GOOD EVIDENCE MATTERS

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Boost Buprenorphine, Save More Lives

GEMs GOOD EVIDENCE MATTERS SPOTLIGHT

Higher First 30-Day Dose of Buprenorphine for Opioid Use Disorder Treatment is Associated with Decreased Mortality

Lei F, Lofwall MR, McAninch J, et al. Higher First 30-Day Dose of Buprenorphine for Opioid Use Disorder Treatment Is Associated with Decreased Mortality. *J Addict Med*. 2024;18(3):319-326. doi:10.1097/ADM.0000000000001300

KEY TAKEAWAY: In adults starting transmucosal buprenorphine (TMbup) for opioid use disorder (OUD), higher first 30-day doses reduce the risk of opioid overdose deaths compared to lower first 30-day doses.

STUDY DESIGN: Retrospective cohort study

LEVEL OF EVIDENCE: STEP 4 (downgraded due to lack of generalizability)

BRIEF BACKGROUND INFORMATION: Buprenorphine is an effective treatment for OUD that reduces mortality. However, the link between the initial treatment dose and the risk of death remains unclear. Understanding this relationship is essential to improving treatment guidelines and patient outcomes in OUD management.

PATIENTS: Adults starting transmucosal buprenorphine for OUD

INTERVENTION: Higher first 30-day doses

CONTROL: Lower first 30-day dose

PRIMARY OUTCOME: Opioid overdose death

Secondary Outcome: Death from other causes

METHODS (BRIEF DESCRIPTION):

- This study included adult Kentucky residents who initiated TMbup treatment for OUD.
  - Participants had no TMbup prescription in the prior 180 days.
- Patients <18 years old, non-Kentucky residents, those who died or switched to long-acting injectable buprenorphine in the first 30 days, and patients with zero days' supply were excluded from the study.
- Patients were categorized based on their average daily TMbup dose in the first 30 days:
  - Low-dose group: ≤8 mg
  - High-dose groups: >8 to ≤16 mg and >16 mg
- Treatment followed Food and Drug Administration (FDA) guidelines, with up to 8 mg on day one and up to 16 mg on day two, adjusted as needed.
- The primary outcome measured opioid-involved overdose deaths and were identified via International Classification of Diseases (ICD) codes on death certificates.
- The secondary outcome measured deaths from other causes and was categorized by the National Center for Health Statistics.
- Data were obtained from the Kentucky All Schedule Prescription Electronic Reporting (KASPER) system and the Kentucky Office of Vital Statistics, linking prescription records with death certificates.

INTERVENTION (# IN THE GROUP): 39,361

COMPARISON (# IN THE GROUP): 10,496

FOLLOW-UP PERIOD: 365 days

RESULTS:

Primary Outcome –

- Patients on higher doses of TMbup had a significantly lower incidence of overdose death compared to lower doses of TMbup.
  - >8 to ≤16 mg (adjusted sub-distribution hazard ratio [aSHR] 0.45; 95% CI, 0.34–0.60)
  - >16 mg (aSHR 0.36; 95% CI, 0.25–0.52)

Secondary Outcome –

- Patients on higher doses of TMbup had a lower risk of death from other causes compared to TMbup.
  - >8 to ≤16 mg (aSHR 0.78; 95% CI, 0.62–0.98)
  - >16 mg (aSHR 0.62; 95% CI, 0.47–0.80)

LIMITATIONS:

- This study was conducted in a single state, which may limit the generalizability of findings to broader populations.
- There is a potential misclassification of patients due to unreported out-of-state prescriptions.
- The study lacks detailed baseline data on comorbidities, socioeconomic factors, and counseling interventions, which could influence outcomes.
- The absence of race and ethnicity data limits the ability to analyze racial disparities in treatment and outcomes.

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Antibiotic Treatment for Bloodstream Infections: Is Seven Days Sufficient?

Antibiotic Treatment for 7 vs 14 Days in Patients with Bloodstream Infections

BALANCE Investigators, for the Canadian Critical Care Trials Group, the Association of Medical Microbiology and Infectious Disease Canada Clinical Research Network, the Australian and New Zealand Intensive Care Society Clinical Trials Group, and the Australasian Society for Infectious Diseases Clinical Research Network, Daneman N, Rishu A, et al. Antibiotic Treatment for 7 versus 14 Days in Patients with Bloodstream Infections. *N Engl J Med*. 2025;392(11):1065-1078. doi:10.1056/NEJMoa2404991

KEY TAKEAWAY: For patients hospitalized with a bloodstream infection, seven-day antibiotic treatment does not reduce the risk of mortality at 90 days compared to a 14-day treatment.

STUDY DESIGN: Multicenter, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: Bloodstream infections are common in hospitalized patients and often life-threatening. Recommendations regarding treatment duration for patients with bacteremia are variable, with median durations of ≥14 days. Previous randomized clinical trials have documented noninferiority of shorter treatment duration for bacterial infections including community acquired pneumonia, cellulitis, pyelonephritis, uncomplicated bacteremia. However, data has not been generalized to patients hospitalized for bloodstream infections.

PATIENTS: Patients hospitalized for bloodstream infection

INTERVENTION: Seven-day course of antibiotic treatment

CONTROL: 14-day course of antibiotic treatment

PRIMARY OUTCOME: Mortality by any cause at 90 days

Secondary Outcome: Death in the hospital or intensive care unit (ICU), relapse of bacteremia, adverse events, *Clostridioides difficile* infection, secondary infection or colonization with antimicrobial-resistant organisms in the hospital, length of stay in the hospital or ICU, duration of invasive mechanical ventilation, duration of vasopressor use.

METHODS (BRIEF DESCRIPTION):

- Eligible patients included those hospitalized across 74 hospitals in seven countries with blood culture positive for a pathogenic bacterium during the study period.
  - The median age of the patient was 70 years old and 53% were men.
- Patients with diverse sources of bacteremia including urinary tract, intra-abdominal, lung, vascular catheter, skin or soft tissues, and other sources, critically ill patients and those admitted to the ICU were included in the study.
- Patients with previous enrollment in the trial, in a severe immunocompromised state, prosthetic heart valves or endovascular grafts, infectious syndrome that required prolonged treatment, *Staphylococcus aureus* or *Staphylococcus lugdunensis* bacteremia, fungemia, or bacteremia from rare organisms that needed a longer treatment course were excluded from the study.
- Patients were randomized in a 1:1 ratio to receive adequate antibiotic treatment for seven days or 14 days.
  - Adequate treatment was defined as antibiotic therapy selected based on organism susceptibilities from local laboratory data.
  - Antibiotic selection and administration were at the discretion of the treatment clinicians and were similar between both treatment groups.
  - Group assignments were concealed until day seven of adequate treatment to minimize bias.
- Group assignments were concealed until day seven of adequate treatment to minimize bias.
- The primary outcome was death by any cause within 90 days from the positive blood culture in the seven-day and 14-day treatment groups.
  - A noninferiority margin of four percentage points was used in the data analysis.
- The secondary outcomes were:
  - Binary measurements included secondary infection, infection relapse, and colonization of drug-resistant organisms.
  - Continuous measurements included ventilator duration, vasopressor duration, days in hospital or ICU, hospital-free days by day 28.

- Study power analysis called for enrollment of 3,626 patients with an expected event rate of 22%. Only 3,608 were enrolled, but the event rate was 15–16%.

INTERVENTION (# IN THE GROUP): 1,802

COMPARISON (# IN THE GROUP): 1,779

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- Seven days of antibiotic treatment did not significantly reduce mortality from any cause compared to 14 days (risk difference [RD] –1.6%; 95% CI, –4.0 to 0.8).

Secondary Outcome –

- Seven days of antibiotic treatment reduced the hospital length of stay compared to 14 days (median difference [MD] –1.0%; 95% CI, –1.5 to –0.5).
- Seven days of antibiotic treatment did not significantly affect death in the hospital or ICU, relapse of bacteremia, adverse events, *Clostridioides difficile* infection, secondary infection or colonization with antimicrobial-resistant organisms in the hospital, ICU length of stay, duration of invasive mechanical ventilation, and duration of vasopressor use compared to 14 days.

LIMITATIONS:

- Nonadherence to treatment could contribute to bias in the finding of noninferiority.
- Late *Clostridioides difficile* infections could have been missed if treated in outpatient setting.
- The results were not applicable to pathogens excluding from the trial, including *Staphylococcus aureus*, *Clostridioides difficile* and antimicrobial-resistant organism infections were infrequent events, which may have contributed to the lack of statistically significant difference between the short and long course of antibiotics with respect to these outcomes.
- The trial was underpowered.

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Does Clarithromycin Work for an Old Man's Friend?

Clarithromycin for Early Anti-Inflammatory Responses in Community-Acquired Pneumonia in Greece (ACCESS): A Randomized, Double-Blind, Placebo-Controlled Trial

Giamarellos-Bourboulis EJ, Siampanos A, Bolanou A, et al. Clarithromycin for early anti-inflammatory responses in community-acquired pneumonia in Greece (ACCESS): a randomized, double-blind, placebo-controlled trial [published correction appears in Lancet Respir Med. 2024 Apr;12(4):e20. doi: 10.1016/S2213-2600(24)00043-2.]. *Lancet Respir Med*. 2024;12(4):294-304. doi:10.1016/S2213-2600(23)00412-5

KEY TAKEAWAY: Adding clarithromycin to the standard of care (SOC) improves early clinical response in patients who are hospitalized for community acquired pneumonia (CAP).

STUDY DESIGN: Phase 3, prospective, double blinded, randomized controlled trial

LEVEL OF EVIDENCE: STEP 2

BRIEF BACKGROUND INFORMATION: CAP is a major cause of hospitalization and mortality in the world. The current mainstay of treatment typically includes beta-lactam (commonly ceftriaxone) in addition to macrolide (azithromycin or clarithromycin). This study aimed to investigate if clarithromycin + a beta lactam antibiotic would improve early clinical response to CAP.

PATIENTS: Hospitalized adult patients with CAP

INTERVENTION: Clarithromycin

CONTROL: Placebo

PRIMARY OUTCOME: Clinical response

Secondary Outcome: Change in procalcitonin kinetics, organ dysfunction, respiratory symptoms, hospital readmission, clinical improvement, mortality, sepsis onset

METHODS (BRIEF DESCRIPTION):

- Adult patients admitted to hospital with at least two symptoms of CAP who were ≥18 years old and have not been hospitalized in the previous 90 days were included in the study.
  - CAP symptoms included cough, purulent sputum production, dyspnea, or pleuritic chest pain.
  - Diagnostic criteria of CAP consisted of auscultatory findings and new consolidation seen on chest x-ray or chest CT.
  - Enrolled patients had a total Sequential Organ Failure Assessment (SOFA) score of two, procalcitonin kinetics of ≥0.25 ng/mL, and positive for two SIRS criteria.
  - SOFA measures organ dysfunction in patients. Scores range from 0–24, with a low SOFA score (≤5) indicating minimal or no organ failure and a high SOFA score (≥11) indicating severe organ failure.
- Patients <18 years old, had recent macrolide or steroid use or covid infection, neutropenic or unknown human immunodeficiency virus (HIV) status were excluded from the study.
- Patients were randomized by computer generated randomization 1:1 to SOC + placebo or SOC + clarithromycin.
  - SOC was given to all patients and this included administration of IV ceftriaxone 2 g once daily or IV β-lactam and β-lactamase inhibitor dose adjustment based on renal clearance with amoxicillin + clavulanic acid, or ampicillin + sulbactam, or piperacillin + tazobactam, administered three or four times daily.
  - In addition to the SOC, the treatment group was also given clarithromycin 500 mg tablet every 12 hours for seven days.
- The primary outcome measured composite clinical response of CAP which required that patients either had a decrease in at least 50% of respiratory symptom score and a 30% decrease in SOFA score or ≥80% drop in procalcitonin at day four.

- The secondary outcomes look at the components in the primary outcome separately, including:
  - Favorable changes in procalcitonin kinetics at day four
  - Drop of at least 30% in SOFA score at day four
  - ≥50% decrease in SOFA score at day eight
  - Improvement in respiratory symptom severity score by at least 50% at day four
  - Readmission to the hospital by 90 days
  - Clinical improvement by day 28
  - Mortality by 28 and 90 days
  - Onset of new sepsis by day 28 days

INTERVENTION (# IN THE GROUP): 134
COMPARISON (# IN THE GROUP): 133

FOLLOW-UP PERIOD: 90 days

RESULTS:

Primary Outcome –

- Clarithromycin improved clinical response compared to placebo (odds ratio [OR] 3.4; 95% CI, 2.1–5.6).

Secondary Outcome –

- Clarithromycin increased the likelihood of favorable changes in procalcitonin at day four compared to placebo (OR 1.9; 95% CI, 1.1–3.1).
- Clarithromycin resulted in a 30% SOFA score reduction on day four compared to placebo (OR 3.1; 95% CI, 1.9–5.1).
- Clarithromycin resulted in a ≥50% decrease in SOFA score at day eight compared to placebo (OR 1.7; 95%, CI 1.1–2.8).
- Clarithromycin improved respiratory symptoms by at least 50% by day four compared to placebo (OR 2.8; 95% CI, 1.7–4.7).
- Clarithromycin resulted in a higher rate of clinical success by day 28 compared to placebo (OR 1.7; 95% CI, 1.02–2.7).
- Clarithromycin reduced the occurrence of new sepsis by day 28 compared to placebo (OR 0.49; 95% CI, 0.26–0.93).
- There was no difference in hospital readmission and mortality at 28 days and 90 days for clarithromycin compared to placebo.

LIMITATIONS:

- The study only included patients with high inflammatory markers, which could introduce selection bias. Patients with high inflammatory markers could have a more severe disease possibly affecting the generalizability of the outcomes compared to the general population with CAP.
- Selection bias may also be introduced due to the physicians being able to choose which antibiotics were part of the standard of care treatment. Physicians tend to use B-lactams with antipseudomonal activity and glycopeptides in patients who are sick or have other comorbidities.
- Only 55% of the study population had at least one of the pathogens isolated, which makes it hard to determine if the antibiotics were effective against specific pathogens or if the results were skewed by noninfectious causes of pneumonia.

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