

June 2024

# EVIDENCE-BASED PRACTICE

A Peer-Reviewed Journal of the Family Physicians Inquiries Network

June 2024  
Volume 27 | Number 6

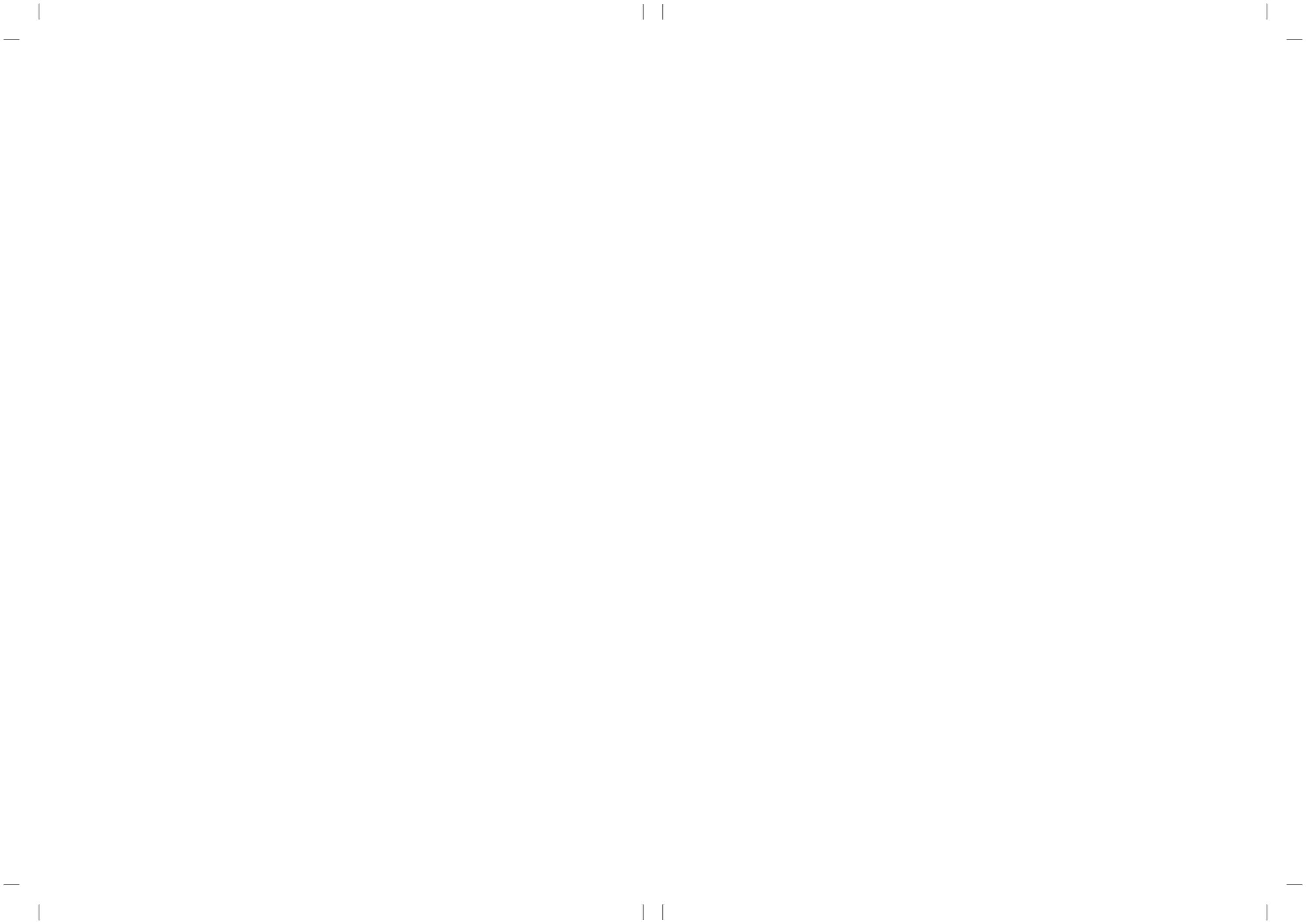
EVIDENCE-BASED PRACTICE

- 01** Editorial
- 02** PURLs
- 05** Diving for PURLs
- 09** GEMS
- 11** In Depth
- 13** Helpdesk Answers
- 38** Spotlight On Pharmacy

Volume 27 | Number 6



*FPIN envisions a primary care workforce that thinks critically, communicates expertly, and utilizes the best current evidence to improve the health of patients.*



# EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

## EDITORIAL

There's Gold in Them Thar...Teeth! . . . . .1

## PURLs

Two-day versus seven-day course of levofloxacin in acute COPD exacerbations . . . . .2

## DIVING FOR PURLs

Can cannabis exposure during pregnancy harm me or my baby? . . . . .5

Mifepristone for management of adenomyosis . . . . .5

MY BODY, MY HOME HPV TESTING . . . . .7

Exploring colchicine: a new angle on joint surgery risk . . . . .7

## GEMS

A new shot for moms-to-be: antepartum vaccine prevents severe RSV infection in infants . . . . .9

## IN DEPTH

Do statins prevent major adverse cardiac events (MACEs) in adults with low-risk or borderline-risk ASCVD? . . . . .11

## HELPDESK ANSWERS

Does melatonin improve sleep-onset insomnia and sleep duration in pediatric patients with ADHD? . . . . .13

After placement of a newer-generation drug-eluting coronary artery stent in a patient with a high bleeding risk, does one month of dual antiplatelet therapy effectively reduce the incidence of major bleeding while also maintaining stent effectiveness? . . . . .14

Is paxlovid effective for prevention of COVID-19 complications in vaccinated patients? . . . . .16

Is topical testosterone less likely to cause polycythemia than IM testosterone in patients on testosterone replacement therapy? . . . . .17

Does decreased sugar consumption improve LDL levels in adults with hyperlipidemia? . . . . .19

Should direct oral anticoagulants (DOACs) be held before dental procedures? . . . . .20

In patients with obstructive sleep apnea (OSA) and nasal obstruction does nasal surgery improve continuous positive airway pressure (CPAP) compliance? . . . . .22

Does intermittent fasting improve markers of glucose tolerance more than caloric restriction diets or usual care in patients at risk for type 2 diabetes mellitus? . . . . .23

Is a restrictive strategy noninferior to a liberal strategy of blood transfusion in adults with acute myocardial infarction and anemia? . . . . .24

Do exercise regimens in patients with heart failure decrease risk of heart failure exacerbations or cardiovascular events? . . . . .25

In patients treated medically for opioid use disorder, is there a correlation between relapse rate and socioeconomic status? . . . . .26

Are systemic steroids effective for treatment of acute low back pain in adults? . . . . .28

Do adverse childhood events (ACEs) increase the incidence of eating disorders in adults? . . . . .29

Is vitamin D supplementation effective in improving patient-oriented outcomes in patients with PCOS? . . . . .30

Does pelvic floor physical therapy after delivery help reduce urinary incontinence? . . . . .31

Are adverse childhood experiences associated with depression and is there a dose-response relationship? . . . . .33

Are children exposed to intimate partner or domestic violence at increased risk of developing childhood obesity? . . . . .35

In patients with acute respiratory distress syndrome (ARDS), does stem cell treatment versus standard of care reduce days of ventilation and mortality? . . . . .36

## SPOTLIGHT ON PHARMACY

Do SGLT-2 inhibitors agents have an effect on all-cause mortality in patients with diabetes type 2? . . . . .38

Evidence-Based Practice, (ISSN: 2473-3717 [online]), is published monthly online on behalf of the Family Physicians Inquiries Network, Inc., by Wolters Kluwer Health, Inc., at 1800 Dual Highway, Suite 201, Hagerstown, MD 21740-6636. Business and production offices are located at Two Commerce Square, 2001 Market St., Philadelphia, PA 19103. All rights reserved. Copyright © 2024 by Family Physicians Inquiries Network, Inc. All rights reserved.

**Postmaster:** Send address changes to Evidence-Based Practice, PO Box 1610, Hagerstown, MD, 21741, USA.

**Permissions and photocopying:** For permission and/or rights to use content from Evidence-Based Practice, please visit <https://shop.lww.com/journal-permission>. For translation rights queries, e-mail [TranslationRights@wolterskluwer.com](mailto:TranslationRights@wolterskluwer.com). For licensing queries, e-mail [HealthLicensing@wolterskluwer.com](mailto:HealthLicensing@wolterskluwer.com).

**Reprints:** For commercial reprints and all quantities of 500 or more, e-mail [reprintsolutions@wolterskluwer.com](mailto:reprintsolutions@wolterskluwer.com). For quantities of fewer than 500, e-mail [reprints@lww.com](mailto:reprints@lww.com) or call 1-866-903-6951.

**Journal customer services:** For ordering information, claims, and any inquiry concerning your journal subscription, please go to [customerservice@lww.com](mailto:customerservice@lww.com), or call 1-800-638-3030 or 1-301-223-2300.

# EVIDENCE-BASED PRACTICE

A PEER-REVIEWED JOURNAL OF THE FAMILY PHYSICIANS INQUIRIES NETWORK

---

## **EBP Editor-in-Chief**

### **Jon Neher, MD, FAAFP**

Valley Medical Center FMR Program  
Renton, WA

## **Founding Editor-in-Chief**

### **Bernard Ewigman, MD, MSPH**

FPIN  
Columbia, MO

## **Executive Editor**

### **Corey Lyon, DO, FAAFP**

University of Colorado (University Hospital)  
Program  
Denver, CO

## **Managing Editor/Executive Director**

### **LuShawna Gerdes**

FPIN  
Columbia, MO

## **Editorial Board**

### **Roselyn Clemente – Fuentes, MD**

USAF-Regional Hospital/Headquarters Air  
Armament Ctr  
Eglin Air Force Base, FL

### **John Delzell, Jr., MD, MSPH**

West Kendall Baptist Hospital / Florida  
International University Program  
Miami, FL

### **Philip Dooley, MD**

University of Kansas (Wichita)/Via Christi  
Hospitals Wichita Program  
Wichita, KS

### **Scott Grogan, DO, MBA, FAAFP**

Madigan Army Medical Center Program  
Gig Harbor, WA

### **Alma Littles, MD**

Tallahassee Memorial FMR  
Tallahassee, FL

### **Doug Maurer, DO, MPH, FAAFP**

Reynolds Army Health Clinic  
Fort Sill, OK

### **Linda Montgomery, MD**

University of Colorado (University Hospital)  
Program  
Denver, CO

### **Mark B. Stephens, MD, MS, - FAAFP**

Penn State Milton S Hershey Medical  
Center / State College Program  
Hershey, PA

## **Senior Editors**

HelpDesk Answers Editor-in-Chief

### **Tom Satre, MD**

University of Minnesota / CentraCare St Cloud  
Family Medicine  
St. Cloud, MN

Clinical Inquiries Editor-in-Chief

### **Rick Guthmann, MD, MPH**

Advocate Health Care Illinois Masonic Medical  
Center Program  
Chicago, IL

GEMs Editor-in-Chief

### **Jennie B. Jarrett, PharmD, BCPS, MMedEd, FCCP**

University of Illinois at Chicago  
Chicago, IL

PURLs Editor-in-Chief

### **Gregory Castelli, PharmD, BCPS, BC-ADM, CDCES**

UPMC Medical Education/St Margaret  
Hospital FMP  
Pittsburgh, PA

Quality Improvement Editor-in-Chief

### **Paul Crawford, MD**

Uniformed Services University  
Bethesda, MD

## **Deputy Editors**

### **Julienne Bemski, DO**

University of Colorado (Healthone Swedish  
Medical Center) Program  
Denver, CO

### **Carina Brown, MD**

Cone Health Program  
Greensboro, NC

### **Whay-Yih Cheng, DO**

David Grant Medical Center Program  
Fairfield, CA

### **Sarah Daly, DO**

Utah Valley FMR  
Provo, UT

### **Dylan Eller, MPH**

FPIN  
Chicago, IL

### **Joel Herness, MD**

David Grant Medical Center Program  
Fairfield, CA

### **E. Seth Kramer, DO, MPH**

University of Colorado (University Hospital)  
Program  
Denver, CO

### **Robert Martin, DO**

Advocate Health Care Illinois Masonic Medical  
Center Program  
Chicago, IL

### **David Moss, MD**

Mike O'Callaghan Federal Medical Center/  
Nellis AFB FMR  
Nellis Air Force Base, NV

### **Rebecca Mullen, MD MPH**

University of Colorado (University Hospital)  
Program  
Denver, CO

### **Chris Vincent, MD**

University of Washington FMR Program  
Seattle, WA

### **Tad White, DO**

Yakima Valley Farm Workers Clinic Program/  
Sollus Northwest Program Grandview, WA

### **Mansoo Yu, PhD, MA, MPH**

FPIN/University of Missouri  
Columbia, MO

## **Publication Staff**

### **Paige Smith, BS**

FPIN  
Columbia, MO

### **Adalayna Hufendiek**

FPIN  
Chicago, IL

## **STATEMENT OF PURPOSE**

Evidence-Based Practice (EBP) addresses important patient care questions asked by practicing family physicians, using the best sources of evidence in a brief, clinically useful format. Our goal is to instruct our authors on how to write peer-reviewed scholarly research for the medical and scientific community.

## **EDITORIAL POLICY**

Statements and opinions expressed in articles and communications in this journal are those of the author(s) and not necessarily those of the editor, publisher, or any organizations endorsing this journal. The Publisher and editors of EBP do not endorse any methods, products, or ideas mentioned in the journal, and disclaim any liability which may arise from any material herein. Unless noted, authors have reported no competing interests and have nothing to disclose.

## **DISCLOSURE**

The PURLs Surveillance System is supported in part by Grant Number UL1RR024999 from the National Center for Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

## There's Gold in Them Thar...Teeth!

When I was about 10 years old, my father gave me a single sheet of gold leaf, crumpled loosely into a small bottle. It weighs only about 0.015 grams and contains about one dollar worth of gold. But it still shines from my bookshelf with the same rich, yellow luster it had when I first put it there over 30 years ago.

Gold is an amazing element that astrophysicists believe arises in the collision of two neutron stars.<sup>1</sup> Once refined, it resists oxidation indefinitely. Gold coins from the Byzantine Empire look as new today as when they left the mint. Because gold is a relatively soft metal, it has also long been used in making jewelry and filling holes in teeth.

Gold teeth may not be fashionable these days, but historically nothing demonstrated success like a gold-toothed smile. Recently, dental researchers decided to see if gold is any better for making crowns and other repairs than the newer, less ostentatious ceramics.<sup>2</sup> Their systematic review identified 2,667 papers that dropped to only four after a rigorous screening process. The final meta-analysis refined the entire data set down to 213 gold repairs versus 212 ceramic repairs. Follow up ranged from five to seven years.

Gold had a lower overall failure rate than ceramic (risk ratio [RR] 0.31; 95% CI, 0.16–0.57) and gold crowns had a lower failure rate than ceramic crowns (RR 0.31; 95% CI, 0.15–0.61). Sub-analyses of inlays and partial crowns

found no differences between materials, but the confidence intervals were wide.

There were significant weaknesses: researchers graded all four studies as low-quality evidence, the follow up period was less than the life of a typical dental crown, studies used different ceramic techniques and bonding protocols, and dental students performed the repairs in two studies.

But still, I must go with the evidence. Should I ever lose an incisor, I think I will ask my dentist to replace it with a shiny gold tooth (after assuring that my dental insurance is paid in full). Maybe then I'll have a smile as wonderfully bright as colliding neutron stars!



Jon O. Neher

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002191

### References

1. Curtis S. Cosmic alchemy. *Sci Am*. 2023; 23(1):30–37.
2. Tennert C, Suárez Machado L, Jaeggi T, Meyer-Lueckel H, Wierichs RJ. Posterior ceramic versus metal restorations: a systematic review and meta-analysis. *Dent Mater*. 2022; 38: 1623–1632.

# Two-day versus seven-day course of levofloxacin in acute COPD exacerbations

## PRACTICE CHANGER

Consider a two-day as opposed to seven-day course of levofloxacin in acute, non-severe chronic obstructive pulmonary disease exacerbations.

Strength of Recommendation: B: Based on a single randomized control trial (RCT)<sup>1</sup>

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002131

## Illustrative case

A 57-year-old female patient with a history of chronic obstructive pulmonary disease (COPD) presents to the emergency department with four days of increasing cough, dyspnea, and sputum production. She stated that symptoms started after a visit to see her grandchildren who were recovering from a “daycare cough.” Physical examination was remarkable for tachycardia (heart rate 100 bpm), SpO<sub>2</sub> 92% on room air, a respiratory rate of 26 breaths per min with decreased breath sounds, and diffuse wheezing appreciated on auscultation. Chest radiography and basic laboratory work obtained in the emergency department were unremarkable for the acute process, and she was diagnosed with an acute COPD exacerbation. In addition to supportive care, bronchodilators, and corticosteroids, the emergency department physician decided to initiate treatment with levofloxacin. What duration of levofloxacin should the admitting physician use?

## Clinical context

COPD is the third leading cause of death worldwide and the seventh leading cause of poor health worldwide, with many exacerbations attributed to infectious etiologies.<sup>2</sup> Exacerbations of COPD are a significant burden to the patient and healthcare system as they represent a significant portion of disease-related morbidity and healthcare costs.<sup>3,4</sup> The Global Initiative for Chronic Obstructive Lung Disease (GOLD) defines an acute exacerbation of COPD as an episode of increased dyspnea and/or cough and sputum that worsens over less than 14 days associated with increased local and systemic inflammation caused by airway infection, pollution, or other insult to the airways.<sup>3</sup>

General treatment for COPD exacerbations may include a combination of oxygen and ventilatory support,

inhaled bronchodilators, and corticosteroids. Adjunctive antimicrobial treatment may also be indicated given common concurrent bacterial infection. Despite concerns regarding antibiotic resistance and adverse effects, antibiotics can shorten recovery time and hospitalization duration and reduce the risk of early relapse or treatment failure.<sup>3</sup> Guidelines and expert opinion vary concerning antibiotic treatment duration, but evidence suggests that shorter courses are noninferior.<sup>4</sup>

Levofloxacin is a fluoroquinolone antibiotic with a broad spectrum of activity that includes common respiratory pathogens and multidrug-resistant organisms, such as pseudomonas. There is reasonable concern about increasing fluoroquinolone resistance and adverse effects associated with this antibiotic class.<sup>5,6</sup> Previous studies have investigated the efficacy and speed of recovery of short-course fluoroquinolone therapy ( $\leq 5$  days) in comparison with standard regimens ( $\geq 7$  days) and suggest that short-course regimens may be as effective as standard therapy and may offer faster resolution of symptoms, faster rate of recovery, fewer relapses, fewer and shorter hospitalizations, and longer time between recurrences.<sup>7,8</sup> Before this RCT, investigations of very short duration levofloxacin ( $< 3$  days) for COPD exacerbation had not been completed.

## Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching Dynamed and UpToDate with the terms “COPD exacerbation,” “antibiotics,” and “levofloxacin” to find additional literature to place this research into the context of current clinical practice.

## Study summary

***A two-day course of levofloxacin is noninferior to a seven-day course in the treatment of acute COPD exacerbation***

A 2022 prospective, double-blinded randomized controlled trial (n=310) evaluated the effectiveness of two days versus seven days of levofloxacin in the setting of COPD exacerbation.<sup>1</sup> Patients were at least 45 years old (mean age 68 years) with at least a 10-year pack per day smoking

history and mild-to-severe COPD with acute exacerbation per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria presenting to the emergency department in four Tunisian hospitals. Most patients (94%) experienced Anthonisen classification type one or two exacerbations. Baseline blood gas, C-reactive protein, white blood cell count, and sputum culture results were similar between groups. Researchers excluded patients with severe COPD exacerbation requiring vasoactive drugs or immediate endotracheal intubation, pneumonia, previous adverse reaction to levofloxacin, recent antibiotic use (cutoff ranges not reported), pregnancy, lactation, creatinine clearance less than 40 mL per minute, hepatic impairment, pulmonary diseases other than COPD, and active alcohol or drug abuse.

Investigators randomized patients to receive either seven days of levofloxacin 500 mg orally once daily or two days of levofloxacin followed by five days of placebo. All patients were initially treated in the emergency department for the first 48 hours of care, with subsequent decision to admit to the hospital or discharge home. All patients received prednisone 40 mg intravenously once daily for a total of five days, which was transitioned to an oral formulation to complete this course if discharged home before the end of five days. All patients also received nebulized bronchodilators and fluid therapy presumably at the treating physicians' discretion (treatment protocols not described). Discharge decisions were made at the discretion of the treating physician. Following treatment, investigators contacted the patients via telephone one, three, six, and 12 months later to assess the clinical course (specific questionnaire for assessment not described).

The primary outcome was the clinical cure rate, defined as the complete resolution of all associated signs and symptoms with no relapse or recurrences within 30 days. Secondary outcomes included the rate of additional antibiotics used, intensive care unit (ICU) admission rate, one-year re-exacerbation rate, exacerbation-free interval days, and one-year death rate. No patients were lost to follow-up. Rates of clinical cure for the two-day group (79%) and seven-day group (74%) were not significantly different (odds ratio [OR] 1.3; 95% CI, 0.78–2.2,  $P=.28$ ). There were no differences observed in any secondary outcomes, including rate of additional antibiotics (3.2% vs 1.9%; OR 0.29; 95% CI, 0.13–2.5,  $P=.43$ ), ICU admission rate (5.1% vs 3.2%; OR 0.55; 95% CI, 0.17–1.8;  $P=.65$ ), one year re-exacerbation rate (35% vs 29%; OR 0.71; 95% CI, 0.42–1.2,  $P=.19$ ), median exacerbation-free interval days (121 days [interquartile

range 99–149] vs 110 days [interquartile range 89–132]; OR 1; 95% CI, 0.9–1,  $P=.73$ ), or one-year death rate (5.2% vs 7.1%; OR 0.51; 95% CI, 0.54–3.6,  $P=.26$ ).

### What's new

#### ***Shortened antibiotic time course compared with current guidelines***

This RCT suggests that in patients with acute COPD exacerbations, a very short, two-day course of levofloxacin does not significantly change rates of clinical cure, need for additional antibiotics, ICU admission, or one-year re-exacerbation or death when compared with a seven-day course. This is a shorter duration than recommended by previously available best evidence and standard-of-care guidelines.

### Caveats

#### ***Antibiotic choice, unique study design, and limited demographics may not be fully representative of care in standard practice***

The study did not attempt to risk-stratify patients based on commonly accepted indications for fluoroquinolones in COPD exacerbation, such as risk of poor outcomes or pseudomonas infection. As such, its findings cannot be directly extrapolated to endorse very short (<3 days) courses of other empiric antibiotics (such as macrolides or cephalosporins, which may be preferable in average-risk patients) without other similar trials. This study's unique design, which provided at least 48 hours of hospitalization and intravenous corticosteroids to all patients, also differs from standard practice and may introduce unseen confounders. Finally, patients were primarily male in their 60s and did not include patients with severe baseline COPD or severe exacerbations.

### Challenges to implementation

#### ***No major challenges found***

There are no major changes to implement this treatment course.

EBP

**Alexis Aust, MD**  
**Danielle Acacio, MD**  
**Brock Cardon, MD**

*Nellis Family Medicine Residency, Nellis Air Force Base, NV*

The Corresponding Faculty Author on the manuscript is: Brock Cardon, MD; Brock.e.cardon.mil@health.mil

The authors declare no conflict of interest. The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the US Air Force at large, or the Department of Defense.

## References

1. Messous S, Trabelsi I, Bel Haj Ali K, et al. Two-day versus seven-day course of levofloxacin in acute COPD exacerbation: a randomized controlled trial. *Ther Adv Respir Dis*. 2022; 16:17534666221099729.
2. World Health Organization. *Chronic Obstructive Pulmonary Disease (COPD)*. World Health Organization; 2023. Accessed June 26, 2023. [https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-\(copd\)](https://www.who.int/news-room/fact-sheets/detail/chronic-obstructive-pulmonary-disease-(copd)).
3. Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease: 2023 Report*. Accessed June 26, 2023. [www.goldcopd.org](http://www.goldcopd.org).
4. *COPD Costs*. 2019. Accessed June 26, 2023. <https://www.cdc.gov/copd/infographics/copd-costs.html>.
5. Baggio D, R Ananda-Rajah M. Fluoroquinolone antibiotics and adverse events. *Aust Prescriber*. 2021; 44(5): 161–164.
6. Redgrave LS, Sutton SB, Webber MA, Piddock LJV. Fluoroquinolone resistance: mechanisms, impact on bacteria, and role in evolutionary success. *Trends Microbiol*. 2014; 22(8):438–445.
7. Stolbrink M, Amiry J, Blakey JD. Does antibiotic treatment duration affect the outcomes of exacerbations of asthma and COPD? A systematic review. *Chron Respir Dis*. 2018; 15: 225–240.
8. Gotfried MH, Grossman RF. Short-course fluoroquinolones in acute exacerbations of chronic bronchitis. *Expert Rev Respir Med*. 2010; 4(5):661–672.

## Can cannabis exposure during pregnancy harm me or my baby?

Prewitt KC, Hayer S, Garg B, et al. Impact of prenatal cannabis use disorder on perinatal outcomes. *J Addict Med*. 2023; 17(3):e192-e198. doi: 10.1097/ADM.0000000000001123.

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002107

A retrospective cohort study using California Vitals Statistics and Patient Discharge Data from 2007 through 2011 examined the effect of cannabis use on maternal and neonatal outcomes in pregnancy and immediately postpartum. The investigators identified maternal and neonatal data in singleton, nonanomalous births from 23 to 42 weeks' gestational age. The study included 2,380,446 pregnancies, of which 9,144 (.38%) had cannabis use during pregnancy. International Classification of Diseases, Ninth Revision (ICD-9) codes for cannabis dependence and abuse were used to identify cannabis use during pregnancy. Adverse maternal effects were gestational hypertension, preeclampsia, preterm delivery, and severe maternal morbidity (SMM). SMM was defined as acute myocardial infarction, aneurysm, acute renal failure, acute respiratory distress syndrome, amniotic fluid embolism, cardiac arrest/ventricular fibrillation, conversion of cardiac rhythm, disseminated intravascular coagulation, eclampsia, heart failure, puerperal cerebrovascular disorders, pulmonary edema/acute heart failure, severe anesthesia complications, sepsis, shock, sickle cell disease with crisis, air and thrombotic embolism, blood products transfusion, hysterectomy, temporary tracheostomy, and ventilation. Adverse neonatal effects were stillbirth, infant death, neonatal intensive care unit (NICU) admission, respiratory distress syndrome (RDS), hypoglycemia, and small for gestational age (SGA). Cannabis use and nonuse groups differed significantly according to race, age, education, prepregnancy BMI, less than five prenatal visits, and alcohol and other substance use during pregnancy. To mitigate these differences, multivariate logistic regression model was used. Prenatal cannabis use was associated with increased odds of preterm delivery (adjusted odds ratio [aOR] 1.45; 95% confidence interval [CI], 1.35–1.55;  $P < .001$ ), preeclampsia (aOR 1.16; 95% CI, 1.04–1.28), gestational hypertension (aOR 1.19; 95% CI, 1.06–1.34), SMM (aOR 1.22; 95% CI, 1.02–1.47) infant respiratory distress syndrome (aOR 1.16; 95% CI, 1.07–1.27), small for gestational age (aOR 1.47;

95% CI, 1.38–1.56), NICU admission (aOR 1.24; 95% CI, 1.16–1.33), and infant death (aOR 1.86; 95% CI, 1.44–2.41).

### Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching UpToDate and ACOG.org with the terms “marijuana” and “pregnancy” to find additional literature to place this research into the context of current clinical practice.

#### Does this meet PURL criteria?

Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	No	Clinically meaningful	Yes

**Bottom line:** Maternal cannabis use during pregnancy is associated with an increase in maternal and neonatal morbidity. This large retrospective cohort study was limited because of the heterogeneity between study groups. Further prospective studies are required to validate these findings and determine the exact clinical effect associated with cannabis exposure.

Jason S. Lanham, MD, MA, FAAFP

Racquel Puranda, MD

J. Scott Earwood, MD, FAAFP

Department of Family and Community Medicine, Medical College of Georgia at Augusta University, Augusta, GA

The corresponding author is J. Scott Earwood; [jearwood@augusta.edu](mailto:jearwood@augusta.edu).

The authors declare no conflict of interest.

## Mifepristone for Management of Adenomyosis

Che X, Wang J, Sun W, et al. Effect of Mifepristone vs Placebo for Treatment of Adenomyosis With Pain Symptoms: A Randomized Clinical Trial. *JAMA Netw Open*. 2023;6(6):e2317860. doi:10.1001/jamanetworkopen.2023.17860

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002108

A 2023 multicenter, placebo-controlled, double-blind, randomized clinical trial (n=134) evaluated the efficacy and safety of mifepristone in the management of

# DIVING FOR PURLs

adenomyosis. Patients were premenopausal women 18 to 50 years old from 10 Chinese hospitals with a diagnosis of adenomyosis, confirmed by ultrasound or magnetic resonance imaging, and adenomyosis-associated dysmenorrhea. Researchers excluded patients with a history of undiagnosed vaginal bleeding, endometrial malignant tumors, uterine fibroids, or endometriosis. Patients who refused to use nonhormonal contraceptive methods were also excluded. Patients were randomly assigned to receive mifepristone 10 mg daily or placebo daily for 12 weeks. They were followed every four weeks with a trial visit until four weeks after the treatment period. The primary outcome was change in adenomyosis-associated dysmenorrhea intensity, evaluated by a zero to 10 visual analog scale (VAS), with higher score indicative of increased pain, from baseline to 12 weeks of treatment. Investigators also evaluated the complete remission and total effectiveness rates (defined as a reduction in VAS score of at least 30%) with respect to dysmenorrhea. Secondary outcomes were changes in menstrual blood loss volume, hemoglobin levels, cancer antigen 125 (CA125) levels, platelet counts, and uterine volume. Menstrual blood loss was analyzed with the Pictorial Blood Loss Assessment Chart (PBAC), a self-reported pictorial tool that grades menstrual bleeding severity with increasing scores indicative of heavier bleeding (no maximum score, with a score of  $\geq 100$  indicative of  $>80$  mL of blood loss and defined as heavy menstrual bleeding). Using PBAC scores, rates of complete remission (change from heavy menstrual bleeding to amenorrhea) and total efficacy (proportion of patients with PBAC scores reduced by at least 30%) of heavy menstrual bleeding were calculated. Baseline VAS pain scores and other demographics were similar between groups. After 12 weeks, the mifepristone group noted a decrease in VAS score of  $-6.63$  compared with the placebo group decrease of only  $-0.95$  (between-group difference  $-5.7$ ; 95% CI,  $-6.4$  to  $-5.0$ ;  $P < .001$ ). Complete remission was noted for 54 patients (89%) in the mifepristone group compared with four patients (6.2%) in the placebo group ( $P < .001$ ). Total efficacy rate was also higher in the mifepristone group (92% vs 23%;  $P < .001$ ). Secondary outcomes showed a reduction in heavy menstrual bleeding with use of mifepristone as noted by both improved complete remission (90% vs 5.4%;  $P < .001$ ) and total efficacy rates (95% vs 38%;  $P < .001$ ). Mifepristone was also superior to placebo for the following: increase in hemoglobin level (2.13 vs 0.48 g/dL;

$P < .001$ ), change in CA125 levels ( $-62$  vs  $27$  U/mL,  $P < .001$ ), change in platelet count ( $-29$  vs  $2.1 \times 10^9$ /L,  $P < .001$ ), and change in uterine volume ( $-29$  vs  $18$  cm,  $P < .001$ ). Safety analysis did not show any differences between the groups. Eight patients were lost to follow-up (5 mifepristone group and 3 control group) and were not included in the statistical analysis. Study limitations included short follow-up (only 4 weeks after treatment) and lack of any long-term safety or efficacy data.

## Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching Cochrane Library, PubMed, and UpToDate with the terms adenomyosis and mifepristone to find additional literature to place this research into the context of current clinical practice.

### Does this meet PURL criteria?

Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	No
Change in practice	Yes	Clinically meaningful	Yes

**Bottom line:** Mifepristone appears to be an effective therapy for the management of dysmenorrhea and heavy menstrual bleeding associated with adenomyosis. As such, mifepristone may provide an important treatment option for adenomyosis, as no currently approved medical therapies are present and little clinical guidance on best treatment practices for adenomyosis available at this time. Medication availability and unknown long-term efficacy and safety data limit immediate implementation.

Alexis Aust, MD

Kattie Hoy, MD

Brock Cardon, MD

Nellis Family Medicine Residency, Nellis Air Force Base, NV

The corresponding author is Brock Cardon; brock.e.cardon.mil@health.mil.

The authors declare no conflicts of interest.

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the U.S. Air Force Medical Department, the Air Force at large, or the Department of Defense.

## MY BODY, MY HOME HPV TESTING

Pretsch PK, Spees LP, Brewer NT, et al. Effect of HPV self-collection kits on cervical cancer screening uptake among under-screened women from low-income US backgrounds (MBMT-3): a phase 3, open-label, randomised controlled trial. *Lancet Public Health*. 2023;8(6):e411-e421. doi:10.1016/S2468-2667(2300076-2).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002097

This randomized controlled trial looked at the effect of mailed human papillomavirus (HPV) self-collection kits and routine scheduling assistance on screening uptake in underscreened women. Patients included adults with an intact cervix who were 25 to 64 years old from North Carolina (N=665) who were randomized (2:1) to mailed HPV self-collection kits and routine scheduling assistance or routine scheduling assistance alone. Researchers included patients who were uninsured or enrolled in Medicaid or Medicare, had an income of 250% or less of the U.S. Federal Poverty Level, and were overdue for cervical cancer screening as defined by cotesting within the last four years or high-risk HPV test within six years. The study spanned from April 2016 to December 2019 and the primary outcome was screening uptake within six months of the start of trial. This included a negative HPV home self-collection test or in-clinic screen. This study found that screening uptake in the intervention group was higher than that in the control group (72% vs 37%; risk ratio 1.93; 95% CI, 1.62–2.31). Rover's Viba-Brush was used in this study and was tolerated well. Only three patients reported adverse effects to at-home self-collection, which was reported as being scratched. The cost of this brush set ranges from 150 to 200€ per 100-piece set; however, this brush is not currently approved for use by the Food and Drug Administration. This increase in screening uptake was observed throughout multiple subgroups in intention-to-treat analysis including age, time since last screening test, ethnicity, insurance status, education status, and annual income.

### Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was

conducted in PubMed with the terms [("self-collect" OR "Self-sampling") AND "HPV" AND "cervical"] to locate additional literature placing this research into the context of current clinical practice.

### Does this meet PURL criteria?

Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	No
Change in practice	Yes	Clinically meaningful	Yes

**Bottom line:** The CDC 2021 Cervical Cancer Screening rates noted a 75.2% cervical cancer screening rate of women in the United States with a Healthy People 2020 goal of 93% nationally. Using mailed HPV self-collection kits can improve cervical cancer screening rates in underscreened women, but application of this currently remains locked behind funding and structural implementation barriers.

**Reiana Mahan, MD**

**University of Missouri Family and Community Medicine,  
Columbia, MO**

The Corresponding Faculty Author on the manuscript is: Carl Tunink, MD, MSAM; tuninkc@umsystem.edu.  
The authors declare no conflict of interest.

## Exploring colchicine: a new angle on joint surgery risk

Heijman MWJ, Fiolet ATL, Mosterd A, et al. Association of Low-Dose Colchicine With Incidence of Knee and Hip Replacements: Exploratory Analyses From a Randomized, Controlled, Double-Blind Trial. *Ann Intern Med*. 2023; 176(6):737-742. doi:10.7326/M23-0289

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002100

This secondary exploratory analysis was conducted within the framework of the Low-Dose Colchicine-2 (LoDoCo2) trial. The original trial was designed to investigate the effects of low-dose colchicine (0.5 mg once daily) on cardiovascular outcomes in patients with chronic coronary artery disease. As a multicenter, randomized, placebo-controlled, double-blind study, it enrolled adults 35 to 82 years old (mean age 66 years) with a history of chronic coronary artery disease who could tolerate colchicine from

# DIVING FOR PURLs

2014 to 2018. After one month of open-label colchicine, those without adverse effects were randomly assigned to either the colchicine (n=2,762) or placebo (n=2,760) group over a median period of 28.6 months. Patients were excluded with a history of moderate-to-severe renal failure (serum creatinine >1.7 mg/dL, estimated glomerular filtration rate <50 mL/min), severe heart failure, severe valvular heart disease, or known intolerance to colchicine. The primary objective of this analysis was to assess the impact of colchicine on the incidence of total knee (TKR) or hip (THR) replacements. Colchicine was associated with a 31% reduced risk of TKR or THR (hazard ratio [HR] 0.69; 95% CI, 0.51–0.95). Incidence rates were 0.90 per 100 person-years for the colchicine group and 1.30 per 100 person-years for the placebo group. This effect remained even after excluding patients with gout (HR 0.68; 95% CI, 0.49–0.94) and those who underwent joint surgeries within the first three months (H: 0.61; 95% CI, 0.44–0.84) and the first six months (HR 0.58; 95% CI, 0.41–0.82) after randomization.

While these findings suggest the potential benefit of colchicine in reducing the need for knee and hip replacements in the short term, several limitations should be acknowledged. The original trial was designed to investigate cardiovascular outcomes, and as a result, it did not collect information on patients' history of osteoarthritis, joint pain, physical function, radiographic progression, and medication use for osteoarthritis. In addition, the outcome of "time to first TKR or THR since randomization" is not commonly used in osteoarthritis clinical trials and may be influenced by various confounding variables such as wait time for surgery. Finally, the results may not be universally generalizable to other patient populations.

## Methods

This article was identified as a potential PURL through the standard systematic methodology that has been described here. An additional literature search was conducted by searching UpToDate, Dyamed, and PubMed with the terms "Colchicine" and "Osteoarthritis" to find additional literature to place this research into the context of current clinical practice.

### Does this meet PURL criteria?

Relevant	Yes	Medical care setting	Yes
Valid	Yes	Implementable	Yes
Change in practice	No	Clinically meaningful	Yes

**Bottom line:** This is an exploratory study on the analysis of the LoDoCo2 trial database which suggests that colchicine may reduce the short-term incidence of total knee or hip replacements in patients with coronary artery disease. Notably however, there is a lack of comprehensive information regarding osteoarthritis related outcomes or the long-term safety and potential side effects of the therapy. Consequently, further research is necessary to expand on these findings.

**Mohammed Saleh, MD**  
University of Missouri, Columbia, MO

The Corresponding Faculty Author on the manuscript is: Carl Tunink, MD [tuninkc@health.missouri.edu](mailto:tuninkc@health.missouri.edu)  
The authors declare no conflict of interest.

# A new shot for moms-to-be: antepartum vaccine prevents severe RSV infection in infants

## Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants

Kampmann B, Madhi SA, Munjal I, et al. Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. *N Engl J Med.* 2023;388(16):1451-1464. DOI 10.1097/EBP.0000000000002071

**KEY TAKEAWAY:** Respiratory syncytial virus prefusion F (RSVpreF) vaccine administered during pregnancy is effective in preventing severe RSV-associated LRTI in infants, and no safety concerns were identified.

**STUDY DESIGN:** Randomized, double-blind phase three placebo-controlled trial.

**LEVEL OF EVIDENCE:** STEP 2.

**BACKGROUND:** RSV is the most common cause of acute lower respiratory tract infection (LRTI) and a leading cause of death in infants younger than 6 months of age. Maternal vaccination leads to transplacental transfer of formed maternal antibodies against antigens, including vaccines. The RSVpreF vaccine recently underwent a phase 2b trial and demonstrated an acceptable safety profile and evidence of transplacental antibody transfer, prompting a phase 3 trial to determine the efficacy and safety of maternal RSVpreF vaccination in preventing RSV-associated LRTIs in infants.

**PATIENTS:** Pregnant women.

**INTERVENTION:** RSVpreF vaccine.

**CONTROL:** Sham vaccine.

**OUTCOME:** Medically attended RSV-associated LRTI (severe and not severe).

**SECONDARY OUTCOMES:** RSV-associated hospitalization, medically attended LRTI of any cause, adverse events in maternal and infants.

### METHODS BRIEF DESCRIPTION:

- Healthy women 49 years and younger at 24 to 36 weeks' gestation with an uncomplicated, singleton pregnancy without increased risk of pregnancy complications were enrolled.
- Researchers excluded high-risk pregnancies: elevated risk of preterm delivery, multiple gestation, or previous child with congenital anomaly.
- Maternal participants had a mean age of 29 years old, mean gestation of 30.8 weeks, and comprised multiple racial and ethnic groups.
- Patients were randomly assigned in a 1:1 ratio to either receive a single intramuscular injection of 120 µg of RSVpreF vaccine or placebo injection.
- A medically attended RSV-related LRTI was defined as a visit for a respiratory illness and with real-time polymerase chain reaction (RT-PCR) positive for RSV, plus tachypnea, SpO<sub>2</sub> < 95%, or retractions on examination.
- A medically attended severe RSV-related LRTI required positive RSV RT-PCR plus tachypnea, SpO<sub>2</sub> < 93%, use of high-flow nasal cannula or mechanical ventilation, admission to ICU for >4 hours, or lack of response/unconsciousness.
- Investigators determined vaccine efficacy by setting a confidence interval lower boundary of 20% for vaccine efficacy for primary endpoints; a lower boundary of 0% was set for secondary endpoints.
- For safety endpoints, point estimates and 95% CIs were based on the percentage of individuals reporting each event.

### INTERVENTION (# IN THE GROUP):

**MATERNAL PARTICIPANTS:** 3,682

**INFANT PARTICIPANTS:** 3,570

### COMPARISON (# IN THE GROUP):

**MATERNAL PARTICIPANTS:** 3,676

**INFANT PARTICIPANTS:** 3,558

**FOLLOW-UP PERIOD:** 12 months

### RESULTS:

Primary outcome

- The RSVpreF vaccine group had a statistically lower rate of medically attended **severe** RSV-related LRTI as compared with placebo.
  - 90-day vaccine efficacy: 82% (99.5% CI, 41–96).
  - 180-day vaccine efficacy: 69% (97.58% CI, 44–84).
- For the primary endpoint of medically attended RSV-associated LRTI of **any severity**, the success criterion was not met at 90 days in the RSVpreF vaccine group as compared with placebo (24 vs 56 infants, 90-day vaccine efficacy 57%; 99.5% CI, 15–80).

#### Secondary outcomes

- No significant safety concerns arose in maternal or infant populations.
- The rates of any adverse events (local reactions including injection site pain or systemic reactions including headache, fatigue, myalgias) in maternal population within one month were similar in the vaccine group (13.8%) and placebo group (13.1%).

#### LIMITATIONS:

- The study only included a healthy pregnancy population with uncomplicated pregnancies which brings generalizability into question.

- The study was sponsored and conducted by the manufacturers of the vaccine.
- The study was performed in multiple medium-income to high-income countries, limited data from low-income countries. EBP

**Ryan Ahn, MD**

*Northern Light Family Medicine Residency Program,  
Bangor, ME*

The corresponding author is: Ryan Ahn; rahn@northernlight.org.  
The author declares no conflicts of interest.

---

# Do statins prevent major adverse cardiac events (MACEs) in adults with low-risk or borderline-risk ASCVD?

## EVIDENCE-BASED ANSWER

Statins reduce the risk of major adverse cardiac events (MACEs) in adults with low-risk or borderline-risk atherosclerotic cardiovascular disease (SOR: **A**, meta-analysis of randomized controlled trials (RCTs) and single, large RCT). However, because the prevalence of MACE is low in this patient population, the absolute benefit of statin therapy may be low and the ultimate decision to initiate statin therapy should be made through a shared decision-making process (SOR: **C**, evidence-based guideline).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002070

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2012 meta-analysis of 22 randomized controlled trials (RCTs) (N=134,537) with intention-to treat analysis evaluated the risk reduction of major vascular events (MVE) in patients using statin therapy.<sup>1</sup> MVE was defined as significant coronary events (ie, nonfatal myocardial infarction or coronary death), strokes, or coronary revascularizations. Reported risk reduction was weighted by the absolute low density lipoprotein (LDL) cholesterol difference in that trial at year one and were reported as effects per 1.0 mmol/L reduction in LDL cholesterol. Subgroups of individuals with lower MVE risk were identified using risk calculators at both less than 5% risk (N=24,790) and 5% to less than 10% (N=28,362) with a median follow-up of about five years. In the less than 5% baseline risk subgroup, patients in the statin group experienced fewer MVE events (167 vs 254) and had significantly greater risk reduction in LDL cholesterol compared with the control group (relative risk [RR] 0.62; 99% CI, 0.47–0.81). In the 5% to less than 10% risk subgroup, patients in the statin group again experienced fewer MVE events (604 vs 847) and had significantly greater risk reduction in LDL cholesterol compared with the control group (RR 0.69; 99% CI, 0.60–0.79). Notably, the observed annual MVE rate in the control groups was low in these subgroups: 0.6% for the <5% group and 1.6% in 5% to <10% group.

A 2021 multicenter RCT (n=12,705) compared rosuvastatin against placebo in reducing major adverse cardiovascular events (MACE).<sup>2</sup> Patients were 54% male and were followed for 8.7 years. Individuals with a history of cardiovascular disease were excluded. An active intervention period of 5.6 years was studied with an additional 3.1 years of passive follow-up of 78% of participants (N=9,326) after cessation of trial medication. A subgroup of low-risk individuals (N=4,735) was identified using the INTERHEART risk score, which measures the collective risk factors contributing to MACE (myocardial infarction, stroke, and/or cardiovascular death). After 8.7 years, the risk of MACE for those in the low-risk group was significantly lower in participants given rosuvastatin versus placebo (hazard ratio [HR] 0.66; 95% CI, 0.50–0.86).

A 2013 American College of Cardiology/American Heart Association evidence-based guideline discussed treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults.<sup>3</sup> The American College of Cardiology/American Heart Association (ACC/AHA) Guidelines recommended offering moderate-intensity statin treatment to adults with a 10-year atherosclerotic cardiovascular disease (ASCVD) risk of 5% to less than 7.5% and LDL-C 70 to 189 mg/dL without clinical ASCVD or diabetes (strength of recommendation: weak, limited by conflicting evidence or nonrandomized studies). The expert panel noted that in patients 40 to 75 years old with less than 5% estimated 10-year ASCVD risk, the net benefit from statin therapy would be small and suggested that before initiation of statin therapy, the clinician–patient discussion should include the consideration for ASCVD risk reduction benefits, adverse effects, and drug–drug interactions. EBP

**Christina Cavanagh, MD**  
**Joanna Greenhalgh, DO**  
**Antony Mikhail, DO**  
**Snigdha Ila, DO**  
**Amy Skiff, PharmD**

*The Florida State University College of Medicine, Family Medicine Residency Program at Lee Health, Fort Myers, FL*

The corresponding author is Christina Cavanagh;  
Christina.cavanagh@leehealth.org.  
The authors declare no conflicts of interest.

### References

1. Cholesterol Treatment Trialists' CTT Collaborators; Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. *Lancet*. 2012;380(9841):581-590. [STEP 1]
2. Bosch J, Lonn EM, Jung H, et al. Lowering cholesterol, blood pressure, or both to prevent cardiovascular events: results of 8.7 years of follow-up of Heart Outcomes Evaluation Prevention (HOPE)-3 study participants. *Eur Heart J*. 2021; 42(31):2995-3007. [STEP 2]
3. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014; 129(25 suppl 2):S1-S45. [STEP 5]

## Does melatonin improve sleep-onset insomnia and sleep duration in pediatric patients with ADHD?

### EVIDENCE-BASED ANSWER

Probably. Pediatric patients with ADHD taking melatonin likely have increased total time asleep (SOR: **B**, single RCT) and decreased sleep onset latency (SOR: **C**, consistent small clinical trials).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002038

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2007 multicentered randomized, double-blind, placebo-controlled study (n=105) performed in the Netherlands analyzed the efficacy of melatonin to improve sleep duration in pediatric patients with ADHD.<sup>1</sup> Children ages 6 to 12 years old (mean age 9.1 years old) with an ADHD diagnosis and sleep-onset insomnia (SOI) defined as delayed sleep onset after 8:30 PM or sleep onset latency (SOL; or time needed to fall asleep nightly) >30 minutes were included in the study. Exclusion criteria included IQ <80, previous use of melatonin or other sleep medications, treatment with a stimulant, or previously diagnosed neurological/psychiatric conditions. Researchers randomized patients to receive 3 mg melatonin or a placebo at the same time daily for four weeks after a one-week period of baseline data collection using a wrist-applied actigraphy in addition to parent-completed sleep logs. Actigraphy data were converted into sleep parameters using a scoring algorithm and verified by sleep log data. Melatonin improved sleep onset by 26.9 minutes compared with 10.5 minutes for placebo ( $P=.0001$ ) and increased mean total time of sleep by 19.8 minutes compared with a decrease of 13.6 minutes for placebo ( $P=.01$ ).

Melatonin also decreased sleep onset latency by 21.3 minutes, whereas it increased with placebo by 3.0 minutes ( $P=.001$ ). Side effects included headache, hyperactivity, dizziness, and abdominal pain. Study limitations were the use of actigraphy to assess sleep performance in place of the more accurate polysomnography, narrowly defined criteria for SOI because of unavailable international consensus criteria, exclusion criteria of stimulant use, and a heterogenous Dutch child population.

A 2006 multicenter double-blind, placebo-controlled, randomized crossover trial (n=19) performed in Canada examined the effectiveness of melatonin and sleep hygiene (consistent bed and wake time with a total sleep duration of 9.5 hours) for children with ADHD and insomnia.<sup>2</sup> Researchers included patients 6 to 14 years old on stimulant medications with no change in dose for two months and willing to maintain the same dose for the duration of the study. Patient also needed an SOL of >60 minutes over the course of 10 consecutive days, willingness to wear an actinograph wrist monitor, and agreement for a consistent bed and wake time. Patient who were unable to comply with sleep hygiene instructions were excluded. All patients received 5 mg melatonin for 10 days, followed by a five-day washout period with a placebo. The primary outcome measure was the mean SOL in each of the melatonin and placebo phases. The secondary outcome measured the efficacy of sleep hygiene on SOL without melatonin. SOL was significantly improved with melatonin (16 minutes) compared with placebo ( $P<.01$ ). Reported side effects were mild or moderate except headaches that some subjects rated as severe.

A 2020 multicenter uncontrolled clinical trial (n=99) examined the efficacy of melatonin for children with insomnia and neurodevelopmental disorders (NDDs).<sup>3</sup> Patients ranged from 6 to 15 years old, mean age 10.4 years old. Patients were enrolled at 17 outpatient pediatric clinics in Japan and met the *Diagnostic and Statistical Manual of Mental Disorders, fifth edition* criteria for NDDs; 60 (60.6%) of these patients were diagnosed with ADHD and had mean SOL lasting >30 minutes for three or more months. Patients with schizophrenia or bipolar disorder were excluded. This was a 30-week, open-label clinical study. Patients were their own controls during a two-week screening phase when they received a placebo and a sleep hygiene pamphlet instructing

patients to do the following: obtain sunlight in the morning, eat breakfast, exercise daily, and avoid lighted screens before bed. During the 26-week medication phase, subjects received 1, 2, or 4 mg of melatonin tablets daily based on weight. During the two-week follow-up phase, melatonin was discontinued. Caregivers received electronic sleep diaries and questionnaires to record metrics. The primary endpoint was significant for shortened SOL during the medication phase compared with the placebo phase for all subjects (median, -30 minutes;  $P < .0001$ ). Subgroup analysis demonstrated an even shorter SOL for patients with ADHD (-33 minutes;  $P < .0001$ ) during the medication phase. Side effects included headaches, irritability, GI upset, and excessive sleepiness during the daytime. This trial was limited because of the lack of randomization, the use of parent reporting instead of actigraphy, the fact that melatonin doses varied, heterogeneity, and underpowered. **EBP**

Laurel Macey, MD  
William Candelori, DO  
Sanjay Singh, MD

Anne C. Jones, DO, MPH  
*Inspira Medical Center-Mullica Hill Family Medicine  
Residency Program, Mullica Hill, NJ  
Rowan-Virtua School of Osteopathic Medicine, Sewell,  
NJ*

The corresponding author is Anne C. Jones, DO, MPH; jonesan@rowan.edu.  
The authors have no financial disclosures or conflicts of interest to disclose.

## References

1. Van der Heijden KB, Smits MG, Van Someren EJ, Ridderinkhof KR, Gunning WB. Effect of melatonin on sleep, behavior, and cognition in ADHD and chronic sleep-onset insomnia. *J Am Acad Child Adolesc Psychiatry*. 2007; 46(2): 233-241. [STEP 2]
2. Weiss MD, Wasdell MB, Bomben MM, Rea KJ, Freeman RD. Sleep hygiene and melatonin treatment for children and adolescents with ADHD and initial insomnia. *J Am Acad Child Adolesc Psychiatry*. 2006; 45:5. [STEP 2]
3. Yuge Kotaro, Nagamitsu Shinichiro, Ishikawa Yuko, et al. Long-term melatonin treatment for the sleep problems and aberrant behaviors of children with neurodevelopmental disorders. *BMC Psychiatry*. 2020; 20:445. [STEP 3]

# After placement of a newer-generation drug-eluting coronary artery stent in a patient with a high bleeding risk, does one month of dual antiplatelet therapy effectively reduce the incidence of major bleeding while also maintaining stent effectiveness?

## EVIDENCE-BASED ANSWER

In patients at high bleeding risk, a one-month course of dual antiplatelet therapy (DAPT) after stent placement is similarly efficacious at preventing thrombotic complications with lower risk of significant bleeding (number needed to treat [NNT]=36) compared with longer courses of DAPT (SOR: **A**, large multicenter randomized controlled trial (RCT) and comparison of single-arm, open-label studies with consistent results). Outcomes are similar when studying all patients, regardless of bleeding risk, although the reduction in bleeding events is more modest where the bleeding risk is low (NNT=75) (SOR: **B**, multicenter, open-label, RCT).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002078

This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2021 multicenter randomized controlled trial (RCT) (n=4,579) investigated the effectiveness and safety of an abbreviated course of dual antiplatelet therapy (DAPT)

poststent placement.<sup>1</sup> The study included patients from 30 European and Asian nations with acute coronary syndrome who had undergone placement of a sirolimus drug-eluting stent and were at elevated bleeding risk (defined as treatment with an oral anticoagulant, recent bleeding requiring medical attention, or having a condition associated with increased bleeding). The intervention group received DAPT with aspirin (dose range 75–162 mg daily) and a P2Y12 inhibitor (clopidogrel 75 mg daily, prasugrel 5–10 mg daily, or ticagrelor 90 mg twice daily) for one month. The control group received DAPT for six months, and both groups were continued on aspirin or P2Y12 monotherapy after DAPT for a total of 12 months. Patients taking oral anticoagulants had antiplatelet monotherapy discontinued at six months total therapy. The hierarchical primary outcomes were a composite of net adverse clinical events (comprised death, MI, stroke, and major bleeding), a composite of major adverse cardiac or cerebral events (death, MI, and stroke), and major or clinically relevant nonmajor bleeding. Follow-up was one year after PCI. The first two outcomes were assessed for noninferiority on the per-protocol study population, with a noninferiority margin of 3.6% for the first outcome and 2.4% for the second. The third outcome was assessed for superiority on the intention-to-treat population. The one-month DAPT arm was noninferior to standard DAPT for both net adverse clinical events (risk difference –0.23%; 95% CI, –1.8% to 1.3%) and major adverse cardiac or cerebral events (risk difference 0.11%; 95% CI, –1.3% to 1.5%). Abbreviated treatment was superior to standard DAPT for major or clinically relevant nonmajor bleeding with an NNT of 36 (risk difference –2.8%; 95% CI, –4.4% to –1.2%). Limitations included variation in therapies across study locations because of differing national standards.

A 2019 multicenter RCT (n=2,974) evaluated bleeding event rates with abbreviated DAPT poststent placement.<sup>2</sup> This study included Japanese adults receiving an everolimus-eluting cobalt–chromium stent. Researchers excluded patients with a history of intracranial bleeding and concomitant anticoagulation or antiplatelet therapy. The treatment group received one month of DAPT with aspirin (dose range 81–200 mg/day) and P2Y12 inhibitor (clopidogrel 75 mg/day or prasugrel 3.75 mg/day) followed by monotherapy with clopidogrel 75 mg daily. The control group received 12 months of DAPT with aspirin and clopidogrel. The primary outcome was a net benefit composite of cardiovascular and bleeding events, including cardiovascular death, MI, stent thrombosis, stroke, and major or minor bleeding. After one year of follow-up, the abbreviated course

of DAPT resulted in a lower rate of the composite cardiovascular and bleeding outcome compared with the standard 12-month course, with an NNT of 75 (absolute rate difference –1.3%; hazard ratio 0.64; 95% CI, 0.42–0.98). Limitations included a homogenous study group with low ischemic risk and lack of placebo control in the treatment arm after the initial one-month DAPT course.

A 2021 exploratory analysis of three single-arm, multicenter prospective studies (N=3,652) evaluated the effect of abbreviated DAPT on bleeding and ischemic events in high bleeding risk poststent patients.<sup>3</sup> Researchers enrolled patients in all three single-arm studies between 2017 and 2020 from over 100 sites in multiple countries with identical inclusion criteria: adults who had received an everolimus-eluting cobalt–chromium stent and were considered high risk for bleeding (at least one of the following criteria: age older than 75 years old, chronic anticoagulant therapy, history of stroke, chronic coagulopathy, major adverse bleeding in the preceding 12 months). The studies excluded patients presenting with ST-segment elevation MI (STEMI) or with more than three stents. Two of the studies were combined for the analysis and used an identical treatment course of one month of open-label DAPT (aspirin 75–100 mg/day and P2Y12 inhibitor, preferably clopidogrel 75 mg/day). The third study treated patients with three months of the same DAPT regimen. All patients continued with aspirin monotherapy after the DAPT course. Owing to the nonrandomized trial design, the two groups were propensity-matched before statistical analysis. The primary endpoint was a composite of all-cause mortality and myocardial infarction. Secondary endpoints included significant bleeding (defined as Bleeding Academic Research Consortium type 2–5). After one year of follow-up, the two treatment groups had similar rates of the composite of death and MI (rate difference –0.2%; 95% CI, –2.2% to 1.7%). Significant bleeding rates were lower in patients receiving one month of DAPT compared with three months, with an NNT of 40 (rate difference –2.5%; 95% CI, –4.6% to –0.3%). The study was limited by its nonrandomized design and funding provided by the stent manufacturer. EBP

**Nicholas DeStefano, MD**

**Alexander Britton, DO**

**Phillip Markey, MD**

*Dwight D. Eisenhower Family Medicine Residency, Fort Gordon, GA*

The corresponding author is Nicholas DeStefano; nicholas.c.destefano@gmail.com.

The authors declare no conflicts of interest.

### References

1. Valgimigli M, Frigoli E, Heg D, et al. Dual antiplatelet therapy after PCI in patients at high bleeding risk. *N Engl J Med*. 2021;385(18):1643-1655. [STEP 2]
2. Watanabe H, Domei T, Morimoto T, et al. Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI: the STOPDAPT-2 randomized clinical trial. *JAMA*. 2019;321(24):2414-2427. [STEP 2]
3. Valgimigli M, Cao D, Angiolillo DJ, et al, XIENCE 90 and XIENCE 28 Investigators. Duration of dual antiplatelet therapy for patients at high bleeding risk undergoing PCI. *J Am Coll Cardiol*. 2021;78(21):2060-2072. [STEP 3]

## Is paxlovid effective for prevention of COVID-19 complications in vaccinated patients?

### EVIDENCE-BASED ANSWER

Yes. Treatment with Paxlovid® for prevention of COVID-19 complications in nonhospitalized vaccinated patients is associated with a reduced likelihood of emergency room visits, hospitalization, and death. Early treatment with Paxlovid (within 5 days of symptom onset) is associated with the greatest clinical benefit (SOR: **A**, consistent findings from retrospective cohort studies).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002079

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2023 matched observational outpatient cohort study (n=133,426) examined the effectiveness of nirmatrelvir-ritonavir (Paxlovid) treatment in preventing all-cause mortality and hospital admission within 30 days

of a positive SARS-CoV-2 index test between April 8 and October 7, 2022.<sup>1</sup> Patients were 12 years old or older, had a positive SARS-CoV-2 polymerase chain reaction test result, had not had another positive test result within the preceding 90 days, and were not hospitalized at the time of their index test or within the preceding seven days. The study used matched controls for the exposure group. The primary exposure group included patients who received Paxlovid ≤5 days of symptom onset and those who received treatment at any point after a positive test regardless of symptoms. Of the patients who received treatment with Paxlovid, 93.9% (n=6,873) had received two or more COVID-19 vaccine doses. In patients who received 2 doses of a COVID-19 vaccine, effectiveness was 83.1% when Paxlovid was dispensed at or before five days of symptom onset (95% CI, 30.4–95.9; P=.01) and 55.3% when dispensed at any time (95% CI, 6.6–78.7; P=.03). In patients who had received 3 doses of a COVID-19 vaccine, effectiveness climbed to 92.2% when Paxlovid was dispensed at or before five days of symptom onset (95% CI, 52.0–98.7; P=.006) and 66.5% when dispensed at any time (95% CI, 24.0–85.3; P=.009). After adjustment for differences among the control and exposure groups, receipt of Paxlovid at or before five days of onset of COVID-19 symptoms had an effectiveness of 79.6% (95% CI, 33.9–93.8; P=.008) against progression to hospital admission or death within 30 days. Receiving Paxlovid at any time had an effectiveness of 53.6% (95% CI, 6.6–77.0; P=.03) for hospitalization or death. Limitations of the study included information bias because of study design and unverifiable treatment adherence in patients who received a prescription for Paxlovid. It should also be noted that the confidence intervals were wide and may reflect low precision of results.

A 2022 retrospective cohort study including several large US health systems examined the effectiveness of Paxlovid for previously vaccinated persons with COVID-19 (n=481,495).<sup>2</sup> Patients were adults diagnosed with COVID-19 between April 1 and August 31, 2022, received care in any outpatient setting including telemedicine and emergency department, were eligible for treatment with Paxlovid (age 50 years old and older or an adult with a documented underlying health condition, with no medical or pharmacologic contraindications), and were confirmed to have received ≥2 COVID-19 mRNA vaccine doses. The treatment group (n=156,248) received an outpatient prescription for five days of Paxlovid ≤5 days of date

of diagnosis, and the control group (n=325,058) did not receive a prescription for Paxlovid. The primary outcome was COVID-19 hospitalization during the 30 days after the date of diagnosis. Among the treatment group, there were 3,212 hospitalizations (0.7% 30-day incidence). When compared with the control group, a prescription for Paxlovid was associated with a significant reduction in hospitalization for vaccinated patients with COVID-19 (adjusted hazard ratio [aHR] 0.5; 95% CI, 0.4–0.6 for 2 prior mRNA vaccine doses; aHR 0.5; 95% CI, 0.5–0.6 for ≥3 prior mRNA vaccine doses). Limitations include information bias because of the study design, sample bias, lack of randomization, and data access constraints.

A 2022 retrospective cohort study (n=2,260) examined the efficacy of Paxlovid in patients between December 1, 2021, and April 18, 2022.<sup>3</sup> Participants in the study were all adults vaccinated against COVID-19, diagnosed with COVID-19 at least one month after vaccination, non-hospitalized, and started on Paxlovid at or before five days of diagnosis. There were 1,130 patients each in the treatment and control groups. The treatment group received Paxlovid, while the control group did not. The primary composite outcome was all-cause emergency room visits, hospitalizations, or death at a 30-day follow up. The rate of primary outcome in the treatment group was 7.9% compared with the control group of 14.4% (odds ratio 0.5; 95% CI, 0.4–0.7;  $P < .005$ ). Survival probability for patients in the intervention group was significantly higher than the control group (88.2% vs 84.2%; HR 0.7; 95% CI, 0.5–0.8,  $P = .002$ ). Limitations of the study included the possibility of unmeasured confounding variables influencing results, although propensity matching was used by the investigators in an attempt to minimize this effect. Furthermore, the primary outcome included all-cause emergency room visits, hospitalizations, or death instead of those directly related to COVID-19. Finally, the study did not differentiate between type or number of vaccines received. **EBP**

**Kari Nilsen, PhD**

**Patrick Allen, MD**

**Karissa Gilchrist, MD**

**Jared Regehr, MD**

*Family Medicine Residency Program at Ascension Via Christi Hospitals, Wichita, KS*

The corresponding author is Kari Nilsen; knilsen@kumc.edu. The authors declare no conflicts of interest.

## References

1. Lewnard JA, McLaughlin JM, Malden D, et al. Effectiveness of nirmatrelvir-ritonavir in preventing hospital admissions and deaths in people with COVID-19: a cohort study in a large US health-care system. *Lancet Infect Dis*. 2023;23(7):806-815. [STEP 2]
2. Shah MM, Joyce B, Plumb ID, et al. Paxlovid associated with decreased hospitalization rate among adults with COVID-19—United States, April-September 2022. *MMWR Morb Mortal Wkly Rep*. 2022;71(48):1531-1537. [STEP 2]
3. Ganatra S, Dani SS, Ahmad J, et al. Oral nirmatrelvir and ritonavir in nonhospitalized vaccinated patients with coronavirus disease 2019. *Clin Infect Dis*. 2023;76(4):563-572. [STEP 2]

## Is topical testosterone less likely to cause polycythemia than IM testosterone in patients on testosterone replacement therapy?

### EVIDENCE-BASED ANSWER

Not completely clear. All forms of testosterone replacement therapy lead to increase in hematocrit. Testosterone given IM may result in a greater hematocrit increase than testosterone patch (SOR: **C**, disease-oriented outcome from meta-analysis of randomized controlled trials [RCTs]). Cases of polycythemia are seen in patients using IM testosterone, a condition not seen with the use of intranasal testosterone gel (SOR: **C**, small RCT and cross-sectional study).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002101

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A systematic review and network meta-analysis of 29 placebo-controlled randomized controlled trials (RCTs; N=3,393) assessed the change in hematocrit

based on route of testosterone replacement therapy in men 18 years old and older being treated for testosterone deficiency.<sup>1</sup> Most studies included patients with total testosterone <350 ng/dL. Trials assessed gel (8 trials), patch (8 trials), oral testosterone undecanoate (TU; 1 trial), intramuscular TU (6 trials), and intramuscular testosterone enanthate/cypionate (TE/C; 11 trials) for analysis of change in hematocrit levels before versus after testosterone replacement therapy (TRT) over an average of 14.5 months. In the network meta-analysis, all the formulations resulted in an increase in mean hematocrit versus placebo (testosterone gel 3.0%, 95% CI 1.8–4.3; oral TU 4.3%, 0.7–8.0; testosterone patch 1.4%, 95% CI 0.2–2.6; IM TE/C 4.0%, 95% CI 2.9–5.1; and IM TU 1.6%, 95% CI 0.3–3.0). When the different routes of TRT modalities were compared with each other, only IM TE/C had a statistically greater increase in hemoglobin compared with the patch (no *P*-value provided). This meta-analysis did not assess whether the formulations ultimately led to polycythemia (defined as Hct >51% in males), so it remains unclear if these results were clinically significant.

An RCT published after the network meta-analysis above evaluated the hematocrit change between intranasal testosterone gel compared with intramuscular testosterone in 54 men with testosterone deficiency.<sup>2</sup> Patients were 18 to 75 years old with a diagnosis of testosterone deficiency (testosterone level <350 ng/dL) and no history of testosterone replacement therapy or a four-month washout period if previously using testosterone replacement treatments. The primary outcome was change in hematocrit level at baseline and after four months of therapy. Patients were randomized to receive intranasal testosterone gel 4.5%, 5.5 mg per nostril three times daily, or testosterone cypionate IM 200 mg every two weeks. Men who received intramuscular injections had a significant increase in mean hematocrit from 42.7% to 46.6% (*P*<.0001), but no significant change was noted in mean hematocrit in men who received intranasal gel (44.4% to 43.8; *P*<.23). Polycythemia (defined as hematocrit >52%) was found in 0% (0/23) of men treated with intranasal testosterone gel and in 9.7% (3/31) of men treated with intramuscular testosterone.

A cross-sectional analysis examined episodes of polycythemia among 60 men 18 to 45 years old who were being treated for testosterone deficiency with intranasal testosterone gel or intramuscular testosterone over at least three months period.<sup>3</sup> Patients were diagnosed with testosterone deficiency (testosterone level <300 ng/dL) and were using intranasal testosterone gel 4.5%, 5.5 mg per nostril three times daily, or testosterone cypionate IM 100 to 200 mg weekly. Intramuscular testosterone increased hematocrit levels more than intranasal testosterone (mean difference 3.2%; 95% CI, 0.74% to 5.7%). Polycythemia (defined as hematocrit ≥54%) was measured in 10% (3/30) of men who received intramuscular testosterone. In addition, in men treated with intramuscular testosterone, 33% (10/30) had a hematocrit ≥50% after four months of TRT. None of the men who received intranasal testosterone had a hematocrit ≥50% during therapy. This study was limited by a small size.

**EBP**
**Alyssa Hill, MD**
**Cristina Rabaza, MD**
*University of Colorado Family Medicine Residency,  
Denver, CO*

The Corresponding Faculty Author on the manuscript is: Cristina Rabaza; CRISTINA.RABAZA@CUANSCHUTZ.EDU  
The authors declare no conflicts of interest.

## References

1. Nackeeran S, Kohn T, Gonzalez D, White J, Ory J, Ramasamy R. The effect of route of testosterone on changes in hematocrit: a systematic review and Bayesian network meta-analysis of randomized trials. *J Urol*. 2022; 207(1): 44–51. [STEP 1]
2. Rivero MJ, Ory J, Diaz P, et al. Comparison of hematocrit change in testosterone-deficient men treated with intranasal testosterone gel vs intramuscular testosterone cypionate: a randomized clinical trial. *J Urol*. 2023; 210(1):162–170. [STEP 2]
3. Best JC, Gonzalez D, Masterson TA, Blachman-Braun R, Pai R, Ramasamy R. A cross-sectional comparison of secondary polycythemia in testosterone-deficient men treated with nasal testosterone gel vs. intramuscular testosterone cypionate. *Can Urol Assoc J*. 2021; 15(2): E118–E122. [STEP 4]

## Does decreased sugar consumption improve LDL levels in adults with hyperlipidemia?

### EVIDENCE-BASED ANSWER

In healthy adults, with or without hyperlipidemia, high added sugar consumption does not affect LDL concentrations (SOR: **C**, systematic review of RCTs with disease-oriented outcomes). Diets with very high fructose content (>100 g/day) may increase LDL by 12 mg/dL (SOR: **C**, subgroup analysis of a meta-analysis of RCTs with disease-oriented outcomes). Increased consumption of sugar-sweetened beverages does not increase LDL concentration, but may decrease LDL particle size (SOR: **C**, RCT with disease-oriented outcome).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002094

This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2022 systematic review and meta-analysis (21 RCTs; N=1,100) examined the effect of added sugar consumption on risk factors for cardiovascular disease.<sup>1</sup> Trials included healthy adults, with or without hyperlipidemia, without existing metabolic comorbidities such as diabetes or cardiovascular disease. Mean baseline LDL concentration was 112 mg/dL. The intervention was either high or low added sugar consumption, including any type of added sugar (ie, sucrose, fructose, or glucose). Researchers did not consider high or low intrinsic sugar diets, such as those from fruits. The comparison group was either placebo or usual diet. Outcomes included change in LDL cholesterol from baseline to at least four weeks of follow-up (mean follow-up 12 weeks). A high compared with low added sugar diet was not associated with a significant difference in LDL concentration (12 RCTs, N=712; mean difference [MD] 0.39 mg/dL; 95% CI, -3.1 to 3.9 mg/dL). The study included patients with and without

hyperlipidemia without subgroup analysis. The researchers excluded patients with comorbid metabolic conditions affecting generalizability, and most studies were deemed at high risk for bias because of blinding and attrition concerns.

A 2013 systematic review and meta-analysis (24 RCTs; N=474) investigated whether high fructose intake altered cholesterol levels.<sup>2</sup> Researchers included adults with or without hyperlipidemia or diabetes. Mean baseline LDL concentrations ranged from 91 to 157 mg/dL. The intervention was consuming oral free fructose (of various amounts) for at least two weeks, compared with consuming a diet similar in composition (calories and percentage of fats, protein, and carbohydrates) with starch, glucose, or sucrose in place of free fructose. Studied outcomes included change in LDL concentration from baseline to study end (ranging from 2-28 weeks). A subgroup analysis was performed based on quantity of daily fructose intake. Compared with a similar diet with a different carbohydrate, consuming a diet with free fructose was not statistically associated with an increase in LDL (19 RCTs, N=300; MD 3.8 mg/dL, 95% CI, -1.1 to 8.6 mg/dL). On subgroup analysis, however, patients consuming very high amounts of fructose (>100 g/day) had an increase in LDL of 12 mg/dL (95% CI, 4.4–19 mg/dL). Many of the included studies had small sample sizes and short follow-up periods. Researchers did not track patient-oriented outcomes.

A 2011 randomized controlled crossover trial (n=29) investigated the effect of sugar-sweetened beverage (SSB) consumption on multiple cardiac and metabolic parameters.<sup>3</sup> This trial was not included in the above meta-analyses. Researchers included normal weight adult male patients (20–50 years old) living in Zurich, Switzerland. All patients received the same six interventions, each lasting three weeks, in randomized order. During five of the intervention periods, patients were supplied three identical-appearing containers to drink at each major meal, containing a specific type and concentration of SSB: 40 g/day fructose, 80 g/day fructose, 40 g/day glucose, 80 g/day glucose, and 80 g/day sucrose. These concentrations are similar to commercially available beverages. Patients and researchers were blinded as to the specific SSB assigned during each intervention. During the sixth intervention period researchers counseled patients to consume a diet low in free fructose. After each intervention, a number of examination and laboratory

measurements pertaining to cardiometabolic risk were obtained, including LDL concentration and particle size. None of the interventions had an effect on LDL concentration, however, patients receiving SSBs high in fructose and sucrose (both 80 g/day) had significant decreases in LDL particle size (fructose:  $-0.51$  nm; 95% CI,  $-0.19$  to  $-0.82$  nm; sucrose:  $-0.43$  nm; 95% CI,  $-0.12$  to  $-0.74$  nm). Researchers noted that decreased LDL particle size at similar LDL concentration may confer an increased risk for atherosclerosis. **EBP**

**Xenia B. Gonzalez, MD**  
**Joel E. Herness, MD**

*David Grant Medical Center Family Medicine Residency Program, Travis AFB, CA*

The corresponding author is Joel E. Herness, MD; joelherness@gmail.com

The authors declare no conflicts of interest.

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force or the Department of Defense.

## References

1. Bergwall S, Johansson A, Sonestedt E, Acosta S. High versus low-added sugar consumption for the primary prevention of cardiovascular disease. *Cochrane Database Syst Rev.* 2022;1(1):CD013320. [STEP 1]
2. Zhang YH, An T, Zhang RC, Zhou Q, Huang Y, Zhang J. Very high fructose intake increases serum LDL-cholesterol and total cholesterol: a meta-analysis of controlled feeding trials. *J Nutr.* 2013;143(9):1391-1398. [STEP 1]
3. Aeberli I, Gerber PA, Hochuli M, et al. Low to moderate sugar-sweetened beverage consumption impairs glucose and lipid metabolism and promotes inflammation in healthy young men: a randomized controlled trial. *Am J Clin Nutr.* 2011;94(2):479-485. [STEP 2]

# Should direct oral anticoagulants (DOACs) be held before dental procedures?

## EVIDENCE-BASED ANSWER

Direct oral anticoagulants (DOAC) therapy is usually safe during most low-risk dental procedures and has a comparable rate of postoperative bleeding to warfarin (SOR: **A**, systematic review of randomized controlled trials). Holding DOAC therapy for 24 hours or more before high-risk dental procedures including osteotomy or bone grafting yields outcomes in line with brief holding of antiplatelet therapy (SOR: **B**, prospective cohort study). Patients may continue DOAC therapy for most dental procedures with low risk of bleeding complications, and an individualized approach that prioritizes brief interruption for higher risk procedures is recommended (SOR: **C**, consensus guideline).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
 DOI 10.1097/EBP.0000000000002085

This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2017 systematic review encompassing 11 heterogeneous studies (N=4,833) evaluated the bleeding and thromboembolic rates associated with direct oral anticoagulants (DOAC) therapy in patients undergoing dental procedures.<sup>1</sup> Included studies, identified using the PRISMA model, comprised a variety of study types and assessed bleeding risk with adults using DOACs undergoing dental procedures. Multiple DOACs and a variety of dental procedures (extractions, implants, and bone grafting) were used among the studies. One randomized controlled trial (RCT) in 2012 (n=459) compared the bleeding risk in patients undergoing dental procedures treated with dabigatran compared with warfarin. Dabigatran and warfarin were held a mean of 49 hours and 114 hours, respectively, before the procedure. The study found no difference in periprocedural bleeding, postsurgical bleeding, or thrombotic events (dabigatran 110 mg 1.9%, dabigatran 150 mg 3.2%, warfarin 4.8%; no *P*-value reported). Another 2014 RCT (n=1,435) similarly examined the bleeding risk in patients undergoing dental procedures with apixaban or warfarin. Likewise, they found that similar rates of major bleeding events and thromboembolism took place in both groups at 30 days follow-up (incidence or *P*-values not reported in this systematic review). Overall, the review authors concluded that

discontinuing DOACs for 12 to 48 hours before procedures was not associated with increased thrombotic events. Likewise, continuing DOACs was not associated with clinically increased bleeding risk with the use of conventional hemostatic interventions. Limitations of this systematic review included a low number of assessed RCTs, heterogeneity hindering ability to assess pooled data, and omission of detailed, cited data from reviewed studies.

A 2021 two-year monocentric prospective cohort study of elderly adult patients (n=195) evaluated postoperative bleeding rates of standardized dental surgeries in patients with uninterrupted dosing of anticoagulants (AT; n=44) or antiplatelet therapy (APT; n=51) compared with control subjects.<sup>2</sup> Anticoagulant subgroups included DOACs (n=27) and vitamin K antagonists (VK; n=17). The mean age of anticoagulated patients was 73 years old compared with 62 years old in the control group, with a 2:1 ratio of men to women in the AT group. Patients with a history of hemorrhagic diatheses, liver cirrhosis, thrombocytopenia, and INR greater than 3.5 were excluded. Patients were reevaluated 10 days post-procedure for wound examination. Primary outcomes measured the frequency and classification of postoperative bleeding as reported by the patient. Secondary outcomes evaluated differences in bleeding severity and rates between low-risk (single tooth extraction), medium-risk (serial tooth extraction of  $\leq 3$  teeth per quadrant), and high-risk (serial tooth extraction  $> 3$  teeth per quadrant, osteotomies, or implant placement) surgeries. Postoperative bleeding occurred more frequently in those in the AT group compared with the control group (26% [25/95] vs 2% [2/100],  $P=.00$ ). Subgroup analysis revealed that patients on DOACs bled more postoperatively than control subjects (30% [8/27] vs 2% [2/100],  $P=.00$ ). Bleeding rates on DOACs (30%) were similar to bleeding rates in the APT group (31%) but more than those in the VK group (6%, no  $P$ -values reported). In total, most cases of bleeding in the treatment groups were classified as mild and lasted less than three days (93%). In the DOAC subgroup, only one case of severe bleeding occurred in a patient treated with a combination of apixaban and clopidogrel. In the AT group, bleeding was more common in high-risk procedures (low-risk: 18%; medium-risk 13%; high-risk 48%;  $P=.013$ ). The authors concluded it was reasonable to continue DOAC therapy for low-risk dental procedures and to hold DOAC therapy

for 24 hours or more before high-risk dental procedures. Limitations included the subjective reporting of bleeding by patients and the variation of surgical invasiveness among multiple surgeons.

According to the 2022 Scottish Dental Clinical Effectiveness Programme (SDCEP) guidelines, DOACs should not be interrupted for dental procedures with low risk of bleeding complications.<sup>3</sup> Guideline authors noted that this advice was based on low certainty evidence with no specific study reference made in the guideline. They stated that a single dose of DOAC should be skipped (apixaban and dabigatran) or delayed (rivaroxaban and edoxaban) for dental procedures with higher risk of bleeding complications. This recommendation was derived from a 2019 low-quality, meta-analysis (no RCTs) that included six studies directly comparing patients continuing or holding DOACs.

EBP

**Dillon Cleary, MD**

**Jami Reece, MD**

*Nellis AFB Family Medicine Residency Program, Las Vegas, NV*

The corresponding author is Dillon Cleary; dillon.m.cleary.mil@health.mil.

The authors declare no conflicts of interest.

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the U.S. Air Force Medical Department, the Air Force at large, or the Department of Defense.

## References

1. Lanau N, Mareque J, Giner L, Zabalza M. Direct oral anticoagulants and its implications in dentistry. A review of literature. *J Clin Exp Dent*. 2017;9(11):e1346-e1354. [STEP 2]
2. Buchbender M, Schlee N, Kesting MR, Grimm J, Fehlhofer J, Rau A. A prospective comparative study to assess the risk of postoperative bleeding after dental surgery while on medication with direct oral anticoagulants, antiplatelet agents, or vitamin K antagonists. *BMC Oral Health*. 2021;21(1):504. [STEP 3]
3. *Management of Dental Patients Taking Anticoagulants or Antiplatelet Drugs: Dental Clinical Guidance. Scottish Dental Clinical Effectiveness Programme, 2022*. Accessed March 4, 2023. <https://www.sdcep.org.uk/media/ypnl2cpz/sdcep-management-of-dental-patients-taking-anticoagulants-or-antiplatelet-drugs-2nd-edition.pdf>. [STEP 5]

## In patients with obstructive sleep apnea (OSA) and nasal obstruction does nasal surgery improve continuous positive airway pressure (CPAP) compliance?

### EVIDENCE-BASED ANSWER

In patients with obstructive sleep apnea (OSA) intolerant of continuous airway pressure (CPAP) because of nasal obstruction, nasal surgery may improve CPAP compliance by approximately 90% and increase nightly CPAP use by approximately 2.5 hours (SOR: **B**, systematic review and meta-analysis with low-quality evidence). Self-reported CPAP intolerance may resolve after nasal surgery in most patients, who also experience moderate improvements in fatigue levels after surgery (SOR: **C**, case series).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002084

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2015 systematic review and meta-analysis of 18 studies (N=279) evaluated the effect of nasal surgery on CPAP compliance and pressures.<sup>1</sup> Mean patient age was 53 years old with a BMI of 30 kg/m<sup>2</sup>. Patients in each study had OSA treated with CPAP before and after isolated nasal surgery. Studies included quantitative outcomes data comparing prenasal and postnasal surgery therapeutic CPAP pressures or CPAP compliance/adherence. Studies without any objective data that included nonnasal surgeries or involved children were excluded. No limitation on follow-up length or languages of the studies was noted. All studies were retrospective or prospective case series except for one randomized controlled trial (RCT). Follow-up ranged from 1 to 21 months and sample size ranged from 7 to 39. The kind of nasal surgery varied between and often within studies and predominately included septoplasty, turbinoplasty, rhinoplasty, or combination procedures. CPAP mask types were not

uniform (nasal vs full). Eleven studies (n=153) described CPAP compliance before and after surgery. Overall, CPAP compliance improved from 39% to 90% in all patients. A subgroup analysis found that 89% of patients not using CPAP before nasal surgery tolerated CPAP after nasal surgery. Only three of the studies (N=40) measured home CPAP use objectively by downloaded CPAP data. In this subgroup, CPAP compliance improved from 43% to 100% after surgery, with all patients not tolerating CPAP before surgery (n=23) becoming compliant after. The available CPAP device data from these studies (N=33) revealed an improvement in hours of CPAP use from 3.0 to 5.5 hours postoperatively (no CI or *P* values reported). The single RCT (n=17) found no difference in duration of CPAP use after surgery but was unique among the included studies in that all patients were already compliant with CPAP use before surgery. Limitations of this review included large heterogeneity, few RCTs, and limited objective CPAP compliance data. In addition, two of the studies with objective CPAP compliance data collected measurements only one month after surgery, which may still be considered the acute postoperative period.

A 2022 prospective case series (n=49) evaluated the effect of surgical correction in patients with nasal obstruction and OSA intolerant to CPAP. Patients (mean age 52 years old) with OSA and inability to tolerate CPAP for at least four hours per night on 70% of nights secondary to nasal obstruction were selected for nasal correction surgery.<sup>2</sup> All patients had an apnea hypopnea index (AHI) greater than 30 and had failed medical correction of nasal obstruction. Investigators excluded patients intolerant of CPAP for reasons other than nasal obstruction, such as skin irritation, pressure sores, noise intolerance, or aerophagia. OSA control was assessed preoperatively and again three to six months postoperatively; nasal obstruction symptoms were assessed by the Nasal Obstruction Symptom Evaluation (NOSE), a 5-item questionnaire with increasing scores (range 0–100) indicative of worsening obstructive symptoms. The Epworth Sleepiness Scale (ESS), an 8-item questionnaire with increasing scores (range 0–24) indicative of worsening fatigue, was also administered. The minimal cross-sectional areas (MCA) of the nasal passages were measured by acoustic rhinometry, and AHI and CPAP metrics were measured by standard polysomnography. All patients had turbinate hypertrophy or turbinate hypertrophy with deviated septum. They were treated with septoplasty with radiofrequency turbinate reduction (n=16), powered turbinoplasty (n=13), and radiofrequency turbinate reduction (n=20). Three to six months after surgery, 100% of patients reported tolerance of CPAP ( $\geq 4$  hours/night

on  $\geq 70\%$  of nights), although the authors did not report how this was measured, and no objective home compliance data were collected. NOSE scores (66–34,  $P < .001$ ) and ESS (10–5,  $P < .001$ ) both improved. Required CPAP pressures decreased (10.5–7.5 cm H<sub>2</sub>O,  $P < .01$ ). Total sleep time on polysomnography increased 41 minutes ( $P < .001$ ). No improvement in AHI scores was noted. Patient CPAP compliance estimates was not corroborated with subjective or objective CPAP data. Additional limitations included a single-site, case series study design, wide follow-up window of three to six months, and predominance of disease-oriented evidence. **EBP**

**Brock Cardon, MD**  
**Samuel Burton, MD**

*Nellis Family Medicine Residency, Nellis Air Force Base, NV*

The corresponding author is Brock Cardon; Brock.e.cardon.mil@health.mil.

The authors declare no conflict of interest.

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the U.S. Air Force Medical Department, the U.S. Air Force at large, or the Department of Defense.

## References

1. Camacho M, Riaz M, Capasso R, et al. The effect of nasal surgery on continuous positive airway pressure device use and therapeutic treatment pressures: a systematic review and meta-analysis. *Sleep*. 2015;38(2):279-286. [STEP 2]
2. Elwany S, Bahgat AY, Ibrahim M, Bazak R. Surgical correction of nasal obstruction in obstructive sleep apnea improves CPAP outcomes and compliance. *Ir J Med Sci*. 2022;191(6):2723-2728. [STEP 4]

# Does intermittent fasting improve markers of glucose tolerance more than caloric restriction diets or usual care in patients at risk for type 2 diabetes mellitus?

## EVIDENCE-BASED ANSWER

Intermittent fasting (IF) is similarly effective for improving some markers of glucose tolerance (fasting glucose, HbA1c, or insulin levels) when compared with calorie restriction (CR; SOR: **C**, disease-oriented evidence from systematic review of randomized controlled trials [RCTs]). However, IF is superior to CR for improving postprandial glucose levels (SOR: **C**, disease-oriented evidence from single RCT). Conflicting evidence of the superiority of IF compared with dietary education alone in reducing fasting blood glucose levels is present (SOR: **C**, conflicting RCTs).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002106

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

In 2022, a systemic review of 13 randomized controlled trials (RCTs; N=940) compared the effects of intermittent fasting (IF) diets to daily caloric restriction (CR) diets on metabolic risk factors for noncommunicable diseases such as diabetes.<sup>1</sup> Researchers included RCTs comparing IF and CR diets of the same energy content (isocaloric) of at least eight weeks of duration in adults who were overweight or obese (body mass index  $> 25$  kg/m<sup>2</sup>). Of the 13 RCTs, three trials compared changes in glucose, HbA1c, or insulin levels between IF and CR over a sufficiently long duration of one year in patients without diabetes at baseline. These trials defined IF as normal eating for five days and fasting for two, and CR as a percent decrease in daily caloric intake. Results could not be pooled because of heterogeneity in outcomes measures. The three trials showed similar improvements in glucose, HbA1c, and insulin levels in both groups. The systematic review did not report numerical results.

In 2023, an RCT (n=209) compared IF, CR, and standard care for improving glucose metabolism in adult patients at risk for developing type 2 diabetes mellitus.<sup>2</sup> Patients had a stable weight for six months, an HbA1c less than 6.5%, and a score of 12 or more on the Australian Type 2 Diabetes Risk Assessment Tool, which uses demographic information, past medical history, and waist circumference to estimate the risk for developing diabetes. A score of 12 denotes at least a 1-in-14 chance of developing diabetes. Participants were randomized to IF (defined as consuming 30% of daily energy requirements between 08:00 and 12:00 hours on 3 nonconsecutive days per week, and ad libitum

eating on other days), CR (defined as consuming 70% of daily energy requirements every day with no timing restrictions), or standard care (weight loss education alone) for six months; each group followed a maintenance diet for another 12 months. The primary outcome was glucose tolerance at six months measured as change from baseline to six months in the area under the curve (AUC) of glucose readings plotted from 0 to 180 minutes after a standardized carbohydrate drink. Glucose tolerance improved to a greater extent with IF versus with CR (change in AUC  $-10$  vs  $-3.6$ ;  $P < .03$ ) at month six; no differences were appreciated by 18 months, and comparison was not made between IF and standard care. No difference was noted in changes in fasting glucose, HbA1c, or insulin levels between IF, CR, or standard care at six or 18 months. Limitations include using a 2:2:1 randomization in which the control group had proportionally fewer participants, decreasing the ability to detect differences between groups. Inherent heterogeneity is also present among individuals regarding diet and food choices.

In 2022, an RCT ( $n=101$ ) examined the effectiveness of IF on cardiometabolic risk reduction.<sup>3</sup> Participants were recruited from a weight management clinic in China and were overweight or obese ( $BMI \geq 23$  kg/m<sup>2</sup>) adults with an average age of 35 years old and with prediabetes defined as having a fasting glucose level of 100 to 125 mg/dL. All participants received dietary education by a dietician and then were assigned to three weeks of IF (alternating days of 600 kcal intake with days of usual caloric intake), time-restricted eating (only eating during an 8-hour window each day), or dietary education only. The primary outcome was change in body weight, and fasting blood glucose level was a secondary outcome. Compared with the dietary education-only group, the IF and time-restricted eating groups showed improvement in fasting blood glucose levels at three months ( $P < .05$  for both comparisons), but actual numerical results were not reported, which precludes determination of the magnitude of effect. No difference was noted in fasting blood glucose between the two intervention groups. No side effects were reported. The study did not account for changes in physical activity. Limitations also exist in controlling for heterogeneity in diet. **EBP**

**Adam Sommers, DO**  
**Eric Christensen, MD**

*University of Minnesota/CentraCare St. Cloud Family  
Medicine Residency, St. Cloud, MN*

The corresponding author is Eric Christensen; ericd.christensen@centracare.com.  
The authors declare no conflicts of interest.

## References

1. Ezzati A, Rosenkranz SK, Phelan J, Logan C. The effects of isocaloric intermittent fasting vs daily caloric restriction on weight loss and metabolic risk factors for noncommunicable chronic diseases: a systematic review of randomized controlled or comparative trials. *J Acad Nutr Diet.* 2023;123(2):318-329.e1. [STEP 1].
2. Teong XT, Liu K, Vincent AD, et al. Intermittent fasting plus early time-restricted eating versus calorie restriction and standard care in adults at risk of type 2 diabetes: a randomized controlled trial. *Nat Med.* 2023;29(4):963-972. [STEP 2].
3. Chair SY, Cai H, Cao X, Qin Y, Cheng HY, Ng MT. Intermittent fasting in weight loss and cardiometabolic risk reduction: a randomized controlled trial. *J Nurs Res.* 2022;30(1):e185. [STEP 2].

# Is a restrictive strategy noninferior to a liberal strategy of blood transfusion in adults with acute myocardial infarction and anemia?

## EVIDENCED-BASED ANSWER

Transfusing for a Hgb  $< 8$  g/dL (called restrictive blood transfusion or RBT) does not increase all-cause mortality, recurrence of myocardial infarction (MI), need for revascularization, or heart failure exacerbations in patients with acute MI and anemia compared with transfusion for Hgb  $< 10$  g/dL (called liberal blood transfusion or LBT). (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). American Society of Hematology (ASH) guidelines recommend adhering to a restrictive transfusion strategy with a threshold of Hgb  $< 8$  g/dL in patients with preexisting cardiovascular disease (SOR: **C**, expert opinion).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002080

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2021, systematic review and meta-analysis of three RCTs (N=821 with 421 patients receiving RBT and 400 patients receiving LBT) compared outcomes of RBT versus LBT in hospitalized adults with acute MI.<sup>1</sup> The systemic review included RCTs involving patients with MI with a primary outcome of 30-day composite of all-cause mortality and the secondary outcomes including recurrent MI, revascularization, and heart failure exacerbation. In the three RCTs studied, patients were randomly assigned to LBT or RBT. One study defined LBT as hematocrit (Hct)<30% with goal to maintain between 30% and 33% and RBT with Hct<24% with goal to maintain between 24% and 27%. If Hct was >5% below targets, 2U packed red blood cells were given before reassessment. In the other two studies, LBT was defined as Hgb≤10 g/dL and RBT with Hgb≤8 g/dL. Statistical analysis was performed by calculating the pooled relative risk (RR) and 95% confidence intervals (CI) using a random effects model. Heterogeneity was assessed with  $I^2$  statistics with an  $I^2$ >50% indicating high heterogeneity. RBT did not demonstrate significant difference compared with LBT in all-cause mortality (RR=1.61, 95% CI=0.38–6.96,  $I^2$ =59%), recurrent MI (RR=0.98, 95% CI=0.48–1.96,  $I^2$ =0%), revascularization (RR=1.18, 95% CI=0.26–5.44,  $I^2$ =23%), and heart failure exacerbation (RR=0.86, 95% CI= 0.23–3.22,  $I^2$ =71%). There were several limitations of the study. Outcomes for all-cause mortality and heart failure exacerbation had high heterogeneity, the studies had problems with blinding, and the small number of RCTs may have reduced validity.

The 2013 American Society of Hematology published practice guidelines discussing the transfusion of red blood cells.<sup>2</sup> The guidelines recommended adhering to a restrictive transfusion strategy, with a threshold of Hgb<8 g/dL, in patients with preexisting cardiovascular disease. The ASH reported that as a weak recommendation based on moderate-quality evidence. Guidelines were based on committee consensus after review of available data.

EBP

**Nicole Nelson, DO, FAAP**  
**Timera Brown, MD**  
**Annie Huang, DO**

*Dwight D. Eisenhower Army Medical Center, Family  
 Medicine Residency, Fort Eisenhower, GA*

The corresponding author is Nicole Nelson; Nicole.k.nelson5.civ@health.mil.

The authors declare no conflicts of interest.

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Army Medical Department, the Army at large, or the Department of Defense.

## References

1. Abdelazeem B, Malik B, Kandah E, et al. Restrictive versus liberal blood transfusion strategy in patients with acute myocardial infarction: a meta-analysis of randomized clinical trials. *J Commun Hosp Intern Med Perspect*. 2022;12(3): 40-47. [STEP 1]
2. Szczepiorkowski ZM, Dunbar NM. Transfusion guidelines: when to transfuse. *Hematol Am Soc Hematol Educ Program*. 2013;2013:638-644. [STEP 2]

# Do exercise regimens in patients with heart failure decrease risk of heart failure exacerbations or cardiovascular events?

## EVIDENCE-BASED ANSWER

Patients with heart failure who participate in exercise-based cardiac rehabilitation have decreased rates of hospitalization (SOR: **A**, meta-analyses of randomized controlled trials). Studies selected did not reliably report cardiovascular events; it could not be determined if exercise altered cardiovascular events.

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
 DOI 10.1097/EBP.0000000000002105

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2020 meta-analysis of 131 randomized controlled trials (RCTs; N=9,761) evaluated the effect of exercise-based rehabilitation and exercise programs on peak oxygen consumption (VO<sub>2</sub>Peak), quality of life (QOL), and hospitalizations of patients with heart failure (HF).<sup>1</sup> All patients had a New York Heart Association

Functional Classification (NYHA) of II or III with mean ages between 46 to 80 years old. Seventy-four percent of patients were male. The average duration of exercise was 50 min (range 10–120 min) and frequency was 3 times per week (range weekly to daily), with total exercise program participation of 12 to 18 weeks. Exercise modalities included aerobic, resistance, or combinations of exercise compared with controls (no exercise). The primary outcome of this study was the effect of exercise on all-cause hospitalizations,  $VO_2$ Peak, and quality of life. The patients belonging to the exercise group had 846 hospitalizations and the control group had 989 hospital admissions, indicating a reduction in hospitalized patients in the experimental group (26 trials,  $N=4,664$ ; odds ratio 0.56; 95% CI, 0.42–0.75;  $I^2=51\%$ ) with no variation in results with subgroup analysis of exercise type. Study limitations included a predominantly male population and the various methods of reporting of outcomes in the included trials.

A 2019 meta-analysis of 44 RCTs parallel group or crossover design groups ( $N=5,783$ ) investigated the effects of exercise-based cardiac rehabilitation on mortality, hospital admission, and health-related QOL in people with HF.<sup>2</sup> This meta-analysis included 20 overlapping trials with the first meta-analysis above. However, compared with the 2020 study, this meta-analysis included stratification of results by HF-related hospitalizations and total hospitalizations. All patients were above 18 years old with a mean ages in studies ranging from 51 to 81 years old. Seventy-nine percent were men. Thirty-seven trials had follow-up in less than 12 months, but all had follow-up for at least six months. Four trials included varied exercise arms of their study. The exercise therapy patient group was predominantly patients with HF with reduced ejection fraction with NYHA classes II and III receiving center-based, exercise-based cardiac rehabilitation programs. The programs included aerobic-only and aerobic plus resistance training exercise programs with a duration of at least six months and was compared with a control group of no exercise intervention with normal medical care. The primary outcome of this study was measured by the total number of hospitalizations and HF-related hospitalizations. Researchers

provided no data on deaths because of HF. Exercise-based cardiac rehabilitation reduced overall hospital admissions up to one year of follow-up (21 trials,  $N=2,182$ ; 17% vs 24%; relative risk [RR] 0.70; 95% CI 0.60–0.83;  $NNT=14$ ) and may have reduced HF-specific hospitalization, based on low-quality evidence (14 trials,  $N=1,114$ ; 7.1% vs 11%; RR 0.59; 95% CI, 0.42–0.84;  $NNT=25$ ).

EBP

**Chase LaRue, MEd, MS****Aaron P. Montgomery, MD***National Capital Consortium Family Medicine Residency, Fort Belvoir, VA*

The corresponding author is Aaron P. Montgomery; aaronp-montgomery@gmail.com

The authors declare no conflicts of interest.

The opinions and assertions contained herein are those of the authors and not to be construed as official or as reflecting the views of the U.S. Navy Medical Department, the Navy at large, the U.S. Army Medical Department, the Army at large, the Defense Health Agency, or the Department of Defense.

## References

1. Dallas K, Dinas PC, Chryssanthopoulos C, et al. The effects of exercise on  $VO_2$ peak, quality of life and hospitalization in heart failure patients: a systematic review with meta-analyses. *Eur J Sport Sci*. 2021; 21(9):1337–1350. [STEP 1]
2. Long L, Mordi IR, Bridges C, et al. Exercise-based cardiac rehabilitation for adults with heart failure. *Cochrane Database Syst Rev*. 2019; 1(1):CD003331. [STEP 1]

---

## In patients treated medically for opioid use disorder, is there a correlation between relapse rate and socioeconomic status?

**EVIDENCE-BASED ANSWER**

Unclear. No difference in retention with buprenorphine therapy is seen between those of high and low socioeconomic status (SES), although a greater proportion of low SES patients on buprenorphine may relapse (SOR: **C**, cross-sectional trial). However, the strongest predictors of relapse for patients on buprenorphine treatment appear largely, but not entirely, independent of SES (SOR: **C**, cross-sectional). Individuals who are recently homeless or incarcerated or unable to access income assistance seem more likely to discontinue methadone maintenance therapy (SOR: **C**, retrospective cohort).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002103

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A retrospective chart review and cross-sectional telephone interview study from 2010 (n=176) investigated the long-term outcomes of office-based treatment with buprenorphine maintenance therapy for opioid use disorder with emphasis on the impact of socioeconomic status (SES) over an 18-month period.<sup>1</sup> The study population was split into a high-SES group (full self-pay/private insurance) and a low-SES group (no insurance or indigent). Treatment consisted of a 23- to 48-hour inpatient admission for induction with buprenorphine–naloxone between 12 and 16 mg/day, five weeks of intensive outpatient therapy, and 12 weeks of weekly aftercare sessions. This was followed up by primary office-based treatment with monthly visits. Full adherence for each level of treatment was required where nonadherence or substance use resulted in referral to the next highest level of care. Of the inducted patients, 110 completed telephone interview follow-ups. Of these follow-up patients, 32% were female, 73% Caucasian, 52% of low SES, and 48% of high SES. At follow-up, 77% of these patients reported continuously remaining on buprenorphine. Relapse was measured by substance use of any kind during the duration of the study. Low-SES subjects were more likely to report still being on buprenorphine at the time of follow-up (80.6% of low-SES patients compared with 72.9% of high-SES patients), although this was not statistically significant. More substance use at follow-up was noted in low-SES patients compared

with high-SES patients (14% vs 3%,  $P=.0123$ ). In the low-SES group, medications were publicly funded.

A cross-sectional study from 2012 (n=703) examined the effect of compliance with buprenorphine on reducing relapse among patients in treatment for opioid dependence.<sup>3</sup> Inclusion criteria included diagnosis of opioid dependence, six months of buprenorphine-naïve period before enrollment, lifetime buprenorphine compliance program naïve, and absence of organic brain disorder. The patient population was on average 34 years old, 41% female, 88% Caucasian, and 81% used opioids during the prior month (62% prescription opioids, 20% heroin, and 13% methadone). Compliance was defined as taking buprenorphine for at least 22 of the prior 28 days, and relapse was classified as use of opioids during follow-up period (months 2 and 3). Of patients in the primary analysis, 20% reported opioid relapse. Noncompliant patients were over 10 times more likely to relapse compared with compliant counterparts (exp  $\beta=10.55$ ;  $P<.001$ ). The strongest predictors for noncompliance included comorbid psychiatric or substance use disorders, which are mostly independent of SES. Demographic indicators including years of education and employment were not predictive of relapses. However, patients who did relapse were more likely to be Medicare/Medicaid beneficiaries (24% vs 13%;  $P<.05$ ). A significant limitation in the study was that the results were based on self-report data, which is prone to significant bias.

A retrospective cohort study from 2018 (n=1,301) examined the sociodemographic characteristics and social–structural exposures associated with methadone maintenance therapy (MMT) discontinuation in a population with opioid use disorder in Vancouver.<sup>2</sup> Patients were HIV-positive and -negative adults at least 18 years old who used illicit drugs at least once in the month before the study. The main endpoint was self-reported MMT discontinuation. Sociodemographic variables included ethnicity, stable relationship status, education, and HIV status. Social–structural risk factors included recent incarceration, homelessness, and not accessing government income assistance. Of the 1,301 patients who accessed MMT in the study, 288 (21%) discontinued at least once during the study period. Factors associated with MMT discontinuation included homelessness (adjusted odds ratio [aOR] 1.5; 95% CI, 1.1–2.1), recent incarceration (aOR 1.5; 95% CI, 1.01–2.1), and not being on any form of income assistance (aOR 2.1; 95% CI, 1.3–3.5). A key limitation was relying on discontinuation events that were self-reported, increasing possible recall bias. EBP

**Jeffrey Daniels, MD**

**Elizabeth Lownik, MD, MPH**

*Baraboo Family Medicine Rural Residency, University of Wisconsin, Madison, WI*

The corresponding author is Elizabeth Lownik; beth.lownik@gmail.com

The authors declare no conflicts of interest.

### References

1. Parran TV, Adelman CA, Merkin B, et al. Long-term outcomes of office-based buprenorphine/naloxone maintenance therapy. *Drug Alcohol Depend.* 2010; 106(1):56–60. [STEP 3]
2. Tkacz J, Severt J, Cacciola J, Ruetsch C. Compliance with buprenorphine medication-assisted treatment and relapse to opioid use. *Am J Addict.* 2012; 21(1):55–62. [STEP 2]
3. Lo A, Kerr T, Hayashi K, et al. Factors associated with methadone maintenance therapy discontinuation among people who inject drugs. *J Subst Abuse Treat.* 2018; 94:41–46. [STEP 2]

## Are systemic steroids effective for treatment of acute low back pain in adults?

### EVIDENCE-BASED ANSWER

In patients with acute radicular low back pain, systemic corticosteroids slightly reduce pain scores in the immediate term and improve function in the short and long term with a number needed to treat of five. There is no benefit in nonradicular low back pain (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). In patients with severe radicular pain and lumbar disk herniation on MRI, systemic steroids may improve function by 7% at one year (SOR: **B**, single RCT). The American College of Physicians (ACP) recommends against systemic steroids in the treatment of low back pain (SOR: **C**, consensus guideline).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002069

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2022 systematic review and meta-analysis (13 randomized controlled trials [RCTs], N=1,047) evaluated the effectiveness of systemic steroid treatment for low back pain in adults.<sup>1</sup> Trials included adult patients (mean ages 36–58 years old) with low back pain of varying chronicity, with some trials looking specifically at patients with spinal stenosis. Review authors excluded trials with serious spinal pathology, studies focusing on pregnant patients, and research on post-operative pain after spinal surgery. The studied intervention was treatment with oral or intramuscular corticosteroids. Regimens were various, with corticosteroids including prednisone, prednisolone, methylprednisolone, and dexamethasone, in doses ranging from 10 to 400 mg prednisone equivalent and treatment courses ranging from 1 to 21 days. Comparison groups received placebo or no treatment. Primary outcomes were various, including improvement in pain on a 10-point rating scale and proportion of patients with at least 30% improvement from baseline on validated functionality scales. Follow-up ranged from two weeks to 12 months. For radicular low back pain, systemic corticosteroids decreased pain in the short-term (2 weeks–3 months) by 5.6% when compared with placebo (5 trials, N=430; mean difference (MD) –0.56, 95% CI –1.08 to –0.04). Systemic steroids improved function in the short term with an number needed to treat (NNT) for 30% improvement of five (3 trials, N=403; risk ratio [RR] 1.52, 95% CI 1.22–1.91), as well as longer-term (12 months) with an NNT for 30% improvement of seven (1 trial, n=267; RR 1.29, 95% CI 1.06–1.56). In patients with nonradicular low back pain and spinal stenosis, systemic steroids had no significant effect on pain or function. Limitations included heterogeneity among studies in dosing and formulation of steroids and follow-up period. Positive findings should also be interpreted with caution given the large number of outcomes and follow-up periods assessed with only a few significant results.

A 2015 double-blinded RCT (n=269) specifically investigated the use of systemic steroids for acute radicular low back pain.<sup>2</sup> This study was included in the Cochrane review above but is discussed here to more specifically describe a potential treatment course. Researchers included adults (18–70 years old) with severe acute radiculopathy (based on Oswestry Disability Index [ODI] score of ≥30) for less than three months with an MRI-confirmed herniated lumbar disc. The intervention was a 15-day oral prednisone taper (60 mg daily for 5 days, 40 mg daily for 5 days, 20 mg daily for 5 days). The comparison group received placebo. All patients were told to not take nonsteroidal anti-inflammatory drugs for three weeks after randomization. Outcomes included change from baseline in ODI score at three weeks and

one year after randomization. Patients treated with prednisone had greater improvement in ODI (range 0–100) at three weeks (MD 6.4; 95% CI, 1.1–10) and 52 weeks (MD 7.4; 95% CI, 2.6–13) compared with placebo. Limitations included only partially successful blinding reported by the study, apparently due to steroid adverse effects, and limited generalizability given inclusion of only those with severe symptoms and positive MRI findings.

A 2017 consensus practice guideline from the ACP recommended against systemic corticosteroids for the treatment of acute low back pain, based on low-quality evidence showing inefficacy for acute or subacute low back pain.<sup>3</sup> The guideline also noted the potential harms associated with systemic steroid treatment countering any potential modest benefit.

EBP

Jennifer Dalrymple, DO

Mawj Al Ani, MD

Tasnim Hussein, MD

Hailon Wong, MD

FSU College of Medicine Family Medicine Residency Program at Lee Health, Fort Myers, FL

The corresponding author is Jennifer Dalrymple; Jennifer.Dalrymple@leehealth.org.

The authors declare no conflicts of interest.

## References

1. Chou R, Pinto RZ, Fu R, et al. Systemic corticosteroids for radicular and non-radicular low back pain. *Cochrane Database Syst Rev.* 2022;10(10):CD012450. [STEP 1]
2. Goldberg H, Firtch W, Tyburski M, et al. Oral steroids for acute radiculopathy due to a herniated lumbar disk: a randomized clinical trial. *JAMA.* 2015;313(19):1915-1923. [STEP 2]
3. Qaseem A, Wilt TJ, McLean RM, et al. Noninvasive treatments for acute, subacute, and chronic low back pain: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2017;166(7):514-530. [STEP 5]

# Do adverse childhood events (ACEs) increase the incidence of eating disorders in adults?

## EVIDENCE-BASED ANSWER

ACEs are associated with an increased incidence of eating disorders in adults (SOR: **B**, cohort retrospective studies). Adults seeking treatment for eating disorders have significantly higher ACE scores (SOR: **B**, cross-sectional study).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002111

This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2016 retrospective cohort study with 192 exclusively female subjects explored the correlation between ACEs subtypes and eating disorder clinical characteristics.<sup>1</sup> Subjects diagnosed with anorexia nervosa (AN), bulimia nervosa (BN), or binge eating disorder (BED) were recruited from a French outpatient eating disorder unit. Eating disorder severity was evaluated with the Eating Disorders Examination Questionnaire (EDE-Q), which measures disordered eating within four core dimensions: eating concern, body shape concern, weight concern, and restraint. The Functioning Assessment Short Test (FAST) was used to measure daily function across six areas, with higher scores indicating more difficulty. The study assessed five ACEs categories—sexual abuse, physical abuse, physical neglect, emotional abuse, and emotional neglect—using the Childhood Trauma Questionnaire (CTQ). Scores ranged from 5 to 25, with higher scores indicating more exposure to ACEs. After adjustment for age, comorbid mental health conditions, substance use, and history of suicide attempts, only emotional abuse was associated with worse daily functioning (odds ratio [OR] 5.82; 95% CI, 2.07–16.4). Emotional abuse was also associated with higher restraint, eating concern, and shape concern (OR range 2.38–2.78). Sexual abuse was only associated with elevated higher eating concern (OR 2.67; 95% CI, 1.13–6.31). After adjusting for the same confounders mentioned above, a dose–response relationship for number of childhood traumas was noted for daily functioning impairment and restraint. The study’s limitations included an inability to analyze eating disorder subtype interactions because of a small sample size, lack of personality disorder assessments that are common among ACEs

and eating disorder patients, and reliance on self-reported ACE scales.

A retrospective cohort study (n=3,346) examined the associations between specific adverse childhood experiences (ACEs) and specific disordered eating behaviors and attitudes among middle-aged men and women.<sup>2</sup> Information was captured originally from generally healthy adults 18 to 30 years old of White or African-American ethnicity without chronic illness or disability who were then followed up several times over 30 years. Eating behaviors were assessed by Questionnaire on Eating and Weight Patterns-Revised (QEWP-R) at year 10, and ACEs were assessed by Risky Family Questionnaire at year 15. The study showed a greater risk of disordered eating behaviors and attitudes among middle-aged adults with a history of ACEs than adults without a history of ACEs, although significance varied depending on sex, ACE type, and disordered eating type. The strongest associations were between women with a history of physical neglect and binge eating (relative risk [RR] 1.45; 95% CI, 1.05–2.00) and men with a history of emotional abuse and unhealthy weight control behaviors (RR 1.92; 95% CI, 1.44–2.56). Limitations of this study included the potential bias of self-reporting and the possibility of reverse causality between ACEs and disordered eating behaviors.

A cross-sectional study of 1,061 adult patients with a DSM5-diagnosed eating disorders examined demographic differences in ACE scores.<sup>3</sup> Subjects completed the Adverse Childhood Experiences Survey on admission for treatment at one of two private facilities providing inpatient, residential, or partial hospitalization levels of care between October 2018 and April 2020. The ACE Survey is a 10-item self-report measure assessing childhood trauma, including physical, emotional, or sexual abuse, emotional or physical neglect, having a mother or stepmother who is a victim of intimate partner violence, having divorced parents, having a family member diagnosed with a mental illness or who attempted suicide, having a family member in prison, and having a parent who struggles with alcoholism or drug use. For the purposes of this study, ACE Survey scores went up to eight points. Patients with eating disorders had significantly higher ACEs scores than the nationally representative sample (1.95 vs 1.57;  $P < .001$ ). Further analyses showed that individuals with eating disorders were more likely to

have experienced sexual abuse (OR 1.87; 95% CI, 1.61–2.18), household divorce (OR 1.46; 95% CI, 1.29–1.66), or have a family member who struggled with mental illness or who had attempted suicide (OR 3.70; 95% CI, 3.28–4.19). As a cross-sectional study, readers are unable to form conclusions about the temporal relationship between the exposure and outcome.

**EBP**

**Kristen Dimas, MD**  
**James O. Breen, MD**  
**April Burton, DO**  
**Stephanie Cruz, DO**  
**Mark Fam, DO**  
*FSU/Lee Health Family Medicine Residency Program,  
Fort Myers, FL*

The corresponding author is Kristen Dimas; [Kristen.dimas@leehealth.org](mailto:Kristen.dimas@leehealth.org).

The authors declare no conflicts of interest.

### References

1. Guillaume S, Jaussent I, Maimoun L, et al. Associations between adverse childhood experiences and clinical characteristics of eating disorders. *Sci Rep*. 2016;6:35761. [STEP 3].
2. Yoon CY, Mason SM, Loth K, Jacobs DR Jr. Adverse childhood experiences and disordered eating among middle-aged adults: findings from the coronary artery risk development in young adults study. *Prev Med*. 2022;162:107124. [STEP 3].
3. Rienecke RD, Johnson C, Le Grange D, et al. Adverse childhood experiences among adults with eating disorders: comparison to a nationally representative sample and identification of trauma. *J Eat Disord*. 2022;10(1):72. Erratum in: *J Eat Disord*. 2022;10(1):115. [STEP 2].

---

## Is vitamin D supplementation effective in improving patient-oriented outcomes in patients with PCOS?

**EVIDENCE-BASED ANSWER**

Vitamin D supplementation in women with polycystic ovarian syndrome (PCOS) does not affect body mass index (SOR: **A**, meta-analysis of randomized controlled trials [RCTs]). Among overweight, vitamin D-deficient women with PCOS, vitamin D supplementation may improve hirsutism scores by 14% and induce menstrual regularity in over 90% of patients (SOR: **C**, small RCT).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002057

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2020 meta-analysis (11 RCTs, N=483) evaluated the effects of vitamin D supplementation on patients with PCOS.<sup>1</sup> Patients included adult women diagnosed with PCOS based on Rotterdam diagnostic criteria, irrespective of prior vitamin D deficiency. Researchers excluded patients with significant comorbidities such as diabetes or Cushing's syndrome. The studied intervention was vitamin D supplementation, generally using 50,000 IU of oral cholecalciferol (vitamin D<sub>3</sub>) administered weekly for eight to 24 weeks. The comparison was placebo. The primary outcomes included change in body mass index (BMI) after treatment, among other biochemical and disease-process measures. Vitamin D supplementation was not associated with a significant change in BMI compared with placebo (5 RCTs, N=201; weighted mean difference [WMD] 0.0; 95% CI, -0.2 to 0.2). Limitations included heterogeneity in vitamin D dosing and treatment duration and the general use of disease-oriented outcomes.

A 2020 double-blinded RCT (n=60) investigated the effect of vitamin D supplementation on hirsutism scores and menstrual regularity.<sup>2</sup> The study population included adult women (18–49 years old) diagnosed with PCOS based on Rotterdam criteria, with BMI between 25 and 29.9 kg/m<sup>2</sup> and serum calcifediol [25(OH)D] levels less than 20 ng/mL. Researchers excluded patients who were pregnant, lactating, or with other comorbidities such as diabetes. The treatment group received 50,000 IU of vitamin D<sub>3</sub> per week for 12 weeks, while the control group received identical placebo capsules

weekly. The primary outcome was change in the Ferriman-Gallwey hirsutism score (scale of 0–36, higher values indicate increased hirsutism) after completing treatment. Secondary outcomes included menstrual regularity (defined as menses every 21–35 days). Patients treated with vitamin D<sub>3</sub> had a 14% reduction in hirsutism score compared with no difference in the placebo group (treatment mean difference [MD] 5.0, placebo MD 0.1; *P*=.01) Among those receiving vitamin D<sub>3</sub> supplementation, the percent of women with regular menstrual cycles improved from 10% to 93% while the placebo group remained unchanged at 14% (*P*=.001). Limitations included the exclusion of women with obesity and other comorbidities, which may affect applicability. EBP

Aaron Salazar, DO

Shelby Takeshita, MD

David Grant Medical Center—Travis AFB Family  
Medicine Residency Program, Fairfield, CA

The corresponding author is Aaron Salazar; aaron.j.salazar2.mil@health.mil.

The opinions and assertions contained herein are those of the authors and are not to be construed as official or as reflecting the views of the US Air Force Medical Department, the Air Force at large, or the Department of Defense.

**References**

1. Miao CY, Fang XJ, Chen Y, Zhang Q. Effect of vitamin D supplementation on polycystic ovary syndrome: a meta-analysis. *Exp Ther Med*. 2020;19(4):2641-2649. [STEP 1]
2. Al-Bayyari N, Al-Domi H, Zayed F, Hailat R, Eaton A. Androgens and hirsutism score of overweight women with polycystic ovary syndrome improved after vitamin D treatment: a randomized placebo controlled clinical trial. *Clin Nutr*. 2021;40(3):870-878. [STEP 2]

## Does pelvic floor physical therapy after delivery help reduce urinary incontinence?

**EVIDENCE-BASED ANSWER**

Compared with usual care, postpartum pelvic floor muscle training (PFMT) taught by a healthcare professional may decrease urinary incontinence (UI) in the early postpartum period (3–6 months) with a number needed to treat of four, but it does not decrease incontinence risk long-term (SOR: **B**, systematic review of low-quality randomized controlled trials [RCTs] and a single-blinded RCT). The World Health Organization (WHO) recommends against routinely starting postpartum PFMT to prevent UI but concedes that self-directed PFMT may help treat UI and is low-risk (SOR: C, evidence-based guideline).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002089

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2020 systematic review and meta-analysis of 19 randomized controlled trials (RCTs) (N=5,452) investigated whether pelvic floor muscle training (PFMT) in the postnatal period could treat or prevent urinary incontinence (UI).<sup>1</sup> Studies were from Europe (6 RCTs), China or Korea (5 RCTs), Canada or the United States (4 RCTs), Australia or New Zealand (2 RCTs), and Brazil (1 RCT); one RCT was from multiple countries. Study size ranged from 20 to 1,800 patients (median 150 patients); 14 included women with and without UI at baseline, and five only enrolled patients with established

UI. Most patients were between 21 and 36 years old and were between six and 16 weeks postpartum at the time of enrollment; eight trials evaluated only primiparous patients. The review excluded RCTs that combined PFMT with another therapy. PFMT was broadly defined as a program to improve the function of the pelvic floor muscles, usually taught by a physical therapist, midwife, or nurse in either a group setting or as one-to-one sessions, augmented by home exercise instructions. Patients in control groups typically received standard postpartum care and instructions without emphasis on PFMT. Primary outcomes were self-reported incontinence and UI-specific quality of life (QOL); QOL was assessed using either the British Female Lower Urinary Tract Symptoms (BFLUT; 34 items, scale range not provided) or Incontinence Impact (1–100 scale) questionnaire; for both questionnaires, a higher score indicated worse QOL. In women with established UI, there was no improvement in incontinence with PFMT compared with control treatments (**TABLE**). Similarly, supervised PFMT did not improve UI-specific QOL (assessed with the BFLUT questionnaire) compared with standard postpartum instructions (1 RCT, n=20; mean difference [MD] -1.7; 95% CI, -3.5 to 0.19). In trials that enrolled patients with and without baseline UI, women who received PFMT within three months postpartum were about 46% less likely to report UI at three months compared with controls; however, there were no significant differences in UI rates in trials lasting six months or longer (**TABLE**) and no difference in UI-specific QOL (1 RCT, n=23; MD 0.5; 95% CI, -5.5 to 6.5; assessed by the Incontinence Impact questionnaire). No studies

**TABLE.** Effect of pelvic floor muscle training vs standard care for postpartum urinary incontinence in (1) patients with urinary incontinence at baseline and (2) patients with and without urinary incontinence at baseline<sup>1</sup>

Postpartum follow-up	No. of trials	No. of patients	RR <sup>a</sup>	95% CI	NNT
Patients with postpartum urinary incontinence at baseline					
6–12 months	3	696	0.55	0.29–1.1	NA
5–10 years	1	516	0.96	0.88–1.1	NA
>10 years	1	471	1.0	0.94–1.1	NA
Patients with and without postpartum urinary incontinence at baseline					
< 3 months	2	321	<b>0.54</b>	<b>0.44–0.66</b>	<b>4</b>
6 months	5	2,800	0.95	0.75–1.192	NA
12 months	3	826	0.88	0.71–1.1	

RR <1 favors pelvic floor muscle training. <sup>a</sup> Statistically significant change in bold type. NNT=number needed to treat; NA=not applicable; RR=risk ratio.

reported adverse effects from the intervention. Limitations included heterogeneity of the trials ( $I^2 \geq 50\%$  in all pooled analyses with more than 2 RCTs). The reviewers deemed the evidence quality to be low to very low in studies enrolling women with baseline UI and moderate to low in trials that included women with and without baseline UI.

A 2019 assessor-blinded RCT (n=84) examined the effectiveness of PFMT on urinary leakage in postpartum patients with UI at baseline.<sup>2</sup> Patients had a mean age of 28.5 years old and were 6 to 13 weeks postpartum after giving birth at a hospital in Iceland. The intervention group received 12 weekly pelvic floor physical therapy sessions which were facilitated with a biofeedback device. The control group had no follow-up after initial recruitment but was not discouraged from performing PFMT. The primary outcome was UI measured at six months postpartum using self-reported data. A secondary outcome was bladder-related “bother” as measured by the question “How much does your bladder problem bother you?” The study also assessed outcomes at a 12-month follow-up. At six months postpartum, fewer patients in the intervention than the control group reported UI (57% vs 82%;  $P=.03$ ; number needed to treat [NNT]=4) and bladder-related bother (27% vs 60%,  $P=.005$ ; NNT=3). However, at 12-month follow-up, there were no differences between intervention and control groups for UI (76% vs 82%,  $P=.6$ ) and bladder-related bother (45% vs 41%,  $P=.82$ ). No side effects were reported in the intervention group. This RCT was limited by a higher dropout rate in the intervention versus control group (7% vs 2%) and lack of a direct measurement of UI such as pad testing.

A 2022 WHO guideline on maternal care recommended against routinely starting postpartum PFMT for the prevention of UI.<sup>3</sup> This recommendation was based on low to very low certainty evidence derived from the above systematic review.<sup>1</sup> The guideline stated that unsupervised pelvic floor muscle exercises performed at home might be beneficial for the treatment of UI after childbirth and would not likely be harmful. The WHO steering group determined that there were no significant conflicts of interest reported by members of the guideline development group. **EBP**

**Ashley Millette Cote, MD**

**Joseph Angel, MD**

*Tacoma Family Medicine Tacoma, WA*

The corresponding author is Ashley Millette Cote; ash.millette@gmail.com.

The authors declare no conflicts of interest.

## References

1. Woodley SJ, Lawrenson P, Boyle R, et al. Pelvic floor muscle training for preventing and treating urinary and faecal incontinence in antenatal and postnatal women. *Cochrane Database Syst Rev*. 2020;5(5):CD007471. [STEP 1]
2. Sigurdardottir T, Steingrimsdottir T, Geirsson RT, Halldorsson TI, Aspelund T, Bø K. Can postpartum pelvic floor muscle training reduce urinary and anal incontinence?: an assessor-blinded randomized controlled trial. *Am J Obstet Gynecol*. 2020;222(3):247.e1-247.e8. [STEP 2]
3. *WHO Recommendations on Maternal and Newborn Care for a Positive Postnatal Experience*. Geneva, Switzerland: World Health Organization; 2022. [STEP 3]

# Are adverse childhood experiences associated with depression and is there a dose–response relationship?

## EVIDENCE-BASED ANSWER

It seems so. Patients with ACEs are more than twice as likely to develop depression as those without ACEs, with higher odds in those with more adverse experiences (SOR: **B**, systematic review of cohort and cross-sectional studies). The number of events is associated with higher use of medications, with rates 30% higher in patients with four or more exposures (SOR: **B**, cohort study). The number of ACEs may give insight into the expected level of depression symptoms over time because patients with high levels of exposure have higher mean depression scores (SOR: **B**, retrospective cohort study).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002117

This clinical question was developed as an HDA through a standardized, systematic methodology (HDA Methods, Supplemental Digital Content).

A 2023 systematic review of nine cohort and cross-sectional studies (N=14,238) focusing on

populations in Asia and Africa examined the relationship of ACEs and depression for both incidence and dose response. Subgroup analyses were also performed based on dose dependence, 12 specific ACEs, and further subcategories: geography, age, and depression management by clinical diagnosis or screening examinations.<sup>1</sup> Included studies used the ACE-IQ questionnaire and used odds ratios (OR), relative risk (RR), or hazard ratios (HRs). The ACE-IQ is a 10-item questionnaire covering traumatic experiences faced before age 18 years and creating a numerical value of the total experience types (abuse, divorce, abuse in the home, parent in jail, substance abuse, or mental illness in family members in the home). The odds of depression were highest for bullying (OR 3.17; 95% CI, 1.86–4.47) and lowest for loss/separation from parents (OR 1.34; 95% CI, 0.87–1.80). Examination of the relationship between depression diagnosed by a physician (OR 2.16; 95% CI, 1.77–2.65) versus a depression screen (CES-D; OR 3.09; 95% CI, 2.14–4.44) showed a consistent relationship between depression and ACEs. Limitations of the review included the retrospective and cross-sectional nature of the available studies as well as the small number of studies included.

A 2017 longitudinal cohort study investigated the relationship between childhood adversity and depression in a cohort of 478,141 Swedish patients born between 1984 and 1988.<sup>2</sup> The study investigated eight events that occurred between birth and age 14 years old using national registers. The eight events include parental factors of death, criminality, psychic morbidity, substance abuse, and separation, as well as household use of public assistance, child welfare interventions, and inconsistent housing. Records were analyzed from 2006 to 2012 to determine how many individuals received a diagnosis of depression or medication for depression. That was then analyzed using Cox hazard modules. Confounding factors considered included parental country of origin and the parental level of education at the time the patient was 18 years old. The HR for the clinical diagnosis of depression ranged from 1.55 (95% CI, 1.50–1.60) with one childhood adversity up to 3.17 (95% CI, 2.94–3.41) for exposure to four or more adversities. Likewise, the HR for use of antidepressant medication ranged from 1.08 (95% CI, 1.06–1.10) for one adversity up to 1.32 (95% CI, 1.24–1.40) for four or more

adversities. Limitations of the study included the inability to measure the intensity of the childhood event, include the full spectrum of adverse child events, or account for the fluid nature of life experiences that may not be seen as distinct events. These limitations are common across most studies because of the nature of the subject.

A 2020 prospective cohort study (n=107) aimed to determine the effects of ACEs on the severity of depression and mania and the effect on recovery over time.<sup>3</sup> Adult patients with a diagnosis of a mood disorder were identified and administered a short Childhood Trauma Questionnaire (CQT) and Lifetime Events Checklist (LEC) to screen for ACEs. The CQT is a 70-item questionnaire that screens 5 subsets: emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. The LEC screens for traumatic events that could have occurred during a lifetime. Patients were then sorted into low-exposure and high-exposure groups and surveyed weekly with a Quick Inventory of Depression Symptomatology (QID) and the Altman Self-Rating Mania Scale (ASRM). The QID is a self-rating assessment tool that evaluates for depressive symptoms occurring in the past week, and the ASRM is a 5-item scale designed to screen for the presence of manic symptoms. Seventy-one patients completed the full 16 weeks. Depression scores and CTQ scores were correlated at the start with a least squares mean of 15.2 (SE 1.26) for the high-exposure group versus 10.9 (SE 1.28) for the low-exposure group. They were also correlated with higher overall depression scores across the 16 weeks, with a week 16 mean of 10.9 (SE 1.407) versus 8.0 (SE 1.4). No significant difference in the rate of improvement over time. Limitations of the study included its susceptibility to recall and response bias, and its small sample size and use of only patients with low education and income. EBP

**Victoria Chisholm, DO**

**Amanda Paramore, DO**

**Carrie Brackett, DO**

**Karen Dixon, PhD**

*Cahaba—UAB Family Medicine Residency Program,  
Centreville, AL*

The corresponding author is Karen Dixon, PhD; karen.dixon@cahabamedicalcare.com.

The authors declare no conflicts of interest.

## References

1. Tan M, Mao P. Type and dose-response effect of adverse childhood experiences in predicting depression: a systematic review and meta-analysis. *Child Abuse Negl.* 2023;139:106091. [STEP 2]
2. Björkenstam E, Vinnerljung B, Hjern A. Impact of childhood adversities on depression in early adulthood: a longitudinal cohort study of 478,141 individuals in Sweden. *J Affect Disord.* 2017;223:95-100. Erratum in: *J Affect Disord.* 2017;236:316. [STEP 3]
3. Ventimiglia I, Van der Watt ASJ, Kidd M, Seedat S. Association between trauma exposure and mood trajectories in patients with mood disorders, *J Affective Disord.* 262:237-246, 2020. [STEP 3]

# Are children exposed to intimate partner or domestic violence at increased risk of developing childhood obesity?

## EVIDENCE-BASED ANSWER

In some cases, a decreased body mass index is noted in childhood exposure to domestic violence (DV; SOR: **C**, cohort study). However, childhood exposure to DV is significantly associated with higher adiposity at age 15 years old (SOR: **C**, large cohort study). Violence exposure in boys at ages 0 to 11 years old and girls at ages zero to five years old is significantly associated with obesity at ages 9 to 14 years old (SOR: **C**, large cohort study).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002115

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2022 prospective cohort study (n=2,412) evaluated the relationship between adverse childhood experiences (ACEs), including exposure to domestic violence (DV), and body mass index (BMI) changes over 12 years.<sup>1</sup> This study used data from the Fragile Families and Child Wellbeing

Study that sampled low-income families in the United States. Mothers had a mean age of 25.6 years old at the time of their child's birth, with 29.7% less than a high school education and 46.2% non-Hispanic Black. Children of mothers under 18 years old, children with disabilities limiting growth, and nonsingleton births were excluded. Follow-up assessments were done at ages 1, 3, 5, 9, and 15 years old. The primary outcome was BMI. DV exposure was measured using the conflict tactics scale (CTS). CTS scores ranged from 0 to 6, with higher scores indicating greater chronicity of DV occurrence. DV exposure from ages three to five years old was significantly associated with a decrease in BMI z-score from age five to nine years old (slope  $b=-0.04$ ;  $P=.04$ ). Study limitations included larger attrition over the period of the study and omitted variables (eg, severity and contributing environmental factors).

A 2017 prospective cohort study (n=9,302) combined data from two longitudinal observational studies in the United Kingdom (n=5,196) and Brazil (n=4,106) to assess the impact of ACEs, including DV, on obesity.<sup>2</sup> The UK researchers recruited pregnant women in Avon between 1991 and 1992, whose mean age at recruitment was 28 years old. Patients' children were followed from birth to 18 years old, with mothers reporting ACEs up to age 9 to 11 years old. For the Brazil cohort, all children were drawn from Pelotas hospitals in 1994. Children self-reported ACEs around age 15 years old and received adiposity assessments at 18 years old. For both studies, patients with incomplete patient questionnaires or loss to follow-up were excluded. Both cohorts assessed for various types of ACEs, including DV, by questionnaires directed to mothers (United Kingdom) or children (Brazil). The primary outcomes included BMI, waist circumference (WC), fat mass index, and android fat percentage. In the United Kingdom study, DV was significantly associated with a higher BMI (mean difference [MD] 0.42 kg/m<sup>2</sup>; 95% CI, 0.04–0.80;  $P=.049$ ) and WC (MD 1.97 cm; 95% CI, 0.86–3.09;  $P=.001$ ) at age 15 years old. The Brazil cohort did not show a significant association between DV and adiposity. Study limitations included a high dropout rate. In addition, differences in sociocultural factors (eg, parental knowledge, concerns, and skills) were not explored between the two cohorts.

A 2011 prospective cohort study (n=10,977) examined the relationship between childhood exposure to DV and BMI trajectories of adolescents between 1996 and 2004.<sup>3</sup> Patients were children 9 to 14 years old whose mothers completed questionnaires. Patients were 45%

male, with 94% White. Researchers excluded patients outside of the age range, and mothers who reported intimate partner violence first occurring after the child was 12 years old. In the primary outcome (BMI), children self-reported height and weight twice during the study. Patients were stratified into four distinct BMI trajectories (healthy growth-reference group, healthy to obese, steady overweight, and consistently obese). For DV, mothers were surveyed twice a year for the presence and timing of any DV (physical, sexual, or emotional) perpetrated by partners. Then, adolescents were placed into one of two categories: “early” (0–5 years) or “later” (6–11 years) childhood exposure to violence. In the cohort of boys exposed to violence in early childhood, DV was significantly associated with “consistent obesity” (odds ratio [OR] 2.0; 95% CI, 1.2–3.5) and “steady overweight” (OR 1.5; 95% CI, 1.1–1.9). Boys exposed to violence in later childhood were significantly more likely to be consistently obese (OR 3.0; 95% CI, 1.4–6.1). Girls were significantly more likely to be in the “steady overweight” group (OR 1.4; 95% CI, 1.1–2.9) if they experienced DV in early childhood. This study was limited by self-reporting, which could impact disclosure of DV because of hesitance to report. **EBP**

**Tanushree Nair, DO**  
**Emily White VanGompel, MD, MPH**  
**Shelly Verma, DO MSGPH**  
*The University of Chicago (NorthShore) Family  
 Medicine Residency Program, Evanston, IL*

The corresponding author is Shelly Verma; sverma2@north-shore.org.  
 The authors declare no conflicts of interest.

### References

- Schuler BR, Vazquez CE, Kobulsky JM, Dumenci L. Adversity and child body mass index in Fragile Families over 15 years: do type and timing matter? *SSM Popul Health*. 2022;19:101197. [STEP 3]
- Soares ALG, Matijasevich A, Menezes AMB, et al. Adverse childhood experiences (ACEs) and adiposity in adolescents: a cross-cohort comparison. *Obesity (Silver Spring)*. 2018; 26(1):150-159. [STEP 3]
- Jun HJ, Corliss HL, Boynton-Jarrett R, Spiegelman D, Austin SB, Wright RJ. Growing up in a domestic violence environment: relationship with developmental trajectories of body mass index during adolescence into young adulthood. *J Epidemiol Community Health*. 2012;66(7):629-635. [STEP 3]

## In patients with acute respiratory distress syndrome (ARDS), does stem cell treatment versus standard of care reduce days of ventilation and mortality?

### EVIDENCE-BASED ANSWER

Mesenchymal stromal cell therapy may reduce all-cause mortality in the management of COVID-19-related acute respiratory distress syndrome (ARDS) when compared with standard of care (SOR: **B**, heterogeneous, randomized, control trials [RCTs]). The effect may not be seen in moderate to severe ARDS (SOR: **C**, single-blind RCT).  
 Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
 DOI 10.1097/EBP.0000000000002093

This clinical question was developed as an HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2023 systematic review and meta-analysis of 13 randomized control trials (RCTs) (N=655) evaluated the safety and efficacy of mesenchymal stromal cell (MSC) in the treatment of acute respiratory distress syndrome (ARDS).<sup>1</sup> Patients were adults with an average age ranged from 53 to 70 years old, and 66% male. Patients were included if they had met the Berlin definition of ARDS or severe/critical COVID-19. Included studies compared MSC with controls (eg, placebo) for ARDS, in addition to standard of care, where MSC and controls of any dosage were intravenously infused. Origin source of MSC included bone marrow, adipose tissue, bone marrow, and umbilical cord with doses ranging from  $1 \times 10^6$  to  $120 \times 10^6$ . The primary outcomes were treatment-related adverse events (eg, cardiac arrhythmias, hypotension requiring vasopressors, hypersensitivity reaction 6 hours to 24 hours after

infusion) and all-cause mortality at 28 days. MSC significantly reduced all-cause mortality rate in ARDS compared with standard of care (13 trials, N=655; odds ratio [OR] 0.66; 95% CI, 0.46–0.96). There were no significant differences in any treatment-related adverse events between the two groups (10 trials, N=579; OR 0.64; 95% CI 0.34–1.2). This study was limited by a skewed male-to-female ratio.

A 2023 RCT (n=222) evaluated the efficacy and safety of MSC in mechanically ventilated patients with moderate-to-severe COVID-19-induced ARDS.<sup>2</sup> Patients had a mean age of 65 years old, with 70% male. Patients were included if they had SARS-CoV-2 confirmed through polymerase chain reaction and required mechanical ventilation for moderate-to-severe ARDS. ARDS was defined as moderate if PaO<sub>2</sub>/FIO<sub>2</sub> was >100 mmHg and ≤200 mmHg and severe if PaO<sub>2</sub>/FIO<sub>2</sub> was ≤100 mmHg, both with ventilator settings that included positive end-expiratory pressure ≥5 cm H<sub>2</sub>O. Patients were excluded if they were receiving extracorporeal membrane oxygenation, had bacterial pneumonia, had body mass index >55 kg/m<sup>2</sup>, had untreated HIV, and had liver function tests eight times the upper limit of normal or malignancy within 12 months of active treatment. Patients were also excluded if they had been intubated for more than 72 hours at the time of randomization or had a history of respiratory disease requiring supplemental oxygen. Patients were randomized to receive intravenous infusion of MSCs plus standard of care (n=112) or to placebo plus standard of care (n=110). Patients were followed for 12 months with the primary endpoint of all-cause mortality within 30 days. The secondary endpoint was days alive off mechanical ventilation within 60 days after randomization. At 30 days, there were no significant differences

between MSC versus control patients in all-cause mortality (relative risk [RR] 0.88; 95% CI, 0.64–1.2) and in resolution or improvement of ARDS (OR 1.4; 95% CI, 0.57–3.2). There were also no significant differences in days alive free from ventilator support within 60 days (MSC, 45% vs control, 43%). In addition, there was no significant difference in serious adverse events (eg, myocardial infarction, hepatic or renal dysfunction deterioration of respiratory status, multisystem organ failure) over 30 days between the two groups. Limitations included a single-blinded study, and the rapid changes of management practices during the pandemic. EBP

**Socorro Shelton, MD**  
**Dois Ogan, DO**  
**Timothy Cox, MD**  
**Jordyn Drake, DO**  
**Nicole Wakimoto, MD**

*Southern Illinois University Family Medicine Residency Program, Carbondale, IL*

The corresponding author is Socorro Shelton; sshelton77@siu-med.edu.

The authors declare no conflicts of interest.

## References

1. Wang F, Li Y, Wang B, Li J, Peng Z. The safety and efficacy of mesenchymal stromal cells in ARDS: a meta-analysis of randomized controlled trials. *Crit Care*. 2023;27(1):31. [STEP 1]
2. Bowdish ME, Barkauskas CE, Overbey JR, et al. A randomized trial of mesenchymal stromal cells for moderate to severe acute respiratory distress syndrome from COVID-19. *Am J Respir Crit Care Med*. 2023;207(3):261-270. [STEP 2]

## Do SGLT-2 inhibitors agents have an effect on all-cause mortality in patients with diabetes type 2?

### EVIDENCE-BASED ANSWER

When used as monotherapy in patients with type II diabetes or cardiovascular disease, sodium–glucose cotransporter-2 (SGLT-2) inhibitors reduce all-cause mortality with a number needed to treat of 82 (SOR: A, meta-analysis of randomized controlled trials [RCTs]). However, when used as add-on therapy to other hypoglycemics, SGLT-2 inhibitors do not reduce all-cause mortality risk (SOR: A, meta-analysis of RCTs).

Copyright © 2024 by Family Physicians Inquiries Network, Inc.  
DOI 10.1097/EBP.0000000000002118

This clinical question was developed as a HDA through a standardized, systemic methodology (HDA Methods, Supplemental Digital Content).

A 2020 meta-analysis (21 randomized controlled trials [RCTs], N=70,364) assessed the effect of SGLT-2 inhibitors on all-cause mortality.<sup>1</sup> Researchers included all studies evaluating adults treated with SGLT-2 inhibitors, regardless of disease status. Most studies evaluated patients with type II diabetes and comorbid cardiovascular disease (CVD); three studies included patients with heart failure or renal disease with or without diabetes. Patients in the treatment groups received an SGLT-2 inhibitor such as dapagliflozin 10 mg, empagliflozin 10 or 25 mg, canagliflozin 100 or 300 mg, or ertugliflozin (dose not provided). Comparison groups received placebo or other hypoglycemics (ie, sulfonylureas or sitagliptin/metformin). Trial duration ranged from 57 to 294 weeks. Treatment with SGLT-2 inhibitors reduced the risk of all-cause mortality relative to all comparators with a number needed to treat of 82 (5 studies, N=38,723; odds ratio [OR] 0.86; 95% CI, 0.81–0.91). Limitations included significant variation in patient inclusion characteristics, therapeutic interventions, and comparisons. Despite this variation, the meta-analysis reported low heterogeneity and consistent findings across various baseline subject characteristics.

A 2019 meta-analysis (42 RCTs, N=61,076) investigated the effect of SGLT-2 inhibitors, as monotherapy or

combined therapy, on cardiovascular outcomes and mortality.<sup>2</sup> Researchers included adult patients (mean age 61 years old) with type II diabetes (mean HbA1c 7.2–8.9%). The five studies evaluating SGLT-2 inhibitors in the above meta-analysis were also included in this study. Treatment groups received SGLT-2 inhibitors, including dapagliflozin, empagliflozin, and canagliflozin (dosing not reported), either as monotherapy (15 studies) or add-on therapy to other hypoglycemic medications (27 studies). Comparison groups received placebo or other hypoglycemic medications. Primary outcomes included all-cause mortality, evaluated after 12 to 338 weeks of follow-up. SGLT2 inhibitors reduced the odds of all-cause mortality by 15% compared with placebo when used as monotherapy (8 studies, N=36,718; OR 0.85; 95% CI, 0.79–0.92). When used as add-on therapy, there was no difference in all-cause mortality between SGLT2 inhibitor therapy and placebo (10 studies, N=5,463; OR 1.0; 95% CI, 0.50–2.0) or other hypoglycemic therapy (7 studies, N=10,650; OR 0.82; 95% CI, 0.67–1.0). The study was limited by variation in baseline patient characteristics, medication dosing, and comparison treatments, although result heterogeneity was noted to be minimal.

EBP

Laura T. Brusky, MD

Denise Kohl, DO

David Johnson, MD

Department of Family and Community Medicine,  
Medical College of Wisconsin, Milwaukee, WI

The corresponding author is Laura T. Brusky, MD; lbrusky@mcw.edu.

The authors declare no conflicts of interest.

### References

1. Silveri G, Monami M, Mannucci E. Sodium-glucose cotransporter-2 inhibitors and all-cause mortality: a meta-analysis of randomized controlled trials. *Diabetes Obes Metab*. 2020; 23:1052–1056. [STEP 2]
2. Zou CY, Liu XK, Sang YQ, Wang B, Liang J. Effects of SGLT2 inhibitors on cardiovascular outcomes and mortality in type 2 diabetes: a meta-analysis. *Medicine* 2019; 98:(49):e18245. [STEP 2]