pyrazinamide, and ethambutol). The primary outcome was a composite of death, ongoing treatment, or active disease at week 96.

RESULTS

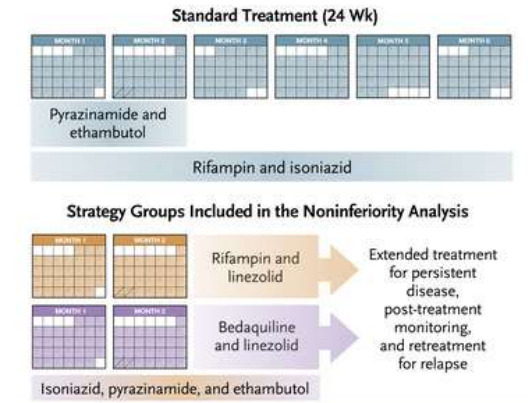
Efficacy: The strategy with an initial rifampin–linezolid regimen did not meet the noninferiority criterion, whereas the strategy with an initial bedaquiline–linezolid regimen was noninferior to standard treatment and was associated with a shorter total duration of treatment.

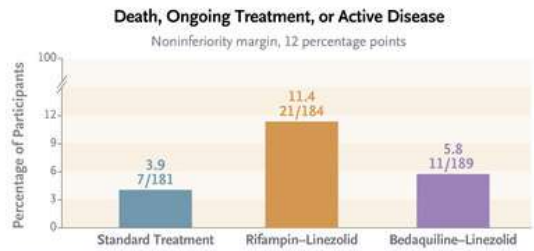
Safety: The incidence of grade 3 or 4 adverse events, serious adverse events, and respiratory disability did not differ significantly between the standard-treatment group and the two strategy groups.

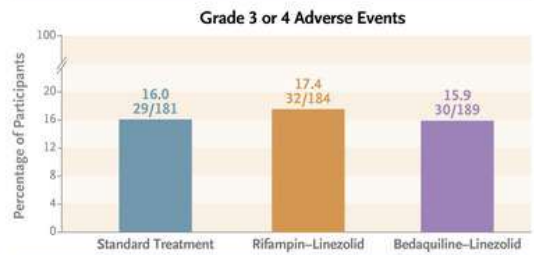
LIMITATIONS AND REMAINING QUESTIONS

- Noninferiority of the treatment strategy was assessed with only two regimens, and the strategy could be refined with the use of alternative regimens.
- No HIV-positive persons were enrolled; further evaluation is warranted in this population.

Links: Full Article | NEJM Quick Take | Editorial







CONCLUSIONS

Among participants with rifampin-susceptible pulmonary tuberculosis, a strategy involving initial treatment with an 8-week bedaquiline–linezolid regimen was noninferior to standard treatment with respect to clinical outcomes, with no apparent safety concerns.

Outcome	Standard Treatment (N=181)	Strategy with Rifampin–Linezolid (N=184)	Strategy with Rifampin–Linezolid vs. Standard Treatment	Strategy with Bedaquiline–Linezolid (N=189)	Strategy with Bedaquiline–Linezolid vs. Standard Treatment
			Difference (95% CI)†		Difference (95% CI)†
Participant-centered outcomes					
Safety outcomes					
Adverse events through wk 96 — no. (%)					
Any grade 3 or 4 adverse event	29 (16.0)	32 (17.4)	1.4 (–6.4 to 9.2)	30 (15.9)	–0.2 (–7.9 to 7.4)
Any serious adverse event	11 (6.1)	18 (9.8)	3.7 (–2.1 to 9.7)	14 (7.4)	1.3 (–4.2 to 6.9)
Death††	3 (1.7)	5 (2.7)	1.1 (–2.4 to 4.8)	1 (0.5)	–1.1 (–4.3 to 1.5)
Respiratory disability at wk 96 — no. (%)‡‡					
Grade on MRC breathlessness scale ≥3	0	2.7 (1.5)	1.5 (–0.5 to 3.5)	2.7 (1.4)	1.4 (–0.5 to 3.3)
FEV_1 <50% of predicted value	24.3 (13.4)	20.5 (11.1)	–1.1 (–8.7 to 6.4)	22.4 (11.8)	0.1 (–7.8 to 7.9)

- WHY
  - Practice changing
- IMPLICATIONS
  - Have we finally found the holy grail of a shorter TB Rx regimen that works?
  - Short regimen higher pill burden, higher *potential* for toxicity
    - Isoniazid+Pyrazinamide+Ethambutol+Bedaquiline+Linezolid
  - ?Cost and availability.

ORIGINAL ARTICLE

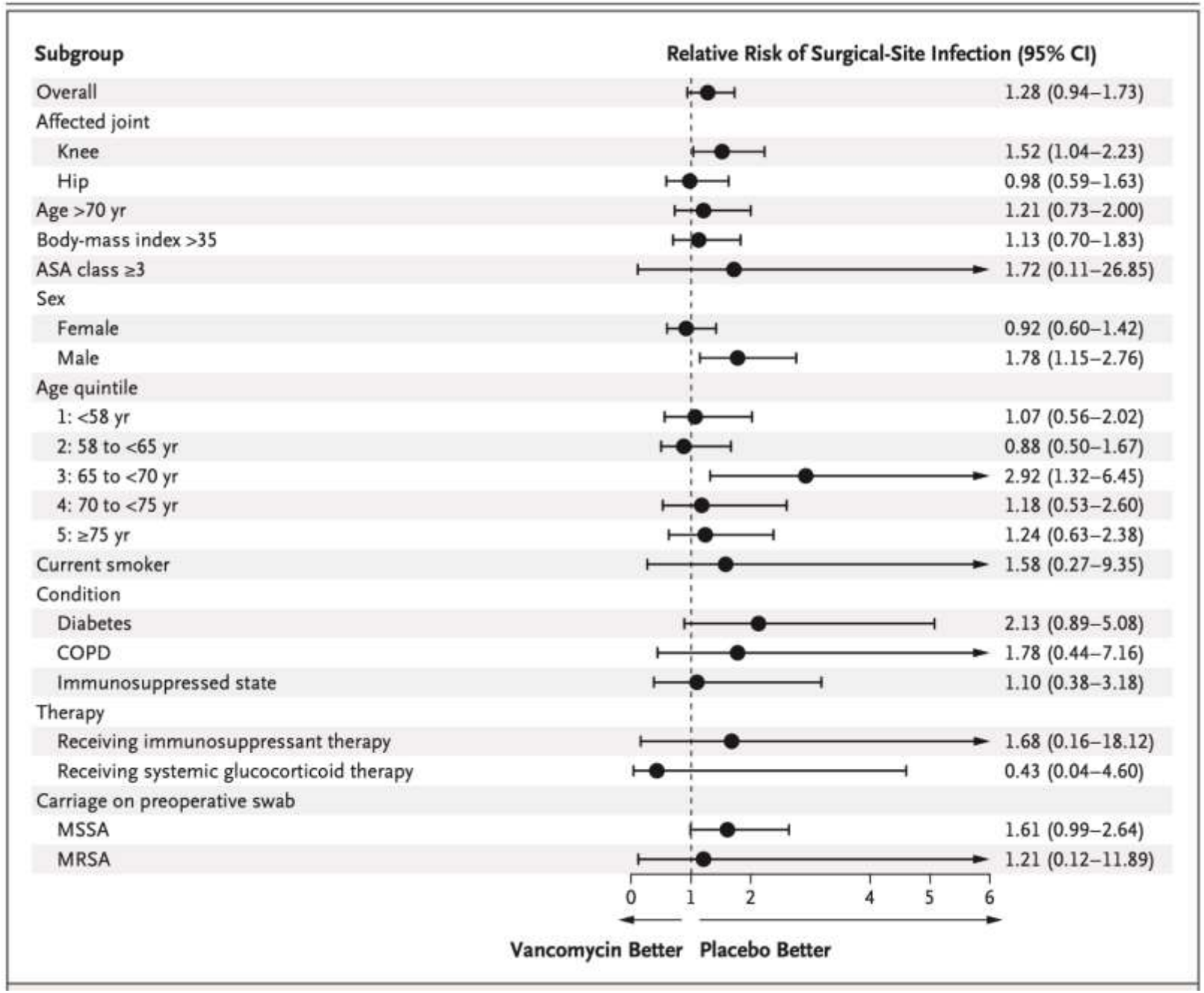
Trial of Vancomycin and Cefazolin as Surgical Prophylaxis in Arthroplasty

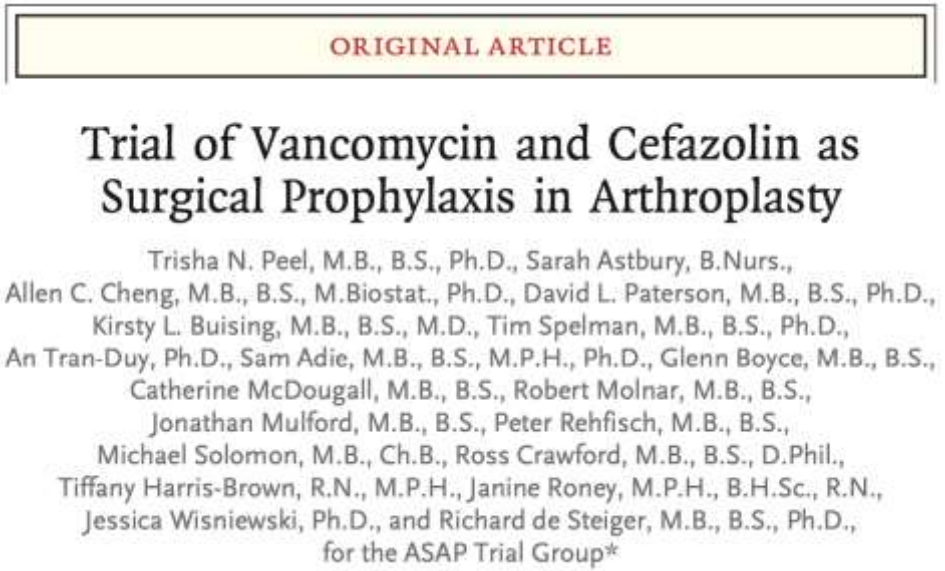
Trisha N. Peel, M.B., B.S., Ph.D., Sarah Astbury, B.Nurs.,
Allen C. Cheng, M.B., B.S., M.Biostat., Ph.D., David L. Paterson, M.B., B.S., Ph.D.,
Kirsty L. Buising, M.B., B.S., M.D., Tim Spelman, M.B., B.S., Ph.D.,
An Tran-Duy, Ph.D., Sam Adie, M.B., B.S., M.P.H., Ph.D., Glenn Boyce, M.B., B.S.,
Catherine McDougall, M.B., B.S., Robert Molnar, M.B., B.S.,
Jonathan Mulford, M.B., B.S., Peter Rehfisch, M.B., B.S.,
Michael Solomon, M.B., Ch.B., Ross Crawford, M.B., B.S., D.Phil.,
Tiffany Harris-Brown, R.N., M.P.H., Janine Roney, M.P.H., B.H.Sc., R.N.,
Jessica Wisniewski, Ph.D., and Richard de Steiger, M.B., B.S., Ph.D.,
for the ASAP Trial Group*

- WHY
  - Practice changing, dogma challenging
- SUMMARY
  - 4,239 patients having elective hip or knee replacement at one of 11 Australian hospitals without known MRSA colonisation, randomised to standard prophylaxis (cefazolin+placebo) or combination (cefazolin+vancomycin)
  - All followed local protocols for pre-op screening and Staph load reduction
  - SSI occurred in 4.5% vanco group versus 3.5% placebo (RR 1.28, 95% CI 0.94 to 1.73)

Table 2. Outcomes in the Modified Intention-to-Treat Population.

Outcome	Vancomycin (N=2044)	Placebo (N=2069)	Relative Risk (95% CI)*
	no./total no. (%)		
Primary			
Surgical-site infection at 90 days	91/2044 (4.5)	72/2069 (3.5)	1.28 (0.94–1.73)†
Knee	63/1109 (5.7)	42/1124 (3.7)	1.52 (1.04–2.23)
Hip	28/920 (3.0)	29/930 (3.1)	0.98 (0.59–1.63)
Shoulder	0/15	1/15 (6.7)	—
Secondary			
Superficial surgical-site infection at 30 days			
Knee	59/1109 (5.3)	39/1124 (3.5)	1.53 (1.03–2.28)
Hip	25/920 (2.7)	24/930 (2.6)	1.05 (0.61–1.83)
Shoulder	0/15	1/15 (6.7)	—
Pooled	84/2044 (4.1)	64/2069 (3.1)	1.33 (0.97–1.83)


Subgroup
Relative Risk of Surgical-Site Infection (95% CI)
Overall
1.28 (0.94–1.73)
Affected joint
Knee
1.52 (1.04–2.23)
Hip
0.98 (0.59–1.63)
Age >70 yr
1.21 (0.73–2.00)
Body-mass index >35
1.13 (0.70–1.83)
ASA class ≥3
1.72 (0.11–26.85)
Sex
Female
0.92 (0.60–1.42)
Male
1.78 (1.15–2.76)
Age quintile
1: <58 yr
1.07 (0.56–2.02)
2: 58 to <65 yr
0.88 (0.50–1.67)
3: 65 to <70 yr
2.92 (1.32–6.45)
4: 70 to <75 yr
1.18 (0.53–2.60)
5: ≥75 yr
1.24 (0.63–2.38)
Current smoker
1.58 (0.27–9.35)
Condition
Diabetes
2.13 (0.89–5.08)
COPD
1.78 (0.44–7.16)
Immunosuppressed state
1.10 (0.38–3.18)
Therapy
Receiving immunosuppressant therapy
1.68 (0.16–18.12)
Receiving systemic glucocorticoid therapy
0.43 (0.04–4.60)
Carriage on preoperative swab
MSSA
1.61 (0.99–2.64)
MRSA
1.21 (0.12–11.89)
0
1
2
4
5
6
Vancomycin Better
Placebo Better



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for the ASAP Trial Group*

- WHY
  - Practice changing, dogma challenging
- IMPLICATIONS
  - Early post-op PJI is often polymicrobial and involves cefazolin-R organisms (CoNS, enterococcus) – so adding vanco to cefazolin should work right?
  - BUT theoretical reasoning for ID (and other) interventions often turns out to be completely wrong when subjected to an RCT

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection

The ACORN Randomized Clinical Trial

JAMA. 2023;330 (16):1557-1567.
do:10.1001/jama.2023.20583

- WHY
  - Dogma-challenging
- SUMMARY
  - 2,511 patients presenting to ED/ICU for whom clinicians started an antipseudomonal antibiotic within 12h of presentation, randomised to Pip-Tazo or Cefepime. The primary outcome of AKI (10.2% cefepime, 8.8% Pip-Tazo) or death (7.0%C vs 6.0%P) by day 14 was no different.
  - Embedded trial – waiver of consent, electronic medical record automatically screened for eligibility, randomised and recommended what to prescribe
  - 77% were receiving concomitant vancomycin at baseline
  - More delirium in the cefepime group

JAMA

QUESTION Does the choice between cefepime and piperacillin-tazobactam affect the risks of acute kidney injury or neurological dysfunction in adults hospitalized with acute infection?

CONCLUSION Among hospitalized adults, the risk of acute kidney injury did not differ between cefepime and piperacillin-tazobactam, but neurological dysfunction was more common with cefepime.

POPULATION

1439 Men **1071** Women

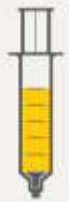
Adults hospitalized with acute infection

Median age: **58** years

LOCATION

1
Medical center
in Nashville, Tennessee

INTERVENTION



2634 Patients randomized
2511 Patients analyzed

1214
Cefepime
Administered as an intravenous push over 5 minutes

1297
Piperacillin-tazobactam
Administered as a bolus for the initial administration and then extended infusion over 4 hours for subsequent doses

PRIMARY OUTCOME

Highest stage of acute kidney injury or death by day 14 (measured on a 5-level ordinal scale; range: no acute kidney injury to death)

FINDINGS

Highest stage of acute kidney injury or death by day 14

Cefepime

Survived with stage 3 acute kidney injury	**7.0%** (85 of 1214 patients)
Died	**7.6%** (92 of 1214 patients)

Piperacillin-tazobactam

Survived with stage 3 acute kidney injury	**7.5%** (97 of 1297 patients)
Died	**6.0%** (78 of 1297 patients)

There was no significant between-group difference:
Odds ratio, 0.95 (95% CI, 0.80 to 1.13); $P = .56$

Qian ET, Casey JD, Wright A, et al; Vanderbilt Center for Learning Healthcare and the Pragmatic Critical Care Research Group. Cefepime vs piperacillin-tazobactam in adults hospitalized with acute infection: the ACORN randomized clinical trial. *JAMA*. Published online October 14, 2023. doi:10.1001/jama.2023.20583

Figure 2. Receipt of Antibiotics by Group

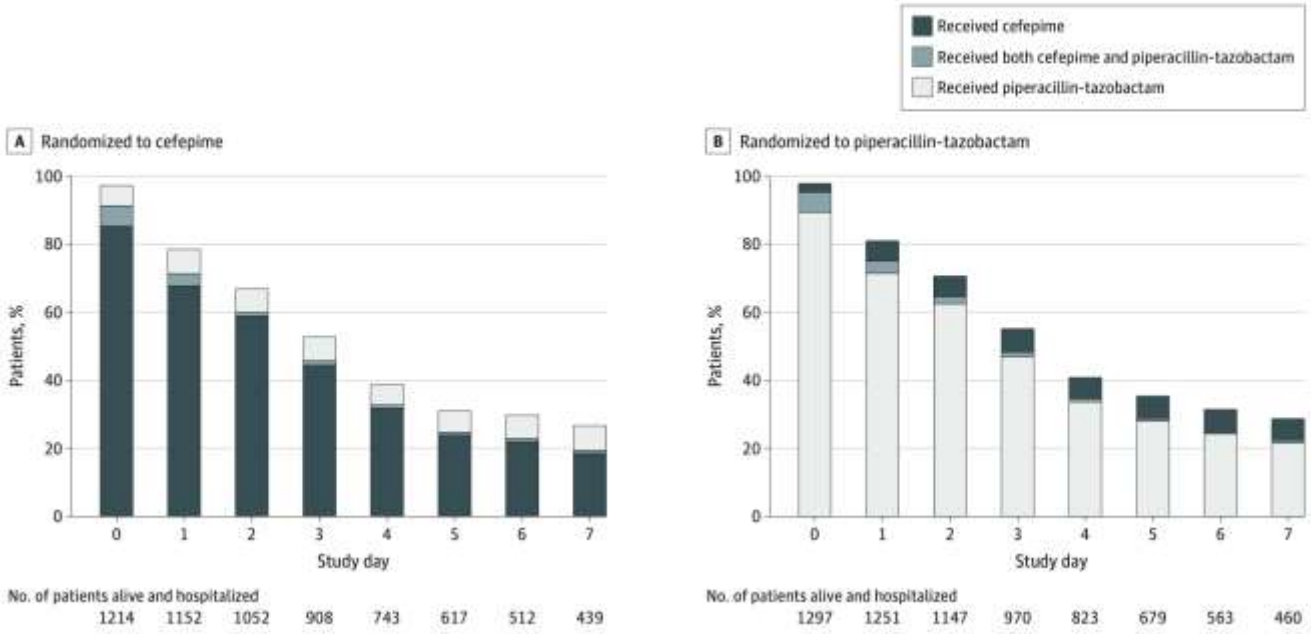


Table 2. Primary, Secondary, and Exploratory Outcomes

	Cefepime (n = 1214)	Piperacillin-tazobactam (n = 1297)	Between-group difference expressed as RD or OR (95% CI)[a]
Primary outcome			
Acute kidney injury or death by day 14, No. (%)			OR, 0.95 (0.80 to 1.13)
No stage (survived)	910 (75.0)	952 (73.4)	
Stage 1 (survived)	86 (7.1)	100 (7.7)	
Stage 2 (survived)	41 (3.4)	70 (5.4)	
Stage 3 (survived)	85 (7.0)	97 (7.5)	
Stage 4 (died)	92 (7.6)	78 (6.0)	
Secondary outcomes			

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

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The ACORN Randomized Clinical Trial

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- WHY
  - Dogma-challenging
- IMPLICATIONS
  - Vanco plus pip-tazo is probably NOT more nephrotoxic than Vanco plus a cephalosporin
  - RCT results are often different from, and should trump observational study results
  - It is possible to do a truly embedded RCT

ORIGINAL ARTICLE

Azithromycin to Prevent Sepsis or Death in Women Planning a Vaginal Birth

A.T.N. Tita, W.A. Carlo, E.M. McClure, M. Mwenechanya, E. Chomba, J.J. Hemingway-Foday, A. Kavi, M.C. Metgud, S.S. Goudar, R. Derman, A. Lokangaka, A. Tshefu, M. Bauserman, C. Bose, P. Shivkumar, M. Waikar, A. Patel, P.L. Hibberd, P. Nyongesa, F. Esamai, O.A. Ekhaguere, S. Bucher, S. Jessani, S.S. Tikmani, S. Saleem, R.L. Goldenberg, S.M. Billah, R. Lennox, R. Haque, W. Petri, L. Figueroa, M. Mazariegos, N.F. Krebs, J.L. Moore, T.L. Nolen, and M. Koso-Thomas, for the A-PLUS Trial Group*

N Engl J Med 2022;387:679-91.

- WHY
  - *Potentially* Practice changing
- SUMMARY
  - 29,278 women having planned vaginal delivery in 7 low or middle income countries (Africa, Asia, Latin America), randomised to a single 2g oral dose of azithromycin or placebo. Maternal death or sepsis within 6 weeks was lower in the azithro group (1.6%) than the placebo (2.4%), RR 0.67, p<0.001
  - No difference in maternal mortality, or in neonatal outcomes

Table 2. Maternal and Neonatal Primary Outcomes and Their Components.

Outcome	Azithromycin	Placebo	Relative Risk (95% CI)*	P Value†
	no./total no. (%)			
Maternal				
Death or sepsis within 6 wk after birth	227/14,526 (1.6)	344/14,637 (2.4)	0.67 (0.56–0.79)	<0.001
Sepsis	219/14,558 (1.5)	339/14,662 (2.3)	0.65 (0.55–0.77)	
Death				
From any cause	11/14,526 (0.1)	9/14,635 (0.1)	1.23 (0.51–2.97)	
From sepsis	4/14,526 (<0.1)	1/14,635 (<0.1)	4.04 (0.45–36.14)	
Neonatal				
Stillbirth or neonatal death or sepsis within 4 wk after birth	1,540/14,658 (10.5)	1,526/14,756 (10.3)	1.02 (0.95–1.09)	0.56

ORIGINAL ARTICLE

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N Engl J Med 2022;387:679-91.

- WHY
  - *Actually probably not* Practice changing!
- IMPLICATIONS
  - Probably not applicable in high-income countries (lower baseline rate of maternal sepsis or death) – although note the LUSCS equivalent is recommended in the USA
  - Superiority driven only by less maternal sepsis (not a mortality reduction, and no benefit to the neonate) – mainly endometritis. Is this worth a NNT of 125?