NW Hospital Medicine: Literature Updates

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R LOGAN JONES MD FACP

Learning Objectives

Understand the necessity and outcomes of prescribing beta-blockers for post-myocardial infarction patients with preserved ejection fraction.

Compare whether cefepime or piperacillin-tazobactam offers superior efficacy and safety for treating acute infections in hospitalized adults.

Recognize the value of a validated clinical decision rule for safely performing direct oral penicillin challenges in low-risk allergy patients to enhance antibiotic stewardship.

Appreciate patient preferences for telemedicine video backgrounds to improve patient satisfaction and engagement during virtual hospitalist consultations.

Disclosures

No financial disclosures relevant to the contents of this talk

I hereby disclose that I am a giant nerd

Question 1:

60 yo woman, BMI 30, Presents with chest pain found to have NSTEMI. Underwent angiography 1 single DES deployed for obstructive CAD. TTE showing LVEF 55%, Already on metformin, ACE-I, Rosuvastatin. What new medications should be recommended at discharge

1. Aspirin, clopidogrel
2. Aspirin, clopidogrel, metoprolol
3. Aspirin, clopidogrel, metoprolol, semaglutide
4. Aspirin, clopidogrel, semaglutide.

ORIGINAL ARTICLE

Beta-Blockers after Myocardial Infarction and Preserved Ejection Fraction

Authors: Troels Yndigegn, M.D., Bertil Lindahl, Ph.D., Katarina Mars, M.D., Joakim Alfredsson, Ph.D., Jocelyne Benatar, Ph.D., Lisa Brandin, Ph.D., David Erlinge, Ph.D., +12, for the REDUCE-AMI Investigators* Author Info & Affiliations

Published April 7, 2024 | N Engl J Med 2024;390:1372-1381 | DOI: 10.1056/NEJMoa2401479 | VOL. 390 NO. 15

Design: REDUCE-AMI

Background

- **Goal:** To evaluate the benefit of beta-blockers in patients post-AMI with preserved left ventricular ejection fraction (LVEF).
- **Hypothesis:** Long-term beta-blockade may reduce mortality or recurrent AMI.
- **Relevance:** The efficacy of beta-blockers is well-documented for reduced LVEF, but evidence in preserved LVEF post-AMI is limited.

Study Design

- **Type:** International, registry-based, open-label, randomized trial.
- **Sample Size:** 5,020 patients.
- **Duration:** Median follow-up of 3.5 years.
- **Interventions:**
  - **Beta-blockers:** Metoprolol or bisoprolol.
  - **Control:** Usual care (beta-blocker tapering in applicable cases).
- **Inclusion Criteria:**
  - AMI within 7 days, coronary angiography, obstructive coronary artery disease, and LVEF ≥50%.
- **Exclusion Criteria:**
  - Contraindication for beta-blockers, alternative indication for beta-blockers.

Patient Characteristics: REDUCE-AMI

Median age: 65 years.

Gender distribution: 23% female.

ST-segment elevation myocardial infarction (STEMI): 35% of patients.

Hypertension prevalence: 46% of patients had hypertension.

Diabetes: 14% of patients had diabetes mellitus.

Percutaneous coronary intervention (PCI): 96% of patients underwent PCI during the index hospitalization

Discharge meds:

95+% in both arms received: DAPT (ASA + P2Y12 inhibitor), Statin

ACE/ARB: ~80% both arms

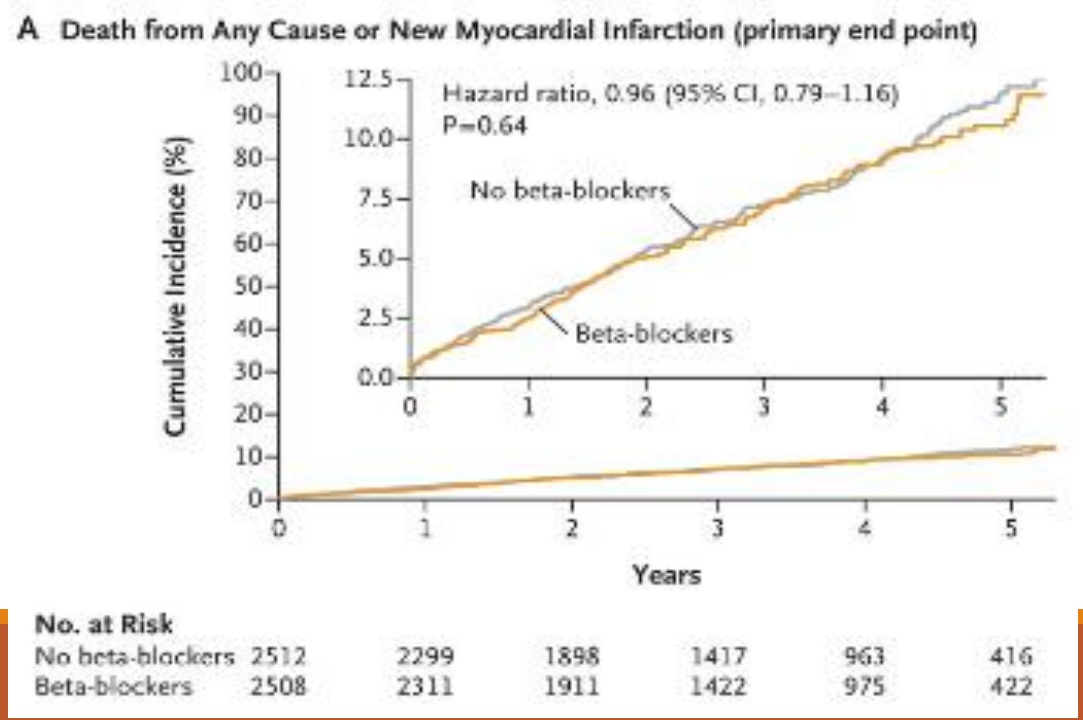
B-Blockade: Intervention 95%, Control 10%

Outcomes: REDUCE-AMI

Primary Outcome:

Composite of all-cause death or nonfatal AMI:

- **Beta-blocker group:** 7.9%.
- **Control group:** 8.3%.
- **HR:** 0.96 (95% CI 0.79-1.16), p = 0.64 (not significant).



Secondary Outcomes:

- **All-cause death:** 3.9% (beta-blocker) vs. 4.1% (control), HR 0.94, p = 0.66.
- **Recurrent AMI:** 4.5% (beta-blocker) vs. 4.7% (control), HR 0.96, p = 0.74.
- **Heart failure hospitalization:** 0.8% vs. 0.9%, HR 0.91, p = 0.76.

Safety Outcomes: <u>no difference</u>

- **Bradyarrhythmia, hypotension, or syncope**
- **Asthma/COPD hospitalization:**

Conclusions: REDUCE-AMI

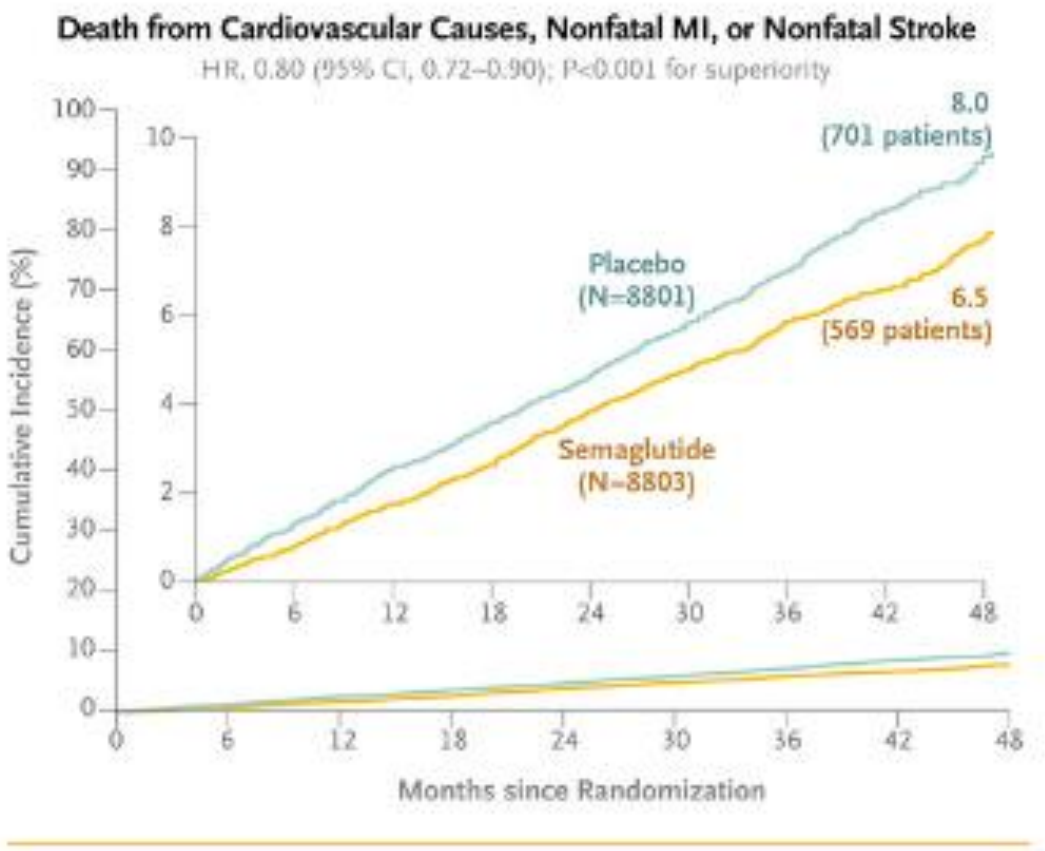
In patients with acute myocardial infarction with angiography proven obstructive coronary disease, with PCI at time of angiography, with preserved LVEF:

- There is a lack of data to demonstrate reduction in MACE in this population by addition of cardio-selective Beta-blockade
- Beta blockade cause plethora of “mild” side effects that impact patient quality of life
- **Personal take:** I wouldn’t take it, share that with patient during SDM
- Optimize & prioritize other medications & lifestyle improvements.
- Trials that focus on non-PCI intervened ACS are underway, Expect updates to guidelines in the coming few years

BONUS CONTENT

SELECT trial - NEJM 2023

Semaglutide and Cardiovascular Outcomes in **Obesity (BMI > 27) without Diabetes**



- **Patients**: Preexisting cardiovascular disease (prior ACS or CVA), overweight or obese, without diabetes.
- **Intervention**: Weekly subcutaneous semaglutide, 2.4 mg
- **Outcome**: Superior to placebo in reducing death from cardiovascular causes, nonfatal MI, or nonfatal stroke.
- **Follow-Up**: Mean of 39.8 months.
- **Recommendation**: Hospitalists should consider starting the prior authorization process for semaglutide at discharge.

Question 2:

Your patient is a 70 year old man, community dwelling, no recent hospitalization encounters, with history of hypertension and well controlled DM on metformin. He has a history of ceftriaxone-resistant E. coli from a simple cystitis 6 months ago. He presents to the emergency department with signs of sepsis: tachycardia, leukocytosis (15k), AKI (baseline Cr 1.0, now 1.6), very mild encephalopathy (GCS still 15), and borderline low blood pressure (MAP 65-70 mmHg). SOFA score is 2. CT chest/abd/pelvis shows possible small pneumonia, no intra-abdominal source. Urine is bland, and there's low concern for head/neck infection (no meningismus). Blood cultures are pending, viral swabs negative. The ED has already loaded a vancomycin dose. Based on recent evidence regarding safety and efficacy of beta-lactams in sepsis treatment, and considering the patient's history of antibiotic-resistant infection, which antibiotic regimen would you choose:

1. Vancomycin monotherapy
2. Vancomycin + Ceftriaxone
3. Vancomycin + Cefepime
4. Vancomycin + Zosyn

Doesn’t Vanc + Pip-Tazo cause AKI?

Do I need Pseudomonal coverage here? Am I being overly cautious and a bad steward?

Isn’t it just safer to start broad coverage and narrow later?

This patient is old, I remember that one time I gave cefepime and my patient got really confused…

JAMA | Original Investigation | CARING FOR THE CRITICALLY ILL PATIENT

Cefepime vs Piperacillin-Tazobactam in Adults Hospitalized With Acute Infection

The ACORN Randomized Clinical Trial

Edward T. Qian, MD, MSc; Jonathan D. Casey, MD, MSc; Adam Wright, PhD; Li Wang, MS; Matthew S. Shotwell, PhD; Justin K. Siemann, PhD; Mary Lynn Dear, PhD; Joanna L. Stollings, PharmD; Brad D. Lloyd, RRT-ACCS; Tanya K. Marvi, MD; Kevin P. Seitz, MD, MSc; George E. Nelson, MD; Patty W. Wright, MD; Edward D. Siew, MD, MSc; Bradley M. Dennis, MD; Jesse O. Wrenn, MD, PhD; Jonathan W. Andereck, MD, MBA; Jin H. Han, MD, MSc; Wesley H. Self, MD, MPH; Matthew W. Semler, MD, MSc; Todd W. Rice, MD, MSc; for the Vanderbilt Center for Learning Healthcare and the Pragmatic Critical Care Research Group

Design:
ACORN - Cefepime vs. Piperacillin-Tazobactam

Goal:

To compare the safety of cefepime and piperacillin-tazobactam in adults with acute infections

Rationale:

Previous studies suggested that cefepime may cause neurotoxicity

Piperacillin-tazobactam may cause acute kidney injury (AKI) when used in conjunction with vancomycin, but direct comparisons are lacking.

Study Design

- **Type:** Pragmatic, open-label, randomized clinical trial.
- **Setting:** Conducted in a single US academic center's emergency department and ICU.
- **Duration:** November 2021 - October 2022.
- **Enrollment:** 2,511 patients randomized to either cefepime or piperacillin-tazobactam.

Intervention:

- Patients were randomized 1:1 to receive either cefepime or piperacillin-tazobactam.

Patient Characteristics: ACORN

BASELINE CHARACTERISTICS NEAR EQUIPOISE

Median age: 58 years.

Gender: 42.7% female.

Sepsis: 54.2% had sepsis at enrollment.

Comorbidities (CCI) : 4 in both groups

Concurrent vancomycin use: 77.2% of patients.

NOTABLE POTENTIAL DIFFERENCES

Higher baseline ICU admission: 6.5% of cefepime patients vs 4.2% for piperacillin-tazobactam (p = 0.011)

Higher baseline coma and delirium: 6.9% coma and 5.1% delirium in the cefepime group vs. 5.9% coma and 3.9% delirium in the pip-tazo group (p= 0.35)

Outcomes: ACORN

Primary Outcome (composite):

- AKI Stage (staged) OR death by day 14 > no difference
  - Odds Ratio 0.95 (0.08 – 1.13)

Secondary Outcomes

- Final Cr level >=2x baseline level RD: −1.0 (−2.2 to 0.1) - > **No significance**
- Delirium: OR, 0.79 (0.65 to 0.95) – **Favors Pip-Tazo**
- Delirium + Coma Free days: OR, 0.80 (0.66 to 0.97) – **Favors Pip-Tazo**

Reassuring Markers

- No difference in hospital free days
- No difference in allergic reactions to study drug

Conclusion: ACORN

”Among adults presenting to the hospital with suspected infection in this pragmatic trial, the highest stage of **AKI or death at 14 days did not differ between patients randomized to cefepime or piperacillin-tazobactam.**

Patients randomized to cefepime experienced more neurological dysfunction, as measured by the number of days alive and free of delirium and coma.”

Pip-Tazo > Cefepime

Is that the last word?

JAMA Internal Medicine | Original Investigation | LESS IS MORE

Mortality of Patients With Sepsis Administered Piperacillin-Tazobactam vs Cefepime

Rishi Chanderraj, MD, MSc; Andrew J. Admon, MD, MSc, MPH; Ying He, PhD; Mark Nuppnau, MSc; Owen R. Albin, MD; Hallie C. Prescott, MD, MSc; Robert P. Dickson, MD; Michael W. Sjoding, MD, MSc

Design:
Mortality of Patients With Sepsis Administered Piperacillin-Tazobactam (PT) vs Cefepime

Objective: To evaluate 90-day mortality for patients with sepsis treated with Piperacillin-Tazobactam (PT) vs. Cefepime.

Hypothesis: Anti-anaerobic coverage without clinical indication may harm patients via mechanism of microbiome depletion

Design: Retrospective cohort study using an ***instrumental variable analysis.***

- The study used a drug shortage to simulate randomization, reducing bias in comparing antibiotic outcomes.

Population:

- Adults with suspected sepsis treated with Vancomycin + PT or Vancomycin + Cefepime.
- **EXCLUSION:** concerns of needs for ant anaerobic coverage such as: *CNS infection, intra-abdominal, head neck, or necrotizing infection*

Time Frame: Data collected from **2014 to 2018** at the University of Michigan.

Sample Size: 7,569 patients:

- PT group: 4,523 patients.
- Cefepime group: 3,046 patients.

Figure 1. Cohort Creation Diagram for the Study of Piperacillin-Tazobactam Shortage and Sepsis

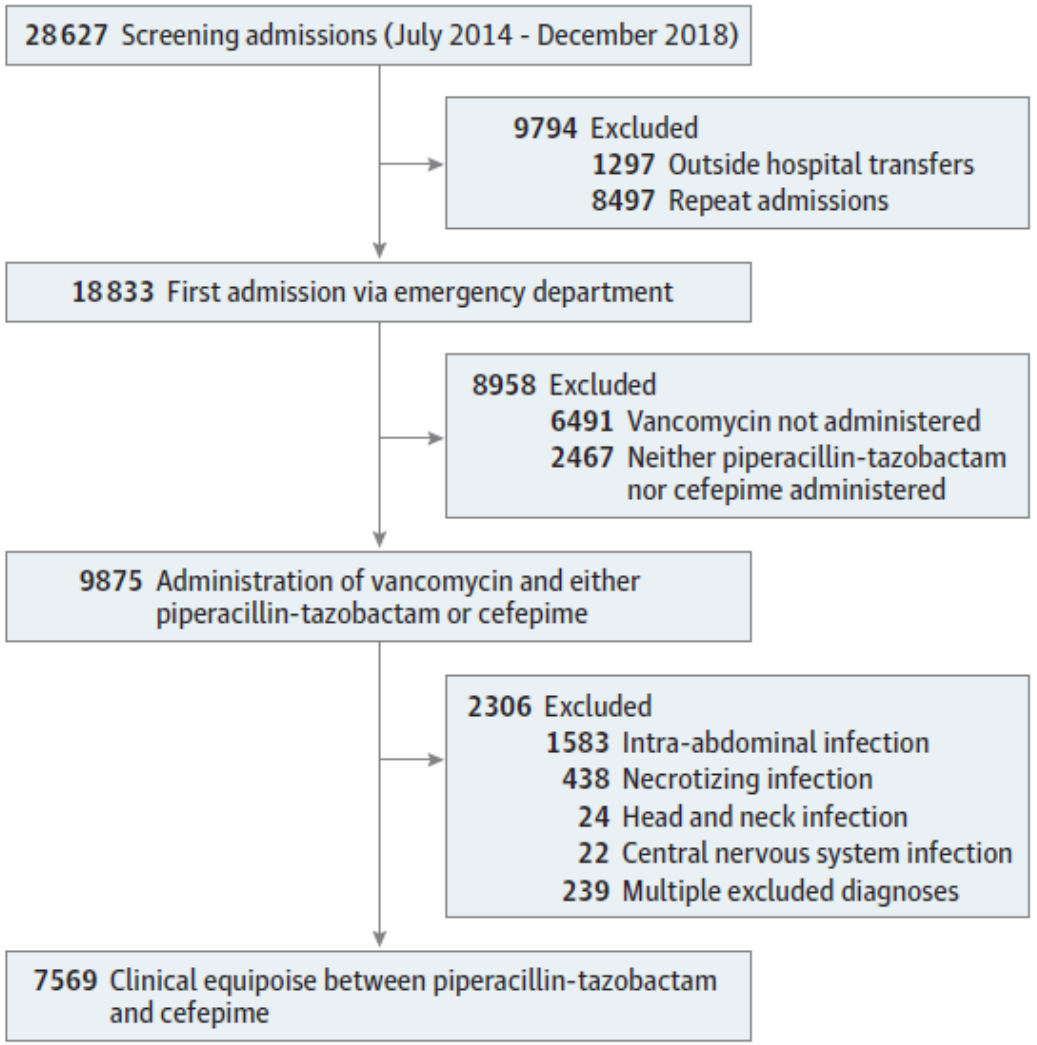
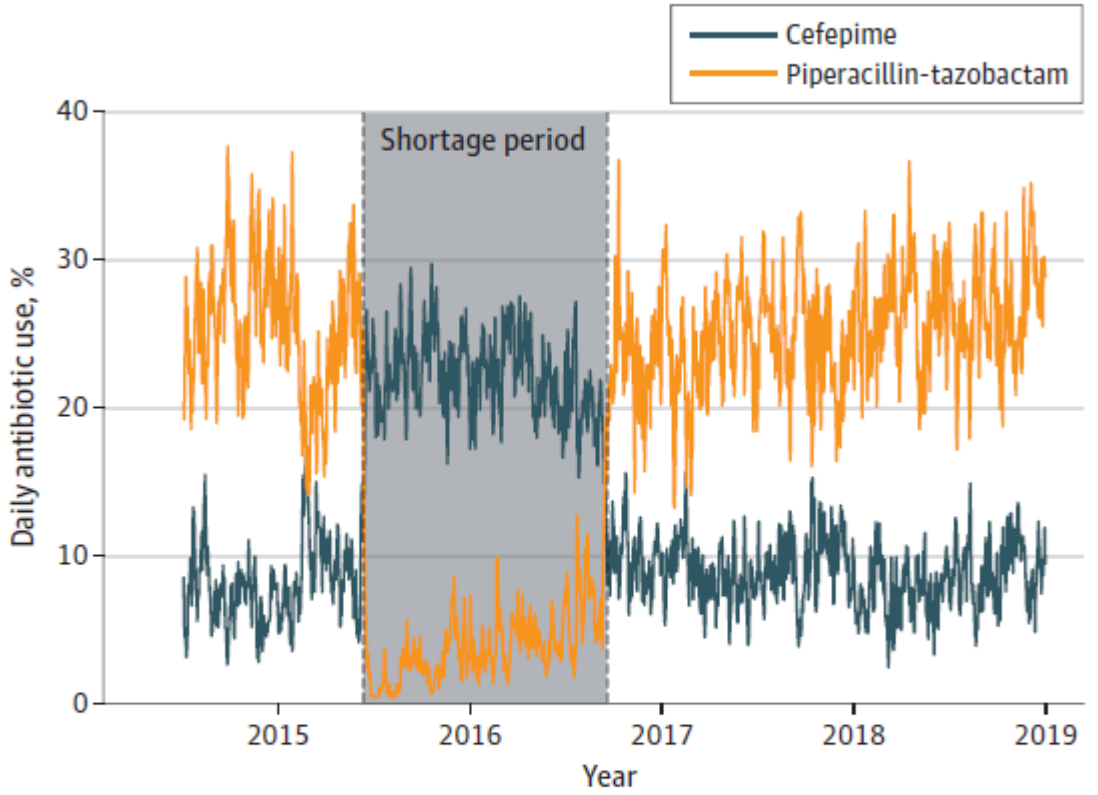


Figure 2. Change in Antibiotic Use During Piperacillin-Tazobactam Shortage



Percentage of daily antibiotic use among hospitalized patients at University of Michigan during piperacillin-tazobactam shortage (June 12, 2015, to September 18, 2016) (calculated as number of doses of piperacillin-tazobactam administered in the hospital on a particular day divided by number of doses of all antibiotics administered in the hospital on a particular day.)

Patient Characteristics

Median Age: 63 years (IQR: 52-73).

Sex: PT group: 57% male. Cefepime group: 52% male.

Severity of Illness (SOFA score): Median: 5 (IQR: 3-6) for both groups.

Key comorbidities:

- Diabetes: PT: 26.1% | Cefepime: 27.2%.
- Chronic pulmonary disease: PT: 22.3% | Cefepime: 25.7%.
- Coronary artery disease: PT: 11.7% | Cefepime: 13.7%.

Infectious Source (within first 24 hours):

Source of Infection	Cefepime (%)	Pip-Tazo
Bacteremia	44 (1.4)	83 (1.8)
Skin Soft Tissue	127 (4.2)	173 (3.8)
UTI	210 (6.9)	312 (6.9)
Pneumonia	568 (18.6)	713 (15.8)
Unclear	2097 (68.8)	3242 (71.7)

Outcomes: Adjusted 90 day death

Figure 3. Ninety-Day Survival for Primary Cohort

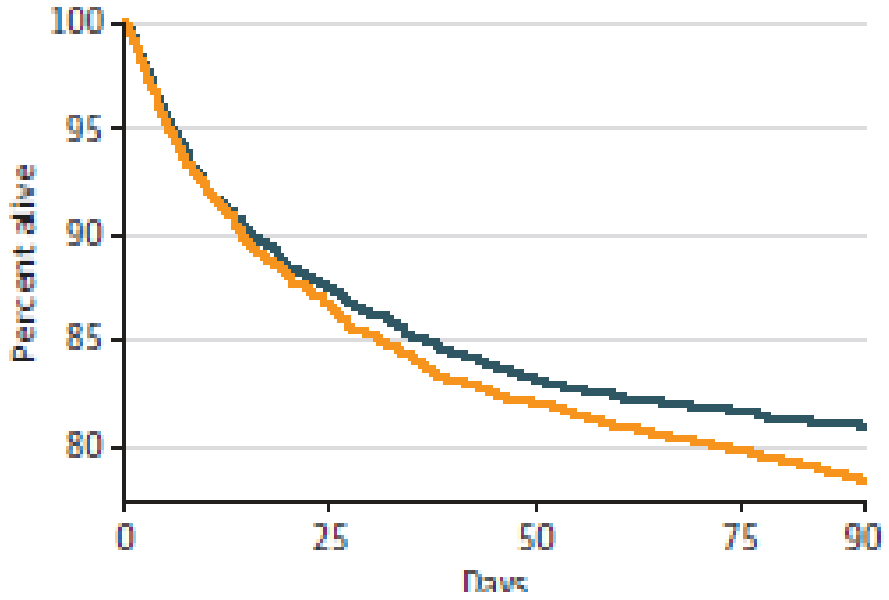
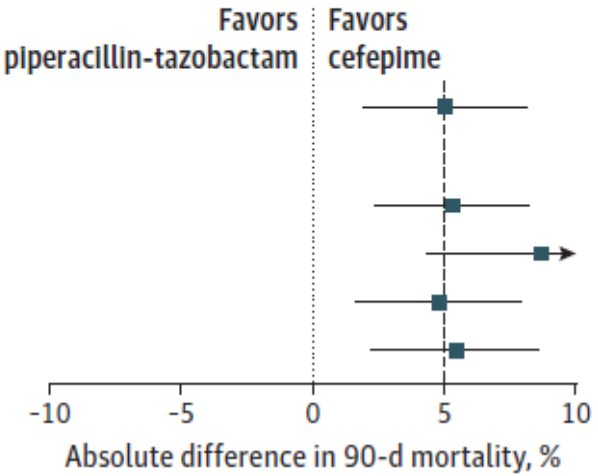


Figure 4. Primary Instrumental Variable and Sensitivity Analyses for 90-Day Mortality Among Adults Hospitalized With Suspected Sepsis Treated With Either Piperacillin-Tazobactam or Cefepime

Model	Absolute difference, % (95% CI)
Primary analysis	5.0 (1.9-8.2)
Sensitivity analyses	
Nonlinear model	5.3 (2.4-8.2)
Including year of admission	8.6 (4.3-13.0)
Including anatomic site of infection	4.7 (1.6-7.9)
Including other antibiotics	5.4 (2.3-8.6)



Outcomes: Adjusted 90 day death

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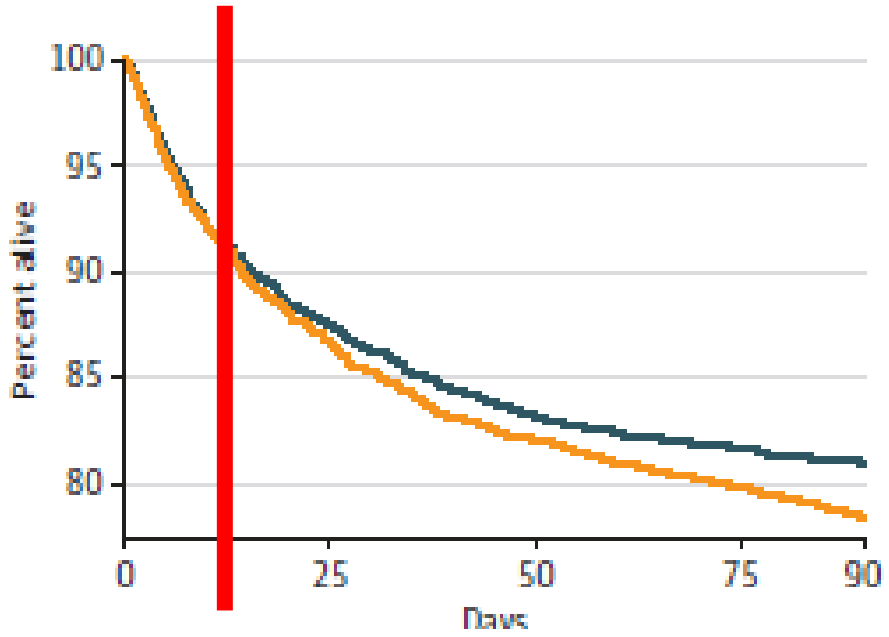

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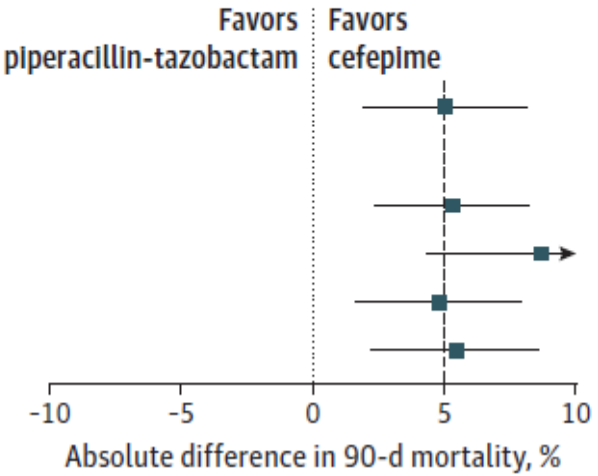


Outcomes:

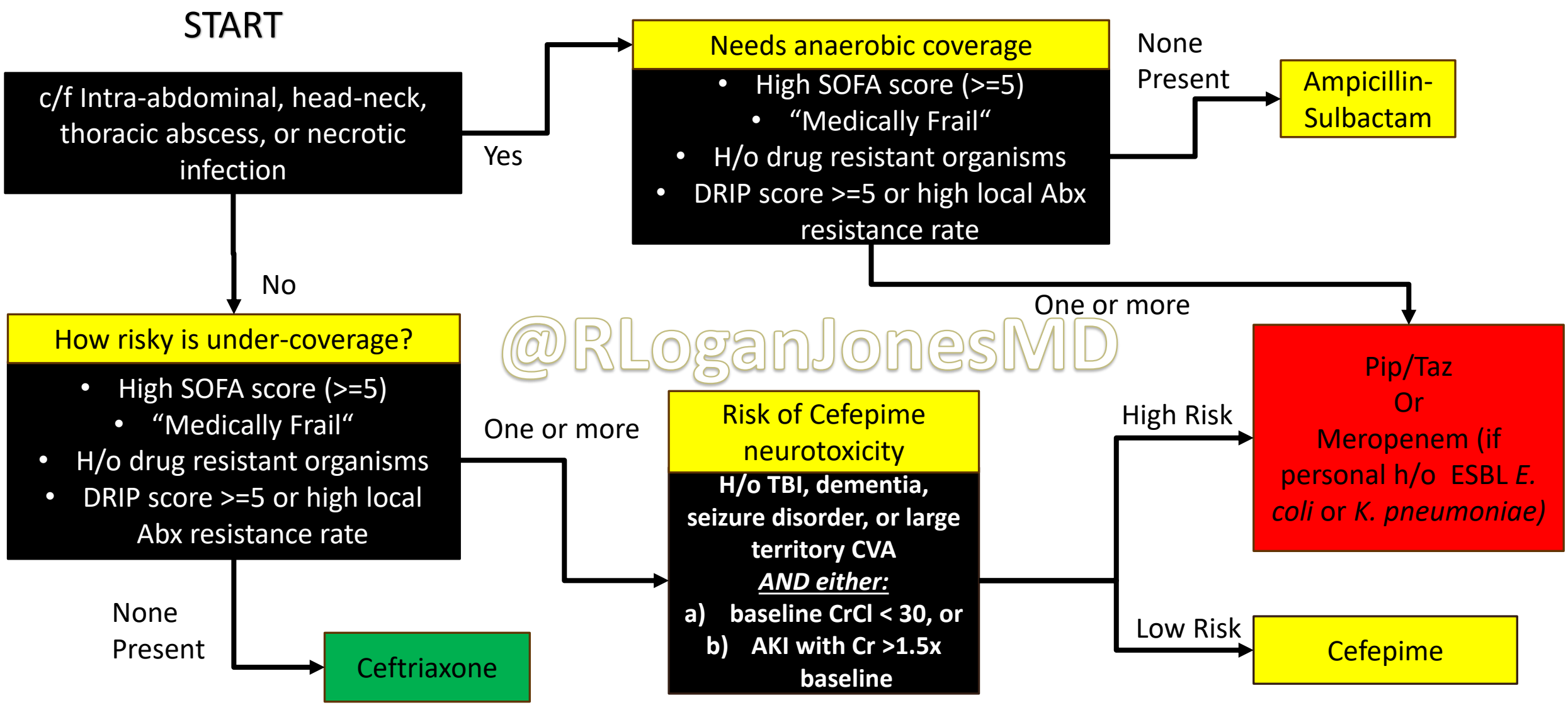
Outcome	Piperacillin-Tazobactam Effect
90-day Mortality (Pip/Tazo vs Cefepime)	22.5% vs 17.5% (P = .002)
Change in 90-day Mortality	5.0% increase (95% CI, 1.9%-8.1%)
Organ Failure-Free Days	2.1 fewer days (95% CI, 1.4-2.7)
Ventilator-Free Days	1.1 fewer days (95% CI, 0.57-1.62)
FeVasopressor-Free Days	1.5 fewer days (95% CI, 1.01-2.01)

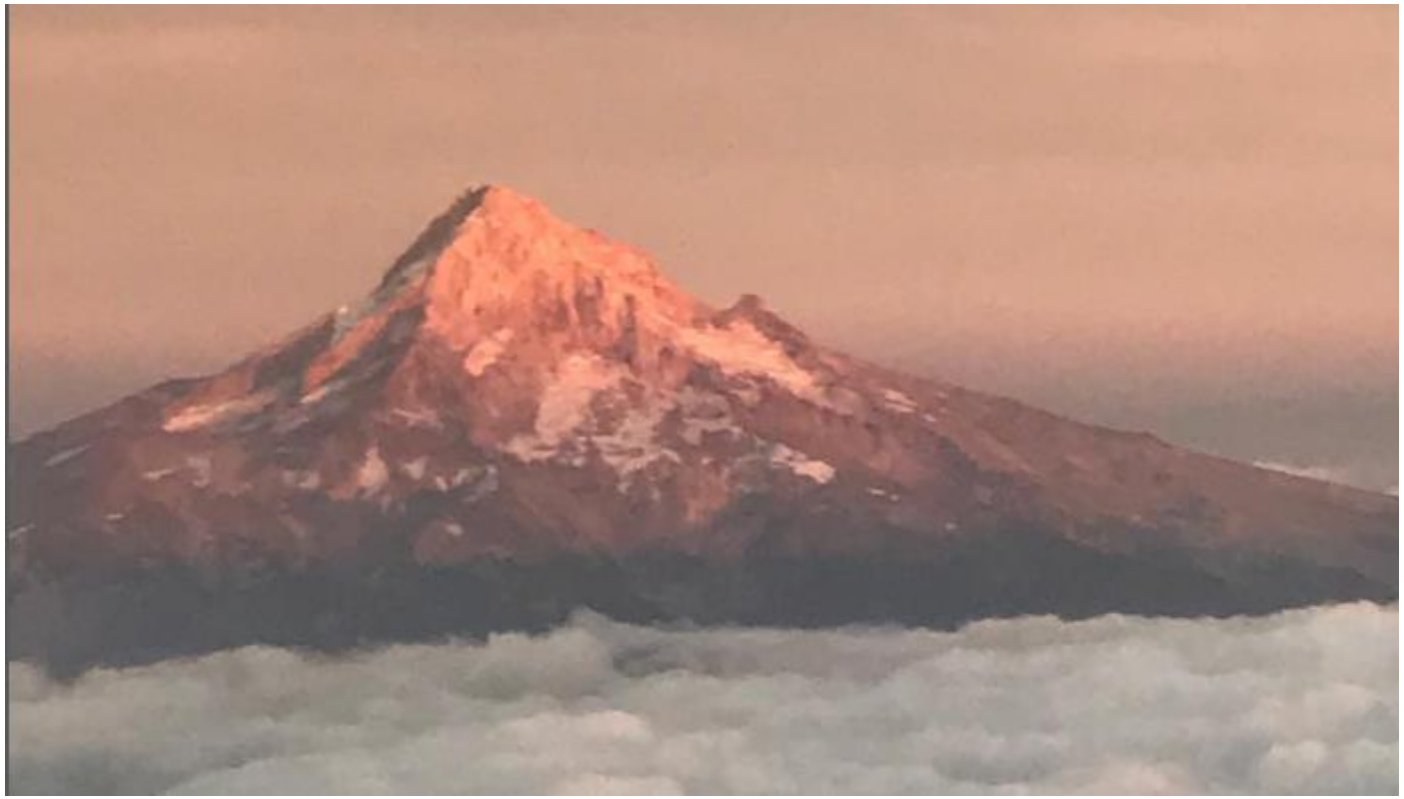
Outcome (compared to cefepime)	Zosyn or Metronidazole Exposure
Change in 90-day Mortality	12% increase (95% CI, 3%-21%; P < .001)
Ventilator-Free Days	0.71 fewer days (95% CI, -0.36 to -1.07)
Vasopressor-Free Days	0.38 fewer days (95% CI, -0.7 to -0.04)
Organ Failure-Free Days	1.82 fewer days (95% CI, -1.35 to -2.28)

Takeaways

- The study provides **compelling evidence that, in conjunction with vancomycin, for patient in equipoise regarding needing anti-anaerobic coverage: pip-tazo is associated with worse outcomes** in patients with sepsis, even after controlling for differences in illness severity.
- While sicker patients might be more likely to receive pip-tazo, the study design (ie drug shortage period, instrumental variable analysis, and sensitivity tests) suggest that this is not the sole reason for the worse outcomes.
- The study supports the hypothesis that **anti-anaerobic antibiotics themselves may contribute to harm**, particularly in patients who do not have clear indications for anaerobic coverage.

B-Lactam Selection Algorithm for Initial Empiric Sepsis Coverage





Question 3

A 68-year-old patient is being admitted for hip fracture surgery. During your history and physical, they report a penicillin allergy. Which of the following characteristics of their reported allergic reaction is LEAST predictive of a severe, clinically significant reaction according to the PEN-FAST score?

1. *The reaction occurred 3 years ago*
2. *The patient required oral antihistamines for the reaction*
3. *The patient experienced lip swelling during the reaction*
4. *The reaction was a mild self-limiting rash on the arms*

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

The PALACE Randomized Clinical Trial

Ana Maria Copaescu, MD[1,2,3,4]; Sara Vogrin, MBiostat[5]; Fiona James, BBiomedSci[1]; et al

» Author Affiliations | Article Information

JAMA Intern Med. 2023;183(9):944-952. doi:10.1001/jamainternmed.2023.2986

Design: PALACE

- **Goal**:
  - To determine if direct oral penicillin challenge in patients with low-risk penicillin allergy is noninferior to the standard method of skin testing followed by oral challenge.
- **Hypothesis**:
  - Direct oral challenge is as safe and effective as the traditional method for **immune IgE-mediated reaction**
- **Design**:
  - Multicenter, international, randomized, parallel, noninferiority trial.
  - Open-label, conducted across six specialized centers.
- **Population**:
  - 382 Adults patients aged ≥18 with a low-risk penicillin allergy (PEN-FAST score <3).
  - Conducted from June 2021 to December 2022.
- **Inclusion Criteria**:
  - PEN-FAST score less than 3.
- **Exclusion Criteria**:
  - Anaphylaxis history, chronic spontaneous urticaria, severe non-IgE reactions (Basically PEN-FAST >= 3)
- **Intervention**:
  - Intervention group: Direct oral penicillin challenge.
  - Control group: Skin testing followed by oral challenge.

PEN-FAST Clinical Decision Rule

PEN	*Pe*nicillin allergy reported by patient	☐ *If yes, proceed with assessment*
F	*F*ive years or less since reaction[a]	☐ **2 points**
A	Anaphylaxis or angioedema	
	OR	☐ **2 points**
S	Severe cutaneous adverse reaction[b]	
T	*T*reatment required for reaction[a]	☐ **1 point**
		☐ **Total points**

Interpretation

Points	
0	**Very low risk** of positive penicillin allergy test <1% (<1 in 100 patients reporting penicillin allergy)
1-2	**Low risk** of positive penicillin allergy test 5% (1 in 20 patients)
3	**Moderate risk** of positive penicillin allergy test 20% (1 in 5 patients)
4-5	**High risk** of positive penicillin allergy test 50% (1 in 2 patients)

[a] Includes unknown

[b] Severe cutaneous adverse reactions include potential Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, and acute generalized exanthematous pustulosis. Patients with a severe delayed rash with mucosal involvement should be considered to have a severe cutaneous adverse reaction. Acute interstitial nephritis, drug-induced liver injury, serum sickness and isolated drug fever were excluded phenotypes from the derivation and validation cohorts.

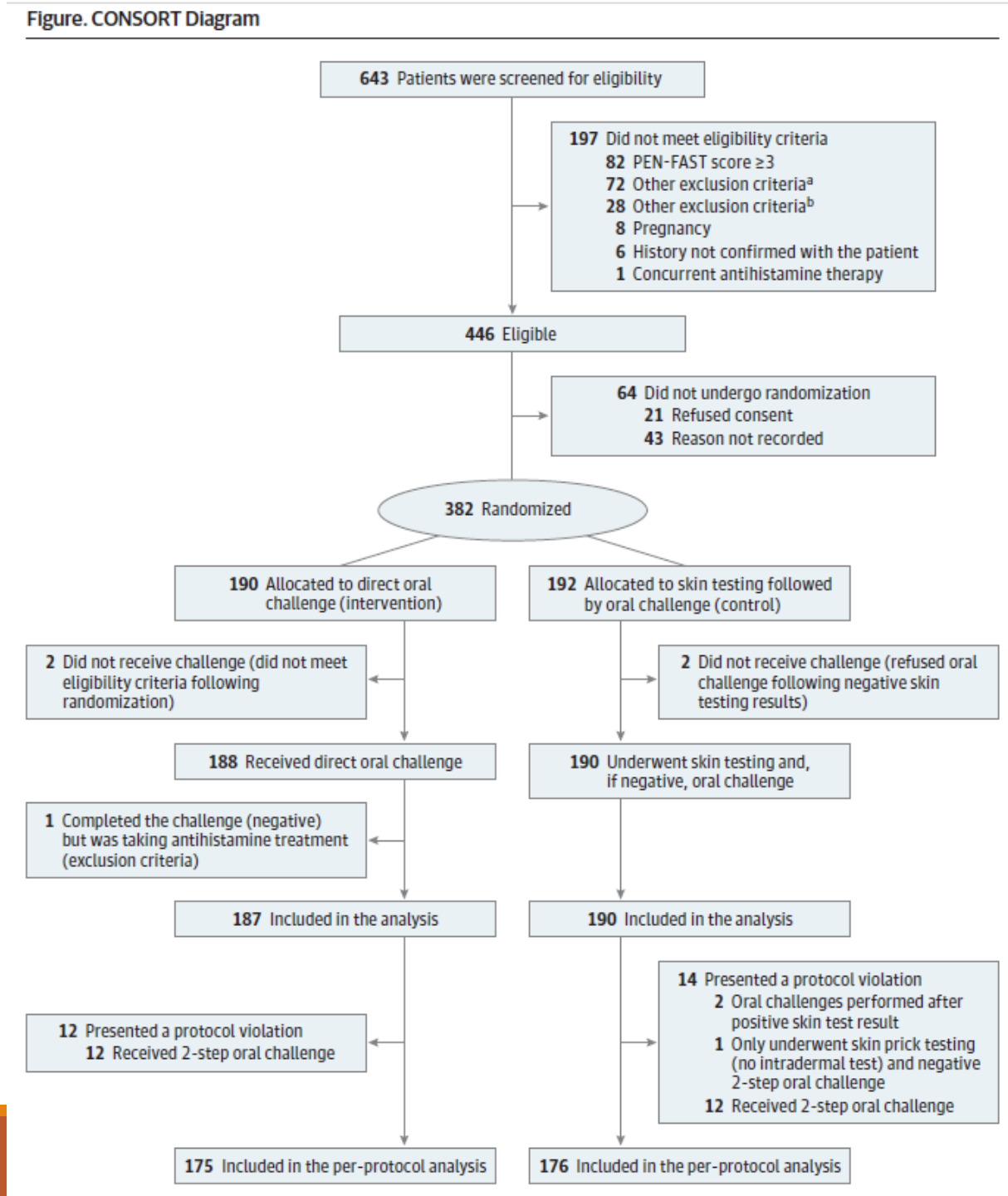
Patient Characteristics:

Key Characteristics:

- Median age: 51 years.
- 65.5% female.
- Majority were White (93%).

Other Notable Characteristics

- Both groups had similar demographic and clinical characteristics.
- No significant differences in the PEN-FAST scores, use of B-Blocker, ACE-I, immunosuppressive medications, or concurrent cephalosporin allergies.
- Slight differences in allergic conditions (e.g., asthma higher in the control group at 26% vs. 19% in intervention).
- The PENFAST score was 0 or 1 for more than 94% of participants enrolled,



Outcomes: PALACE

Primary Outcome (Immediate IgE Mediated Rash) within 1 hour of exposure:

- **1 of 187 in intervention, 1 of 190 control = 0.5%** in both arms
- **Noninferiority confirmed**: Risk difference (RD) = **0.0084**

- **Secondary Outcomes**:
  - **Mild Rash: Intervention Group -** 4.2% vs Control Group - 3.7%
  - **Nausea: Intervention Group -** 1.6% vs Control Group - 1.0%
  - **Headache: Intervention Group -** 1.0% vs Control Group - 0.5%
  - **Diarrhea: Intervention Group -** 0.5% vs Control Group - 0.5%
  - **Anaphylaxis or Serious Adverse Events:** Intervention Group - 0.0% vs Control Group - 0.0%

- **Efficacy**:
  - **99.5%** of patients in the intervention group and **97.9%** in the control group successfully had their penicillin allergy label removed. No patients suffered “severe” reaction from any part of the enrollment

Subgroup Outcomes: PALACE

Key Points for Counseling Patients with PEN-FAST Score of 1:

- **Risk of Reaction**:
  - The risk of a positive reaction to an oral penicillin challenge in patients with a PEN-FAST score of 1 is **very low** (approximately 1.0% in both intervention and control groups).
  - Reactions were **mild to moderate** and managed with oral antihistamines.
  - The control patient **did NOT have a positive skin test prior to oral challenge**

Takeaways: PALACE

- **Low Risk, High Yield:** Patients with a remote (>5 years) history of non severe reaction (anaphylaxis, angioedema, SJS/TEN, DRESS, AGEP) that the risk of severe adverse reactions is 0.5% or less with direct oral challenge
- **Simplified Allergy De-labeling:** Direct oral penicillin challenge eliminates the need for skin testing in low-risk patients, saving time and resources while improving antibiotic stewardship.
- **Mild, Manageable Reactions:** The most common reactions, such as mild itching or rash, are effectively managed with oral antihistamines, and no severe reactions (e.g., anaphylaxis) were reported in this cohort of ~ 400 patients.
- **Enhanced Stewardship:** De-labeling low-risk penicillin allergies can lead to more appropriate antibiotic use, reduce the need for broad-spectrum antibiotics, and help prevent antimicrobial resistance.

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JAMA Network | Open

Research Letter | Health Policy

Patient Preferences for Telemedicine Video Backgrounds

Nathan Houchens, MD; Sanjay Saint, MD, MPH; Latoya Kuhn, MPH; David Ratz, MS; Jason M. Engle, MPH; Jennifer Meddings, MD, MSc

- **Method:** Cross-sectional survey of 1,213 adult patients.
- **Participants:** Rated photos of a physician in different video backgrounds.
- **Environments Compared:** Office with diplomas, exam room, home settings (bedroom, kitchen).
- **Outcome:** Preferences scored on trust, professionalism, and comfort.

Most Preferred Backgrounds:

- **Physician's Office with Diplomas**: Rated highest by patients for professionalism and trust.
- **Traditional Healthcare Settings**: Preferred over informal home settings.

Least Preferred Backgrounds:

- **Bedroom and Kitchen**: Rated lowest; associated with reduced patient comfort and trust.

Considerations:

- Avoid informal backgrounds like kitchens or bedrooms.
- Emphasize professionalism through visible credentials and a traditional healthcare environment.

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