VOLUME 91 • NUMBER 4 • APRIL 2024 • www.ccjm.org

CME MOC

Cleveland Clinic Journal of Medicine

Corticosteroids: Giving and taking away

Acquired reactive perforating collagenosis in a patient with diabetes

Microscopic colitis: What is it, and what are the treatment options?

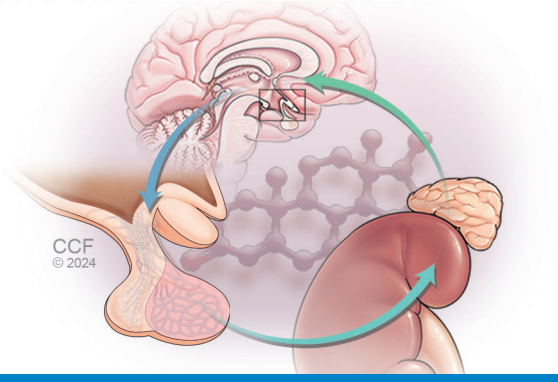
When should patients with *Pneumocystis* pneumonia receive corticosteroids?

Severe hyponatremia: Are you monitoring the urine output?

Management of lower-extremity venous thromboembolism

Nonhormone therapies for vasomotor symptom management

Glucocorticoid-induced adrenal insufficiency and glucocorticoid withdrawal syndrome: Two sides of the same coin



CLEVELAND CLINIC JOURNAL OF MEDICINE

ADVERTISING
Sima Sherman, Director of Sales and Marketing
SHERMAN MEDICAL MARKETING GROUP
1628 John F. Kennedy Blvd., #2200, Philadelphia, PA 19103
(610) 529-0322 • sima@shermanmmg.com

SUBSCRIPTIONS
U.S. and possessions: Personal $160; institutional $188; single copy/back issue $20

Foreign: $205; single copy/back issue $20

Institutional (multiple-reader rate) applies to libraries, schools, hospitals, and federal, commercial, and private institutions and organizations. Individual subscriptions must be in the names of, billed to, and paid by individuals.

Please make check payable to *Cleveland Clinic Journal of Medicine* and mail to: Cleveland Clinic Education Foundation, P.O. Box 373291, Cleveland, OH 44193-3291. To purchase a subscription with a credit card, please visit www.ccjm.org.

REPRINTS
(610) 529-0322 • sima@shermanmmg.com

CHANGE OF ADDRESS
To report a change of address, send a recent mailing label along with new information to:

AMA, Data Verification Unit, 330 N. Wabash Ave., Suite 39300, Chicago, IL 60611-5885 • Phone (800) 621-8335 • Fax (312) 464-4880 • dpprodjira@ama-assn.org

Cleveland Clinic Journal of Medicine uses the AMA database of physician names and addresses. The database includes all US physicians and not just AMA members. Only the AMA can update changes of address and other data.

SUBSCRIPTIONS, EDITORIAL, BILLING, AND PRODUCTION
9500 Euclid Avenue, JJ44, Cleveland, OH 44195 • Phone (216) 444-2661 • Fax (216) 444-9385 • ccjm@ccf.org • www.ccjm.org

Cleveland Clinic Journal of Medicine [ISSN 0891-1150 (print), ISSN 1939-2869 (online)] is published monthly by Cleveland Clinic at 9500 Euclid Avenue, JJ44, Cleveland, OH 44195.

2024

APRIL

THYROID SUMMIT 2024: ADVANCES IN THYROIDOLOGY
April 11
Cleveland, OH

CLEVELAND CLINIC NEPHROLOGY UPDATE
April 18–20
Cleveland, OH

MAY

DIABETES DAY
May 2
Cleveland, OH

CARDIOVASCULAR DISEASE AND MODIFIABLE CARDIOMETABOLIC RISK FACTORS: CURRENT AND EMERGING THERAPIES
May 3
National Harbor, MD

COMPREHENSIVE MULTIPLE SCLEROSIS CARE: NAVIGATING CHALLENGES AND ENHANCING TREATMENT
May 4
Las Vegas, NV

CLEVELAND CLINIC ULTRASOUND COURSE: INTEGRATING POCUS INTO YOUR PRACTICE
May 8–11
Cleveland, OH

THE PRESENT AND FUTURE OF EP PRACTICE: THE CLEVELAND CLINIC PERSPECTIVE
May 16
Boston, MA

MEDICAL DERMATOLOGY THERAPY UPDATE
May 29–31
Cleveland, OH

JUNE

SHAPING THE MANAGEMENT OF PARKINSON DISEASE
June 8–9
Bonita Springs, FL

INTENSIVE REVIEW OF INTERNAL MEDICINE
June 10–14
Live stream

ADVANCED DIAGNOSTIC BRONCHOSCOPY WORKSHOP
June 14–15
Cleveland, OH

INTERNAL MEDICINE UPDATES AND BOARD REVIEW: CERTIFICATION, RECERTIFICATION, AND MOC PREPARATION
June 17–21
Live stream

INNOVATIONS IN CEREBROVASCULAR CARE
June 18–19
Cleveland, OH

MELLEN CENTER UPDATE IN MULTIPLE SCLEROSIS
June 21
Cleveland, OH, and Live stream

AUGUST

NEUROLOGY UPDATE: A COMPREHENSIVE REVIEW FOR THE CLINICIAN AUGUST 2–4
Washington, DC

STATE-OF-THE-ART TOPICS IN THE PREVENTION AND MANAGEMENT OF CARDIOVASCULAR DISEASE
August 2–4
Cleveland, OH

SEPTEMBER

HOSPITAL MEDICINE 2024
September 5–6
Cleveland, OH

GLOBAL EP 2024
September 20–21
Cleveland, OH

OCTOBER

OBESITY SUMMIT
October 6–8
Cleveland, OH, and Live stream

GENETICS EDUCATION SYMPOSIUM
October 9
Cleveland, OH, and Live stream

INTENSIVE REVIEW OF ENDOCRINOLOGY AND METABOLISM
October 18–20
Cleveland, OH, and Live stream

CENTER FOR EXCELLENCE IN COACHING AND MENTORING: HEALTHCARE PROFESSIONAL COACH TRAINING
October 23
Live stream

CARDIOVASCULAR UPDATE 2024
October 31–November 1
Cleveland, OH

NOVEMBER

CLEVELAND CLINIC CANCER CONFERENCE: INNOVATIONS IN MULTIDISCIPLINARY CARE
November 1–3
Hollywood, FL

ADVANCING CARDIOVASCULAR CARE
November 8
Columbus, OH

DIMENSIONS IN CARDIAC CARE
November 10–12
Cleveland, OH

PRIMARY CARE AND UPDATES IN PRIMARY CARE, WOMEN'S HEALTH, AND BEHAVIORAL HEALTH
November 13–16
Beachwood, OH

DECEMBER

A RAPIDLY EVOLVING TREATMENT LANDSCAPE IN MYELOID MALIGNANCIES: EMERGING POSSIBILITIES AND LINGERING UNCERTAINTIES
December 6
San Diego, CA

MASTERING THE MITRAL VALVE
December 6–7
New York, NY

2025

JANUARY

PULMONARY HYPERTENSION SUMMIT
January 16–17
Hollywood, FL

FEBRUARY

INTERNATIONAL COLORECTAL DISEASE SYMPOSIUM
February 13–15
Fort Lauderdale, FL

FOR SCHEDULE UPDATES AND TO REGISTER, VISIT: WWW.CCFCME.ORG/LIVE

Table of Contents

CONTINUED ON PAGE 202

Upcoming Features

- Functional dyspepsia: How to manage the burn and the bloat
- Do I always need a central venous catheter to administer vasopressors?

CONTINUED FROM PAGE 200

Corticosteroids: Giving and taking away

In Dickensian terms, corticosteroids are the best of drugs and the worst of drugs. As I often tell patients, we will both love them and hate them. The paradoxes of "steroids" are many. I have seen patients rise from their bed or wheelchair upon initiation of corticosteroid therapy, and, unfortunately, I have seen patients sink back down due to the incremental adverse effects of long-term therapy.

Two articles in this issue of the *Journal* highlight selected issues at opposite ends of the treatment spectrum. Gupta and Bebell[1] discuss the purposeful introduction of corticosteroids as adjunctive treatment of an active infection in *Pneumocystis jirovecii* pneumonia (PJP), and Nachawi et al[2] outline the challenges of recognizing and managing glucocorticoid withdrawal syndromes.

Although questions about corticosteroid type and dosing remain, treating certain active infections with corticosteroids has become reasonably accepted practice. Examples include children with bacterial meningitis, adults with severe bacterial pneumonia, patients with ocular syphilis, and certain patients with severe PJP. And here is a striking paradox: we must remain vigilant regarding the increased risk for infections, including PJP and various other fungi and opportunistic vectors, when treating patients with mid- and high-dose corticosteroids.[3] Currently, the emphasis in treating patients with chronic systemic autoimmune disease, as reflected by several recent clinical trials that have reevaluated long-accepted practice approaches, is to markedly limit corticosteroid administration. At the same time, we recognize that an overexuberant inflammatory response to an infection can result in physiologic decompensation and tissue damage, and we reflexively reach for corticosteroids. We were certainly reminded of this during the height of the prevaccine stage of the COVID-19 epidemic, as many patients suffered delayed clinical decompensation due to a hyperinflammatory reaction to the infection. And, despite decades of study, I am still not certain that we have reached equipoise regarding the therapeutic role of corticosteroids when treating patients with sepsis.

At the other end of the treatment spectrum is the tapering and discontinuation of long-term corticosteroid therapy, which has many associated challenges. Scenarios can be complex when treating patients with any of a wide assortment of inflammatory ailments. Perhaps the most straightforward physiologic issue is the true primary adrenal insufficiency that develops after long-term high-dose corticosteroids are rapidly withdrawn, manifesting with hypotension, hypoglycemia, eosinophilia, and other symptoms. But as Nachawi et al[2] discuss, recognizing and diagnosing adrenal insufficiency may not always be straightforward and the risk factors not always clear.

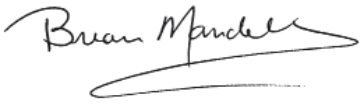
To me and my patients, the vexing challenge oftentimes is trying to distinguish among the various withdrawal syndromes that can occur, often in combination. I often explain to patients that the malaise that can accompany corticosteroid tapering is akin to the bodily cravings that accompany withdrawal from chronic opioid use—their body has gotten used to high levels of exogenous steroids, likely saturating receptors, and feels the need for a higher dose. An intense malaise with

doi:10.3949/ccjm.91b.04024

myalgias, generalized pain, fatigue, and sleep disturbance can occur in the setting of physiologic "normal" adrenal function, or even when the patient is taking what ordinarily are supraphysiologic doses of corticosteroid.

Dixon and Christy in 1980[4] published what I believe is a classic observational description of 5 patients demonstrating different etiologies for their corticosteroid withdrawal syndromes. This paper is straightforward, and I have found it to be of great conceptual value. If you are not familiar with it, it is worth the quick read. They described 4 withdrawal "subgroups" comprising patients having (1) biochemically demonstrable symptomatic adrenal insufficiency, (2) a flare in their underlying disease as a result of tapering, (3) dependence—physiologic, psychological, or both—on higher corticosteroid levels despite normal measured adrenal function (and no active underlying disease), and (4) no symptoms despite physiologically measured adrenal insufficiency. They pointed out that several of these subgroup patterns can coexist in the same patient, and astutely admonished physicians to be alert to the tendency of patients to overuse their steroids, not recognizing the different reasons that dose reduction might be contributing to them not feeling good. Simplistic but helpful constructs.

As I reflect on patients with issues relating to discontinuation of corticosteroid therapy who I have seen in consultation or cared for over time, some of the more challenging scenarios I recall relate to patients who had been on corticosteroids appropriately as treatment for polymyalgia rheumatica, or perhaps inappropriately as treatment for unrecognized fibromyalgia (perhaps as a comorbidity accompanying their systemic lupus or other inflammatory disorder). Patients in Dixon and Christy's subgroup 3 may express symptoms that can most certainly mimic an active inflammatory or musculoskeletal syndrome and respond to a bump in corticosteroid dose, a therapeutic pothole that I have stepped into on more than one occasion.



Brian F. Mandell, MD, PhD
Editor in Chief

1. **Gupta S, Bebell LM.** When should I give corticosteroids to my patient with *Pneumocystis* pneumonia? Cleve Clin J Med 2024; 91(4):217–219. doi:10.3949/ccjm.91a.23082
2. **Nachawi N, Li D, Lansang MC.** Glucocorticoid-induced adrenal insufficiency and glucocorticoid withdrawal syndrome: two sides of the same coin. Cleve Clin J Med 2024; 91(4):245–255. doi:10.3949/ccjm.91a.23039
3. **Park JW, Curtis JR, Kim MJ, Lee H, Song YW, Lee EB.** Pneumocystis pneumonia in patients with rheumatic diseases receiving prolonged, non-high-dose steroids—clinical implication of primary prophylaxis using trimethoprim-sulfamethoxazole. Arthritis Res Ther 2019; 21(1):207. doi:10.1186/s13075-019-1996-6
4. **Dixon RB, Christy NP.** On the various forms of corticosteroid withdrawal syndrome. Am J Med 1980; 68(2):224–230. doi:10.1016/0002-9343(80)90358-7

Trial Designs in Implementation Science Research

Tuesday, May 7, 2024 | Noon-1:00 pm | Virtual

Roger J. Lewis, MD, PhD
- Senior Physician, Los Angeles County Department of Health Services
- Professor of Emergency Medicine, David Geffen School of Medicine at University of California, Los Angeles
- Senior Medical Scientist, Berry Consultants, LLC

Robert B. Saper, MD, MPH
- Chair, Department of Wellness and Preventive Medicine
- Nancy J. and Michael F. Roizen Chair in Wellness Cleveland Clinic

MODERATOR:

Anita Misra-Hebert, MD, MPH, FACP
- Director, Healthcare Delivery and Implementation Science Center Cleveland Clinic
- Cleveland Clinic Site Lead, Clinical and Translational Science Collaborative of Northern Ohio

REGISTER for this event: www.ccfcme.org/HDISCSpeakerSeries-register

LEARNING OBJECTIVES

› Discuss clinical trial designs that can be utilized in implementation science studies
› Discuss the role of adaptive trial designs in implementation research
› Discuss a case example of a clinical trial capturing implementation outcomes

This activity has been approved for *AMA PRA Category 1 Credit*™

CASE WESTERN RESERVE UNIVERSITY
Clinical and Translational Science Collaborative

This event has been endorsed by the Clinical and Translational Science Collaborative of Northern Ohio (CTSC).

24-LRI-4703489

The Role of Behavioral Medicine in Reducing OPIOID USE

Provided by Cleveland Clinic | The France Foundation

Complimentary, CE-certified Online Education

Participate in education that focuses on utilizing behavioral medicine to reduce opioid use and covers all aspects of the core content outlined in the revised FDA Blueprint, with an emphasis on behavioral health and how the application of behavioral methods can help control pain.

The content in this complimentary, CE-certified online education is broken down into four modules: The Basics of Pain Management, Creating the Pain Treatment Plan, Managing Patients with Pain on Opioid Analgesics, and Addiction Medicine Primer. This is a FDA REMS-compliant accredited CE activity.

Hosted by Cleveland Clinic

Robert Bales, MD
Department of Family Medicine, Primary Care Institute
Center for Behavioral Health, Neurological Institute

Richard W. Rosenquist, MD
Chairman, Pain Management Department

Pavan Tankha, DO
Medical Director, Center for Comprehensive Pain Recovery

Amy Zack, MD
Vice Chair of Education, Primary Care Institute

Participate today!

ccfcme.org/opioid-use-cme

This activity has been approved for *AMA PRA Category 1 Credit*™, ANCC contact hours, and AAPA Category 1 CME credits.

When should we consider SGLT-2 inhibitors in patients with acute decompensated heart failure?

To the Editor: I read with great interest the excellent narrative review by Badwan et al[1] regarding the use of sodium-glucose cotransporter 2 (SGLT-2) inhibitors in acute heart failure. I thank the authors for their analysis of this complex and exciting topic.

SGLT-2 inhibitors have been shown to be beneficial in the treatment of chronic heart failure as an adjunct to existing guideline-directed medical therapy (angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers/angiotensin-receptor–neprilysin inhibitors plus beta blockade plus mineralocorticoid receptor antagonist with or without device therapy) in several landmark studies. However, I wonder whether the available data have unequivocally shown exactly when and in what sequence SGLT-2 inhibitors should be initiated as adjuncts to loop diuretic therapy in patients with acute decompensated heart failure.

Participants in the DICTATE-AHF (Efficacy and Safety of Dapagliflozin in Acute Heart Failure) trial[2] were prescribed dapagliflozin in addition to protocolized diuretic therapy on day 1 of admission. This trial failed to show a statistically significant change in its primary end point of diuretic efficiency at 5 days compared with placebo, despite augmented natriuresis and 24-hour diuresis.[3] In the DAPA-RESIST (Dapagliflozin Versus Thiazide Diuretic in Patients With Heart Failure and Diuretic Resistance) trial,[4] dapagliflozin was not shown to be more effective than metolazone in improving systemic congestion (note that Badwan et al in Table 1 of their article[1] highlighted a significant weight reduction in DAPA-RESIST participants). In the SOLOIST-WHF (Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure) trial,[5] patients were prescribed sotagliflozin, a combined SGLT-1/2 inhibitor, after they had already been transitioned from intravenous to oral diuretics, with 51.2% of patients prescribed the drug a median of 2 days after discharge.

As such, I would propose that the best evidence informs the use of SGLT-2 inhibitors after stabilization of acute decompensated heart failure with transition to oral diuretic therapy (with lingering questions about SGLT-1/2 combined vs SGLT-2 therapy). Also, in patients who have not tolerated thiazide-like diuretics due to electrolyte derangements or significant hypotension, SGLT-2 inhibitors may provide a less effective but safer alternative as adjunct sequential nephron-blockade in the acute heart failure setting.

Aditya Sharma, MD, MHPE, FRCPC
Assistant Professor, Department of Internal Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Canada

doi:10.3949/ccjm.91c.04001

REFERENCES

1. **Badwan OZ, Braghieri L, Skoza W, Agrawal A, Menon V, Tang WHW.** When should we consider SGLT-2 inhibitors in patients with acute decompensated heart failure? [published correction appears in Cleve Clin J Med 2024; 91(2):118]. Cleve Clin J Med 2024; 91(1):47–51. doi:10.3949/ccjm.91a.23034
2. **Cox ZL, Collins SP, Aaron M, et al.** Efficacy and safety of dapagliflozin in acute heart failure: rationale and design of the DICTATE-AHF trial. Am Heart J 2021; 232:116–124. doi:10.1016/j.ahj.2020.10.071
3. **European Society of Cardiology; Cox ZL.** DICTATE-AHF: efficacy and safety of dapagliflozin in acute heart failure. August 28, 2023. www.acc.org/-/media/Clinical/PDF-Files/Approved-PDFs/2023/03/04/ESC23/28Aug/DICTATE-AHF-esc-2023.pdf Accessed March 15, 2024.
4. **Yeoh SE, Osmanska J, Petrie MC, et al.** Dapagliflozin vs metolazone in heart failure resistant to loop diuretics. Eur Heart J 2023; 44(31):2966–2977. doi:10.1093/eurheartj/ehad341
5. **Bhatt DL, Szarek M, Steg PG, et al.** Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021; 384(2):117–128. doi:10.1056/NEJMoa2030183

In Reply: We thank Dr. Sharma for the valuable contribution and concur with the opinion about optimal timing of initiating SGLT-2 inhibitors in hospital settings. In several pivotal trials, the timing for administering SGLT-2 inhibitors varied, and the data so far suggest that SGLT-2 inhibitors can augment loop diuretic efficiency. Some trials have started SGLT-2 inhibitors within 12 hours of admission for acute heart failure, and others, after heart failure was stabilized or shortly after hospital discharge. For instance, in the EMPAG-HF (Empagliflozin in Acute Decompensated Heart Failure) trial,[1] empagliflozin was started within 12 hours of admission alongside standard diuretic therapy and continued for 5 days, resulting in a 25% increase in cumulative urine output without adverse effects on renal function compared with the placebo group. Similarly, in EMPA-RESPONSE-AHF (Effects of Empagliflozin on Clinical Outcomes in Patients With Acute Decompensated Heart Failure),[2] patients were started on empagliflozin within 24 hours of presentation while on intravenous loop diuretics, significantly reducing the combined end point of in-hospital worsening heart failure, rehospitalization for heart failure, or all-cause mortality at 60 days compared with the placebo group.

We agree that in the DICTATE-AHF trial's preliminary report the primary end point of cumulative

diuretic efficiency did not achieve statistical significance (P = .06).[3] However, starting dapagliflozin within 24 hours of presentation alongside protocolized titration of intravenous loop diuretics demonstrated favorable trends toward enhancing diuretic efficiency, evidenced by increased 24-hour natriuresis and diuresis, decreased total dose and duration of loop diuretic, and shortened time to hospital discharge compared to protocolized diuretic titration alone (all P < .01).[3] These synergistic effects of SGLT-2 inhibitors with intravenous loop diuretics were largely attributed to substantial redistribution of intrarenal sodium delivery and reabsorption.[4]

Nevertheless, Dr. Sharma underscores an important point regarding SGLT-2 inhibitor initiation after medical stabilization. In fact, it is common for SGLT-2 inhibitors to be held or their initiation deferred when patients have concomitant acute illness or are scheduled for major surgery to avoid the risks of ketoacidosis and urinary tract infections, even though increased risks have not been observed in the above-mentioned acute heart failure studies. We look forward to seeing the outcomes of ongoing trials such as EMPA-AHF (Early Treatment With a Sodium-glucose Co-transporter 2 Inhibitor in High-risk Patients With Acute Heart Failure)[5] aiming to elucidate the safety and efficacy of early SGLT-2 inhibitor initiation before clinical stabilization in high-risk acute heart failure.

Despite approval by the US Food and Drug Administration and clinical guideline recommendations, there is a gap in the use of SGLT-2 inhibitors among potentially eligible patients with ejection fraction greater than 40%. A recent retrospective analysis pointed to a strong association between hospitalization for heart failure and initiation of SGLT-2 inhibitors in this patient cohort.[6] In addition, in-hospital initiation of SGLT-2 inhibitors was associated with improved postdischarge outcomes in patients with acute heart failure irrespective of heart function.[7] These observations suggest that standardized approaches for in-hospital initiation may enhance prescription of these life-saving medications.[6] We therefore highlight Dr. Sharma's acknowledgment that upfront initiation of SGLT-2 inhibitor therapy during acute heart failure (as opposed to deferring it to outpatient settings) appears safe and presents an opportunity to facilitate its use as a long-term beneficial outpatient therapy.

Osamah Z. Badwan, MD
Department of Internal Medicine,
Cleveland Clinic, Cleveland, OH

Venu Menon, MD
Department of Cardiovascular Medicine,
Cleveland Clinic, Cleveland, OH; Professor,
Cleveland Clinic Lerner College of Medicine of
Case Western Reserve University, Cleveland, OH

W. H. Wilson Tang, MD
Department of Cardiovascular Medicine,
Cleveland Clinic, Cleveland, OH; Professor,
Cleveland Clinic Lerner College of Medicine of
Case Western Reserve University, Cleveland, OH

doi:10.3949/ccjm.91c.04002

■ REFERENCES

1. **Schulze PC, Bogoviku J, Westphal J, et al.** Effects of early empagliflozin initiation on diuresis and kidney function in patients with acute decompensated heart failure (EMPAG-HF). Circulation 2022; 146(4):289–298. doi:10.1161/CIRCULATIONAHA.122.059038
2. **Damman K, Beusekamp JC, Boorsma EM, et al.** Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). Eur J Heart Fail 2020; 22(4):713–722. doi:10.1002/ejhf.1713
3. **European Society of Cardiology; Cox ZL.** DICTATE-AHF: efficacy and safety of dapagliflozin in acute heart failure. August 28, 2023. www.acc.org/-/media/Clinical/PDF-Files/Approved-PDFs/2023/03/04/ESC23/28Aug/DICTATE-AHF-esc-2023.pdf Accessed March 14, 2024.
4. **Rao VS, Ivey-Miranda JB, Cox ZL, et al.** Empagliflozin in heart failure: regional nephron sodium handling effects. J Am Soc Nephrol 2024; 35(2):189–201. doi:10.1681/ASN.0000000000000269
5. **Horiuchi Y, Matsue Y, Nogi K, et al.** Early treatment with a sodium-glucose co-transporter 2 inhibitor in high-risk patients with acute heart failure: rationale for and design of the EMPA-AHF trial. Am Heart J 2023; 257:85–92. doi:10.1016/j.ahj.2022.12.005
6. **Martyn T, Saef J, Bansal A, et al.** Patient and provider factors associated with initiating sodium-glucose cotransporter-2 inhibitors (SGTL2is) following FDA approval for heart failure with preserved and mildly reduced ejection fraction. J Card Fail Published online February 16, 2024. doi:10.1016/j.cardfail.2024.01.006
7. **Mizobuchi S, Saito Y, Kitano D, et al.** Sodium-glucose co-transporter 2 inhibitors in acute heart failure: real-world prescription trends and outcomes analysis. ESC Heart Fail 2024; 11(1):410–421. doi:10.1002/ehf2.14597

Li-wen Zhang, MD
Department of Dermatovenereology, Chengdu Second People's Hospital, Chengdu, Sichuan, China

Juan Wu, MD, PhD
Sexually Transmitted Disease Institute, Shanghai Skin Disease Hospital, School of Medicine, Tongji University, Shanghai, China

Rong-hua Xu, MD
Institute of Dermatology, Chengdu Second People's Hospital, Chengdu, Sichuan, China

Tao Chen, MD, PhD
Department of Dermatovenereology, Chengdu Second People's Hospital, Chengdu, Sichuan, China

Acquired reactive perforating collagenosis in a patient with diabetes

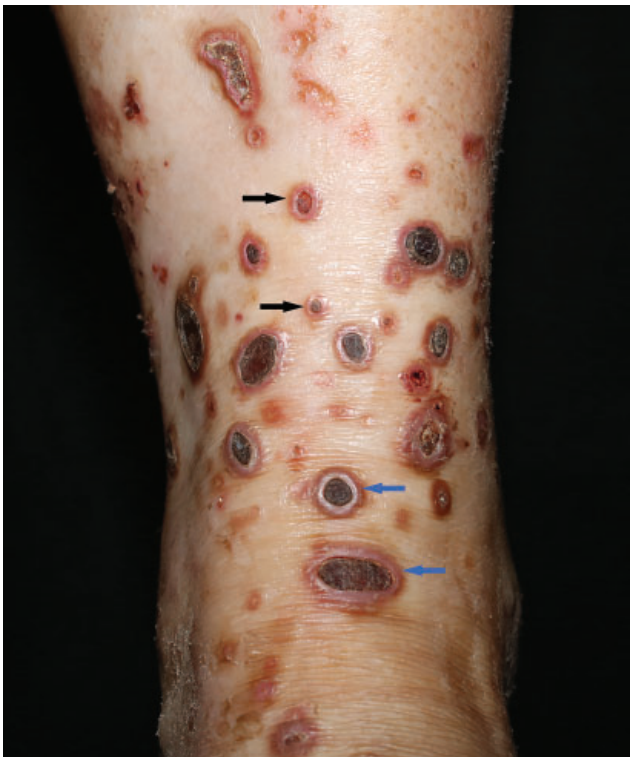


Figure 1. Multiple umbilicated hyperkeratotic papules (black arrows) and nodules (blue arrows) with a central round crusted ulcer on the left ankle.

A 47-year-old woman presented with a 2-month history of pruritic eruptions on the left ankle and a complaint of thirst and polyuria for the past year. She was previously healthy and denied a history of insect bites.

Physical examination revealed multiple umbilicated hyperkeratotic papules and nodules with a central round crusted ulcer on the left ankle (**Figure 1**). Histologic study of the lesions revealed cup-shaped invagination of the epidermis plugged with necrotic inflammatory debris and transepidermal elimination of dermal collagen (**Figure 2**). Laboratory testing showed the following:

- Fasting glucose 7.8 mmol/L [140.4 mg/dL] (reference range 3.9–5.6 [70–100])
- Hemoglobin A1c 6.9%
- Triglycerides 2.38 mmol/L [210.6 mg/dL] (< 1.7 [< 150])
- Total cholesterol 7.21 mmol/L [278.4 mg/dL] (< 5.18 [< 200]).

Based on the clinical presentation and the results of histologic study and blood testing, we diagnosed acquired reactive perforating collagenosis and type 2 diabetes. The patient was referred to endocrinology for management, and her lesions improved after 4 weeks of treatment with loratadine and halometasone cream.

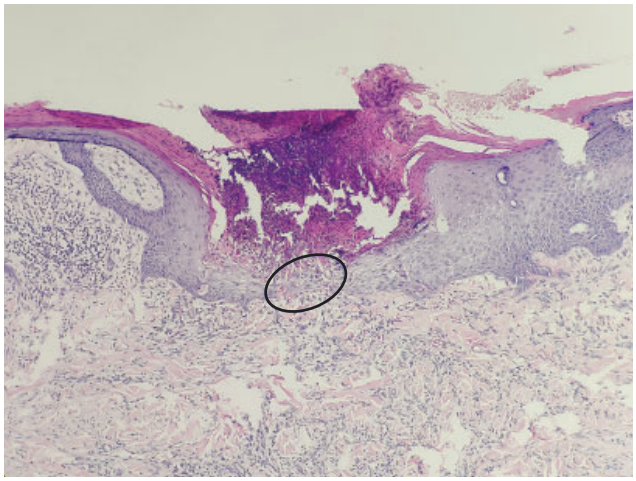


Figure 2. Histologic study of a papule revealed cup-shaped invagination of the epidermis, plugged with necrotic inflammatory debris, and transepidermal elimination of dermal collagen (circled area) (hematoxylin and eosin stain, magnification × 100).

doi:10.3949/ccjm.91a.23074

ACQUIRED PERFORATING DERMATOSIS

Perforating dermatoses are a group of chronic pruritic cutaneous disorders characterized histologically by transepidermal elimination of dermal components, ie, the components "perforate" the epidermis. They are divided into primary and secondary (ie, acquired) forms and, based on the dermal components of transepidermal elimination, can be further classifed into 4 subtypes: Kyrle disease, reactive perforating collagenosis (as in our patient), elastosis perforans serpiginosum, and perforating folliculitis.[1]

Acquired perforating dermatosis (APD) usually affects the extensor surfaces of the extremities and trunk and presents as multiple, nonfused, umbilicated, hyperkeratotic papules or nodules consisting of a central round crusted ulcer with a reddish brown raised border.

Symptoms and other features

Epidemiologic studies of APD are lacking. Seven retrospective case series studies have summarized a total of 282 cases of APD.[1–7] The condition mainly affects patients in their 40s and 50s. Pruritus was the most common symptom, with a few complaining of pain. Koebner phenomenon was seen in 32% to 56% of patients.[2–4,6,7]

Patients with APD often have an underlying systemic disease, particularly diabetes (type 1 or type 2) or chronic kidney disease.[1–7] Other underlying comorbidities include cardiovascular disease, infection (human immunodeficiency virus, hepatitis virus, and tuberculosis), rheumatic disease, pulmonary disease, malignancy, psychiatric disease, hypothyroidism, pregnancy, and dermatoses (atopic dermatitis, psoriasis, scabies).[1–7]

Pathogenesis still unclear

The pathogenesis of APD remains unknown. Possible theories include microtrauma caused by scratching prompted by pruritus, microangiopathy, and overloading of urinary metabolites due to renal insufficiency.[4] In 1 study, pruritus was the most common symptom, and the presence of the Koebner phenomenon suggests that trauma plays a role in the pathogenesis of APD.[4] Chronic pruritus is a symptom of many systemic diseases, including diabetes and chronic kidney disease. Diabetic microangiopathy may be involved in the formation of local hypoxia and necrosis.[4]

The differential diagnosis

The differential diagnosis includes insect bites, atopic dermatitis, and lichen planus. The lesions of APD typically have a crater-like structure, presenting as rounded, necrotic, dark brown crusts of variable size in the center of papulonodular lesions surrounded by a reddish brown halo. When lesions are atypical or the diagnosis is in doubt, histologic evidence of transepidermal elimination can confirm the diagnosis.

Treatment

Treatment of the underlying disease may help to improve APD.[8] First-line therapies include antihistamines and topical emollients, corticosteroids, and keratolytics. Second-line options include intralesional corticosteroid injections and topical tretinoin, tazarotene, and imiquimod. Other potentially effective treatments include systemic drugs (retinoids, allopurinol, doxycycline, and corticosteroids), dupilumab,[6] nemolizumab,[9] narrow-band ultraviolet B light, and psoralen plus ultraviolet A light.[1,2,8]

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **García-Malinis AJ, Del Valle Sánchez E, Sánchez-Salas MP, Del Prado E, Coscojuela C, Gilaberte Y.** Acquired perforating dermatosis: clinicopathological study of 31 cases, emphasizing pathogenesis and treatment. J Eur Acad Dermatol Venereol 2017; 31(10):1757–1763. doi:10.1111/jdv.14220
2. **Saray Y, Seçkin D, Bilezikçi B.** Acquired perforating dermatosis: clinicopathological features in twenty-two cases. J Eur Acad Dermatol Venereol 2006; 20(6):679–688. doi:10.1111/j.1468-3083.2006.01571.x
3. **Kim SW, Kim MS, Lee JH, et al.** A clinicopathologic study of thirty cases of acquired perforating dermatosis in Korea. Ann Dermatol 2014; 26(2):162–171. doi:10.5021/ad.2014.26.2.162
4. **Gore Karaali M, Erdil D, Erdemir VA, Gurel MS, Koku Aksu AE, Leblebici C.** Evaluation of clinicopathological and treatment characteristics of 80 patients with acquired perforating dermatosis. Dermatol Ther 2020; 33(6):e14465. doi:10.1111/dth.14465
5. **Garrido PM, Queirós C, Borges-Costa J, Soares-Almeida L, Filipe P.** Acquired perforating dermatosis: clinicopathologic study of a 10-year period at a tertiary teaching hospital. Int J Dermatol 2020; 59(4):445–450. doi:10.1111/ijd.14760
6. **Gao Z, Lu SJ, Shan SJ.** Acquired perforating dermatosis: a clinicopathologic study, and the features of dermoscopy and reflective confocal microscopy of 37 cases. Skin Res Technol 2023; 29(7):e13416. doi:10.1111/srt.13416
7. **Akoglu G, Emre S, Sungu N, Kurtoglu G, Metin A.** Clinicopathological features of 25 patients with acquired perforating dermatosis. Eur J Dermatol 2013; 23(6):864–871. doi:10.1684/ejd.2013.2237
8. **Lukács J, Schliemann S, Elsner P.** Treatment of acquired reactive perforating dermatosis—a systematic review. J Dtsch Dermatol Ges 2018; 16(7):825–842. doi:10.1111/ddg.13561
9. **Ohmori S, Sawada Y.** Perforating dermatosis in a patient on haemodialysis successfully treated with nemolizumab. Clin Exp Dermatol 2023; 48(8):929–941. doi:10.1093/ced/llad119

Address: *Tao Chen, MD, PhD, Department of Dermatovenereology, Chengdu Second People's Hospital, 165 Caoshi Street, Chengdu 610017, Sichuan, China; 13980427003@163.com; and Rong-hua Xu, MD, Institute of Dermatology, Chengdu Second People's Hospital; elvis0508@sina.com*

Katherine E. Westbrook, DO
Department of Internal Medicine,
Cleveland Clinic, Cleveland, OH

Ari Garber, MD, EdD, MS, EdM
Department of Gastroenterology,
Hepatology & Nutrition, Cleveland Clinic,
Cleveland, OH

ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Microscopic colitis: What is it, and what are the treatment options?

A: Microscopic colitis, an inflammatory disorder characterized by chronic diarrhea, is so named because its diagnosis requires histologic evaluation with mucosal biopsy. It may be overlooked as a cause of chronic diarrhea because cross-sectional imaging and endoscopic evaluation are usually normal in the absence of a microscopic evaluation. A standard approach to therapy improves symptoms and quality of life.

DIAGNOSTIC CONSIDERATIONS

Microscopic colitis has 2 subtypes: the collagenous subtype features the development of a subepithelial collagen band, and the lymphocytic subtype is characterized by intraepithelial lymphocytosis.[1]

The quintessential clinical presentation, regardless of the subtype, is chronic, nonbloody, watery diarrhea with concomitant urgency, abdominal pain, and weight loss. Likely causes are multifactorial and include the following:

- Alteration of gut microbiota, or dysbiosis[2]
- Immune system dysregulation
- Medications such as proton pump inhibitors, selective serotonin reuptake inhibitors, nonsteroidal anti-inflammatory drugs, and checkpoint inhibitors[2,3]
- Bile acid malabsorption
- Smoking
- Genetic susceptibility, with protective human leukocyte antigen loci implicated.[2]

Because the clinical presentation of microscopic colitis often overlaps with other diagnoses such as celiac disease and irritable bowel syndrome, competing diagnoses should be excluded.[2] The diagnosis of microscopic colitis can be confirmed with colonoscopy with biopsy of the ascending and descending colon.

doi:10.3949/ccjm.91a.23057

Despite the inflammatory nature of microscopic colitis, there is little benefit to obtaining C-reactive protein and erythrocyte sedimentation rate values, as neither is elevated in most cases of microscopic colitis.[4]

A recent meta-analysis determined the worldwide incidence of microscopic colitis to be about 5 per 100,000 patient-years, with a female predominance.[2] Although microscopic colitis occurs at all ages, it is more common in patients older than 60.

TREATMENT: BUDESONIDE FOR INDUCTION AND MAINTENANCE OF CLINICAL REMISSION

First-line therapy for microscopic colitis, regardless of the subtype, is budesonide 9 mg/day for 8 weeks.[5] If the patient is symptom-free after 8 weeks, budesonide therapy can be stopped. If the patient remains symptomatic at the end of 8 weeks or if symptoms recur, then budesonide can be continued or resumed at the lowest effective dose, usually 6 mg/day or less, for 6 to 12 months.[2]

Patients should be advised to avoid smoking and using nonsteroidal anti-inflammatory drugs. If possible, they should discontinue all associated medications, including proton pump inhibitors, statins, aspirin, immune checkpoint inhibitors, and selective serotonin reuptake inhibitors.[3]

Alternative therapies

When budesonide therapy is unfeasible or ineffective, other treatment options include secondary medications such as the bile acid sequestrant cholestyramine, loperamide, or bismuth salicylate, all with varying degrees of efficacy.[4,5] Some authors note that starting loperamide with budesonide might augment symptomatic relief, but few studies suggest that this combination is superior to budesonide alone.[4,5]

Some evidence supports the use of immunomodulators, including azathioprine and mercaptopurine, in the treatment of microscopic colitis.[2,6] Biologic therapies such as antitumor necrosis factor agents infliximab or adalimumab or the anti-integrin antibody agent vedolizumab have shown some success.[2] Data are emerging regarding Janus kinase inhibitors for treating microscopic colitis, but to date their efficacy is uncertain.[2] Mesalamine compounds have not proven effective. The American Gastroenterological Association Institute guideline[5] recommends mesalamine as a potential alternative to budesonide, but the European guidelines[7] do not.

Studies of probiotics have also generated little evidence to support their use in mitigating microscopic colitis.[5] The Institute guideline and other authors recommend against the use of probiotics for microscopic colitis.[4,5]

DISEASE COURSE

With effective treatment, symptoms and quality of life improve with microscopic colitis. Predictions of sustained remission vary widely among studies.[1] Although remission occurs for many patients, in most, the typical disease course is chronic or relapsing.[8]

As a general rule, continued budesonide therapy may be indicated for patients who are not in remission after 6 to 12 months.[8] Unlike ulcerative colitis and Crohn disease, which carry a longitudinal risk of colorectal cancer, microscopic colitis carries no such increased risk. The goal of continued treatment is clinical (ie, symptomatic) remission.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Lazenby AJ, Yardley JH, Giardiello FM, Jessurun J, Bayless TM.** Lymphocytic ('microscopic') colitis: a comparative histopathologic study with particular reference to collagenous colitis. Hum Pathol 1989; 20(1):18–28. doi:10.1016/0046-8177(89)90198-6
2. **Nielsen OH, Fernandez-Banares F, Sato T, Pardi DS.** Microscopic colitis: etiopathology, diagnosis, and rational management. Elife 2022; 11:e79397. doi:10.7554/eLife.79397
3. **Tong J, Zheng Q, Zhang C, Lo R, Shen J, Ran Z.** Incidence, prevalence, and temporal trends of microscopic colitis: a systematic review and meta-analysis [published correction appears in Am J Gastroenterol 2015; 110(7):1121]. Am J Gastroenterol 2015; 110(2):265–277. doi:10.1038/ajg.2014.431
4. **Pisani LF, Tontini GE, Marinoni B, et al.** Biomarkers and microscopic colitis: an unmet need in clinical practice [published correction appears in Front Med (Lausanne) 2020; 7:4]. Front Med (Lausanne) 2017; 4:54. doi:10.3389/fmed.2017.00054
5. **Nguyen GC, Smalley WE, Vege SS, Carrasco-Labra A; Clinical Guidelines Committee.** American Gastroenterological Association Institute guideline on the medical management of microscopic colitis. Gastroenterology 2016; 150(1):242–246. doi:10.1053/j.gastro.2015.11.008
6. **Ashraf MU, Aslam M, Zaheer MS, Rabbani MU, Khan SA, Ashraf J.** Microscopic colitis: an overview. Interdiscip J Microinflammation 2014; 1:1. doi:10.4172/2381-8727.1000108
7. **Miehlke S, Guagnozzi D, Zabana Y, et al.** European guidelines on microscopic colitis: United European Gastroenterology and European Microscopic Colitis Group statements and recommendations. United European Gastroenterol J 2021; 9(1):13–37. doi:10.1177/2050640620951905
8. **Tome J, Sehgal K, Kamboj AK, et al.** Budesonide maintenance in microscopic colitis: clinical outcomes and safety profile from a population-based study. Am J Gastroenterol 2022; 117(8):1311–1315. doi:10.14309/ajg.0000000000001774

Address: *Katherine E. Westbrook, DO, Department of Internal Medicine, NA10, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; westbrk@ccf.org*

Simran Gupta, MD
Department of Medicine, Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA; Harvard Medical School, Boston, MA

Lisa M. Bebell, MD, MSc, FIDSA
Department of Medicine, Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA; Harvard Medical School, Boston, MA

ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: When should I give corticosteroids to my patient with *Pneumocystis* pneumonia?

A: Nonpregnant adult patients with human immunodeficiency virus (HIV) and *Pneumocystis jirovecii* (formerly *carinii*) pneumonia (PJP) with hypoxemia should receive early adjunctive corticosteroids, along with anti-*Pneumocystis* therapy. Hypoxemia is defined as oxygen saturation less than 92% on room air, partial pressure of arterial oxygen (PaO_2) less than 70 mm Hg, or an alveolar-arterial oxygen (A-a O_2) gradient of 35 mm Hg or greater. Select patients without HIV infection who have hypoxemia may benefit from early adjunctive corticosteroids, but there is no clear evidence that they should be used routinely.

WHEN SHOULD YOU SUSPECT PJP?

PJP is a fungal infection that most commonly affects immunocompromised persons, such as those with HIV infection, those taking long-term corticosteroids or other immunosuppressive medications, and transplant recipients.[1] PJP should be considered in any immunocompromised patient who presents with fever and dyspnea, with or without nonproductive cough.[2] This is especially important in patients with defects in cell-mediated immunity. Almost all patients with PJP will have hypoxemia at rest or with exertion.

Typical radiographic findings include bilateral, diffuse, perihilar interstitial infiltrates with ground-glass opacities.[3] Diagnosis is typically made by identification of the organism on polymerase chain reaction testing or direct fluorescence antibody staining of a respiratory specimen from a sputum sample, bronchoalveolar lavage fluid, or endotracheal aspirate. If respiratory samples cannot be obtained, significantly elevated serum 1,3-beta-D-glucan—a cell wall component of many fungi, including *Pneumocystis*—and elevated serum lactate dehydrogenase levels can also support a PJP diagnosis in the appropriate clinical and radiographic context.

doi:10.3949/ccjm.91a.23082

SEVERITY OF DISEASE

PJP severity can be classified as mild, moderate, or severe as follows:

- Mild: A-a O_2 gradient of less than 35 mm Hg, PaO_2 greater than or equal to 70 mm Hg, or both
- Moderate: A-a O_2 gradient of 35 mm Hg or greater but less than 45 mm Hg, PaO_2 greater than or equal to 60 but less than 70 mm Hg, or both
- Severe: A-a O_2 gradient greater than or equal to 45 mm Hg, PaO_2 less than 60 mm Hg, or both.[4]

Additional signs pointing to severe disease include fatigue with impending respiratory failure or intubation. Some trials defined disease severity by the hypoxemia ratio, ie, PaO_2 divided by the fraction of inspired oxygen, with mild disease defined as a ratio greater than 350, moderate disease as greater than 250 but less than or equal to 350, and severe disease as less than or equal to 250 but greater than 75.[5]

TREATMENT

The mainstay of treatment of PJP for patients with and without HIV infection is antimicrobial therapy with trimethoprim-sulfamethoxazole (TMP-SMX).[6,7] Dosing of TMP-SMX is typically 15 to 20 mg/kg daily divided into 3 or 4 doses, with oral and intravenous formulations having equal bioavailability.[8] Although TMP-SMX is strongly preferred as first-line PJP treatment, its side

TABLE 1
Recommendations for adjunctive corticosteroids in patients with *Pneumocystis* pneumonia

Patient population	Recommendation
HIV-positive **WITH** baseline hypoxemia	**Strong** recommendation that adjunctive corticosteroids improve outcomes with *Pneumocystis jirovecii* pneumonia treatment
HIV-positive **WITHOUT** baseline hypoxemia	Steroids should be **considered** if respiratory status worsens after *Pneumocystis jirovecii* pneumonia treatment is started
HIV-negative **WITH** hypoxemia or respiratory failure	Steroids should be **considered**—evidence is unclear
HIV-negative **WITH** mild to moderate respiratory disease	Steroids **should not** be given routinely and may result in worse outcomes

HIV = human immunodeficiency virus

Based on information in references 5–13.

effects can include myelosuppression, hyperkalemia, and acute kidney injury. In the case of intolerance, alternatives include dapsone-trimethoprim or clindamycin-primaquine in patients with mild to moderate disease, or clindamycin-primaquine or intravenous pentamidine for patients with moderate to severe disease.[8] The recommended duration of treatment is 21 days, regardless of regimen.[8]

WHAT IS THE EVIDENCE FOR CORTICOSTEROIDS?

Multiple studies suggest that patients with HIV infection and PJP who are hypoxemic should be treated with glucocorticoids. In this clinical scenario, the use of adjunctive corticosteroids in patients with HIV can decrease mortality and respiratory failure associated with PJP, specifically in patients with substantial hypoxemia (moderate or severe disease) at the time of presentation.[5,9–11] Current guidelines suggest that steroids should be initiated within 72 hours of starting anti-*Pneumocystis* therapy in patients with PJP and resting room air oxygen saturation less than 92%, PaO_2 less than 70 mm Hg on room air, or A-a O_2 gradient greater than 35 mm Hg.[8,12] Many clinicians also advocate for giving corticosteroids to patients whose respiratory symptoms worsen after starting anti-*Pneumocystis* therapy. No studies have determined the optimal corticosteroid regimen, but clinicians often administer a 21-day course, starting with prednisone 40 mg twice daily (or equivalent) for 5 days, followed by 40 mg once daily for 5 days, and then 20 mg once daily for 11 days.

There is limited evidence, however, on the role of adjunctive corticosteroids for PJP treatment in patients without HIV. Society guidelines also do not address this topic. A meta-analysis from 2020 found a probable decrease in mortality in patients negative for HIV who had PJP with hypoxemia (PaO_2 < 70 mm Hg) and were treated with adjunctive corticosteroids compared with those not given steroids (odds ratio [OR] 0.69, 95% confidence interval [CI] 0.47–1.01, P = .05).[13] Mortality was significantly lower in patients without HIV who had respiratory failure (PaO_2 < 60 mm Hg) and were treated with adjunctive corticosteroids vs those not given steroids (OR 0.63, 95% CI 0.41–0.95, P = .03). However, the meta-analysis also found increased mortality in a mixed population of HIV-negative patients with PJP treated with adjunctive corticosteroids (OR 1.37, 95% CI 1.07–1.75, P = .01), leading to the conclusion that corticosteroids should be considered for patients without HIV who have hypoxemia or respiratory failure, but not added to PJP treatment for other patients without HIV.[13]

Another retrospective cohort study evaluated PJP treatment in 323 adults without HIV, 80% of whom received adjunctive corticosteroids within the first 48 hours of antimicrobial treatment or PJP diagnosis.[14] After adjusting for baseline hypoxemia severity, the authors found that early corticosteroid administration was associated with less improvement in the Sequential Organ Failure Assessment score at day 5 compared with no steroids (P = .001), indicating a possible negative effect of steroid administration on organ recovery. Adjunctive corticosteroid administration also was not associated with changes in mortality, length of stay, intensive care unit admission, or need for mechanical ventilation,[14] leading to the conclusion that adding corticosteroids to anti-*Pneumocystis* therapy did not benefit patients without HIV.

THE BOTTOM LINE

The data are clear and compelling regarding the use of adjunctive corticosteroids in patients with PJP who are positive for HIV and are hypoxemic on presentation. Based on the currently available evidence, these patients should be started on adjunctive corticosteroids within 72 hours of initiating antimicrobial therapy. Adjunctive corticosteroids should also be considered for HIV-positive patients with PJP who are not hypoxemic at baseline but develop worsening respiratory status after starting anti-*Pneumocystis* therapy.

The data regarding adjunctive corticosteroid therapy for patients with PJP who don't have HIV infection are less robust. There may be a mortality benefit in some HIV-negative patients with PJP who are hypoxemic and have severe respiratory disease, but worse outcomes have been reported in patients without HIV who have mild to moderate disease and are treated with steroids. Corticosteroids should not be routinely used for adjunctive treatment of PJP in patients without HIV. **Table 1** summarizes these recommendations.[5-13]

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Truong J, Ashurst JV.** *Pneumocystis jirovecii* pneumonia. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2023.
2. **Apostolopoulou A, Fishman JA.** The pathogenesis and diagnosis of *Pneumocystis jirovecii* pneumonia. J Fungi (Basel) 2022; 8(11):1167. doi:10.3390/jof8111167
3. **Thomas CF Jr, Limper AH.** *Pneumocystis* pneumonia. N Engl J Med 2004; 350(24):2487–2498. doi:10.1056/NEJMra032588
4. **Sax PE.** Treatment and prevention of *Pneumocystis* infection in patients with HIV. UptoDate. Updated September 12, 2022. https://www-uptodate-com.ccmain.ohionet.org/contents/treatment-and-prevention-of-pneumocystis-infection-in-patients-with-hiv?search=Treatment%20and%20prevention%20of%20Pneumocystis%20infection%20in%20patients%20with%20HIV&source=search_result&selectedTitle=1 ~150&usage_type=default&display_rank=1. Accessed March 11, 2024.
5. **Bozzette SA, Sattler FR, Chiu J, et al; California Collaborative Treatment Group.** A controlled trial of early adjunctive treatment with corticosteroids for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. N Engl J Med 1990; 323(21): 1451–1457. doi:10.1056/NEJM199011223232104
6. **Hughes W, Leoung G, Kramer F, et al.** Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat *Pneumocystis carinii* pneumonia in patients with AIDS. N Engl J Med 1993; 328(21):1521–1527. doi:10.1056/NEJM199305273282103
7. **Safrin S, Finkelstein DM, Feinberg J, et al.** Comparison of three regimens for treatment of mild to moderate *Pneumocystis carinii* pneumonia in patients with AIDS. A double-blind, randomized, trial of oral trimethoprim-sulfamethoxazole, dapsone-trimethoprim, and clindamycin-primaquine. ACTG 108 Study Group. Ann Intern Med 1996; 124(9):792–802. doi:10.7326/0003-4819-124-9-199605010-00003
8. **Clinicalinfo.** Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. Updated September 25, 2023. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-opportunistic-infections/whats-new. Accessed March 11, 2024.
9. **Ewald H, Raatz H, Boscacci R, Furrer H, Bucher HC, Briel M.** Adjunctive corticosteroids for *Pneumocystis jirovecii* pneumonia in patients with HIV infection. Cochrane Database Syst Rev 2015; 2015(4):CD006150. doi:10.1002/14651858.CD006150.pub2
10. **Montaner JS, Lawson LM, Levitt N, Belzberg A, Schechter MT, Ruedy J.** Corticosteroids prevent early deterioration in patients with moderately severe *Pneumocystis carinii* pneumonia and the acquired immunodeficiency syndrome (AIDS). Ann Intern Med 1990; 113(1):14–20. doi:10.7326/0003-4819-113-1-14
11. **Gagnon S, Boota AM, Fischl MA, Baier H, Kirksey OW, La Voie L.** Corticosteroids as adjunctive therapy for severe *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome. A double-blind, placebo-controlled trial. N Engl J Med 1990; 323(21):1444–1450. doi:10.1056/NEJM199011223232103
12. **National Institutes of Health–University of California Expert Panel for Corticosteroids as Adjunctive Therapy for Pneumocystis Pneumonia.** Consensus statement on the use of corticosteroids as adjunctive therapy for *Pneumocystis* pneumonia in the acquired immunodeficiency syndrome. N Engl J Med 1990; 323(21): 1500–1504. doi:10.1056/NEJM199011223232131
13. **Ding L, Huang H, Wang H, He H.** Adjunctive corticosteroids may be associated with better outcome for non-HIV *Pneumocystis* pneumonia with respiratory failure: a systemic review and meta-analysis of observational studies. Ann Intensive Care 2020; 10(1):34. doi:10.1186/s13613-020-00649-9
14. **Wieruszewski PM, Barreto JN, Frazee E, et al.** Early corticosteroids for *Pneumocystis* pneumonia in adults without HIV are not associated with better outcome. Chest 2018; 154(3):636–644. doi:10.1016/j.chest.2018.04.026

Address: *Simran Gupta, MD, Department of Medicine, Division of Infectious Diseases, Massachusetts General Hospital, 55 Fruit Street, Boston, MA 02114; sgupta@mgh.harvard.edu*

Cleveland Clinic

28th Annual

Diabetes Day

Therapeutics, Technology and Surgery

Attend In Person or Live Stream

Thursday, May 2, 2024

InterContinental Hotel and Conference Center | Cleveland, OH and Live Stream

Register Today! **ccfcme.org/diabetesday24**

This course will provide up-to-date reviews of management strategies and research on the complications of diabetes. Key topic areas that will be addressed include:

- A review of therapeutic options to manage both Type 1 and 2 diabetes and their complications, including a pump update, new insulins, and continuous glucose monitoring updates.
- New data regarding metformin in pregnancy will be discussed.
- Importance of maintaining muscle mass during obesity management.
- Gastroparesis associated with GLP-1 therapy and its effect on pre-op management.
- New roles for GLP1 receptor agonists SGLT-2 inhibitors and mineralocorticoid receptor antagonists in preserving cardiac function and preventing strokes.

This year's curriculum will also feature discussions about:

- Research from Cleveland Clinic on non-nutritive sweeteners.
- New treatment for nephropathy.
- Pre-prandial vs post prandial exercise.
- Diabetes and dementia.
- Mental health and diabetes.
- Effects of high-fat and high-protein diets on glucose control.
- Dermatologic considerations in diabetes.

The goal of this symposium is to increase practitioners' competence and clinical performance in treating diabetes and its complications and, ultimately, to improve patient outcomes.

There will be an optional workshop on continuous glucose monitoring designed for healthcare providers to advance the care of their patients with diabetes using continuous glucose monitoring (CGM) and other diabetes technology.

Join your colleagues in person or participate virtually from the convenience of your home or office

This activity has been approved for *AMA PRA Category 1 Credits*™, ABIM MOC points, ANCC Contact Hours, AAPA Category 1 CME Credits, ACPE Pharmacy credit and Interprofessional Continuing Education (ICPE) credit.

GREGORY W. RUTECKI, MD, Section Editor

Elias Bassil, MD
Department of Kidney Medicine, Medical Specialties Institute, Cleveland Clinic, Cleveland, OH

Georges N. Nakhoul, MD, MEd
Department of Kidney Medicine, Medical Specialties Institute, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Jonathan J. Taliercio, DO, FASN
Department of Kidney Medicine, Medical Specialties Institute, Cleveland Clinic, Cleveland, OH; Associate Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Ali Mehdi, MD, MEd, FACP, FASN
Department of Kidney Medicine, Medical Specialties Institute, Cleveland Clinic, Cleveland, OH; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Severe hyponatremia: Are you monitoring the urine output?

A 52-year-old woman was brought to the emergency department by her friend because she was concerned about the woman's new state of confusion. Her friend provided most of the history. She stated that the patient had not been acting like herself for several days. The patient reported mild nausea and anorexia for the past month, resulting in significant weight loss (estimated at 15 lb), as well as a drastically increased alcohol intake after being laid off from work. The patient was an active smoker and had a 60-pack-year smoking history. She had no other past medical history and was not on any prescription medications.

Vital signs taken in the emergency department were as follows:

- Blood pressure 124/73 mm Hg
- Heart rate 84 beats per minute
- Respiration rate 14 breaths per minute
- Oxygen saturation 96% on room air
- Temperature 37°C (98.6°F).

No orthostasis was noted. Her weight was 86 kg (189.6 lb), with a body mass index of 32 kg/m^2.

Physical examination revealed a disheveled woman in no acute distress. She was alert and oriented only to self. Her mucous membranes were moist. There was no jugular venous distention. Cardiovascular examination was normal, and there was no lower-extremity edema. Lung auscultation revealed bronchial breath sounds over the right lower base. The abdomen was examined and found to be normal. **Table 1** lists the results of laboratory testing.

Chest radiography revealed a consolidation in her right middle lobe—there was no prior image for comparison. Electrocardiography showed normal sinus rhythm, and computed tomography of the head with contrast showed no acute intracranial abnormalities.

doi:10.3949/ccjm.91a.23052

FURTHER TESTING

1 What studies would help differentiate the etiology of the patient's main electrolyte disturbance?

- ☐ Serum osmolality
- ☐ Urine osmolality
- ☐ Random urine sodium
- ☐ Random urine potassium
- ☐ Serum antidiuretic hormone (ADH) test

This patient's clinical picture is consistent with severe hyponatremia, defined as a plasma sodium concentration less than 120 mmol/L or symptoms ascribed to low sodium levels,[1] resulting in encephalopathy. Initial evaluation of hyponatremia should include serum osmolality, urine osmolality, and urine sodium tests, which ideally should be obtained before initiating therapy.

Serum osmolality

The first step when evaluating hyponatremia is to determine whether the hyponatremia is due to a hypoosmolar state (< 275 mOsm/kg).[2] This is referred to as true hyponatremia and is the most common category of hyponatremia. Hyperosmolar hyponatremia (> 295 mOsm/kg), also referred to as translocational hyponatremia, occurs when water shifts out of the intracellular fluid into the extracellular space because of highly osmolar substances in the serum such as glucose and mannitol.

Iso-osmolar hyponatremia (275–295 mOsm/kg) can also be translocational, as seen with moderate hyperglycemia. A more uncommon possibility is pseudohyponatremia, which is seen in hyperproteinemia and hyperlipidemia. Measured hyponatremia in hyperlipidemia and hyperproteinemia is the result of the indirect measurement techniques used in the laboratory. Direct

TABLE 1
Laboratory results at presentation

Test	Results	Reference range
Sodium	109 mmol/L	136–144
Potassium	3.4 mmol/L	3.7–5.1
Blood urea nitrogen	18 mg/dL	7–21
Creatinine	0.9 mg/dL	0.58–0.96
Estimated glomerular filtration rate	87 mL/min/1.73 m^2	≥ 60
Carbon dioxide	23 mmol/L	22–30
Chloride	79 mmol/L	97–105
Glucose	75 mg/dL	74–99
Albumin	3.1 g/dL	3.9–4.9
Calcium	8 mg/dL	8.5–10.2
Aspartate transaminase	118 U/L	14–40
Alanine transaminase	68 U/L	10–54
Lactate	0.8 mmol/L	0.5–2.2

techniques, such as those that employ ion-selective electrodes and blood gas analyzers, would show the true normal sodium concentration.[3]

Urine osmolality

Urine osmolality is a direct surrogate for the presence of circulating ADH, also referred to as arginine vasopressin. ADH is produced by the supraoptic and paraventricular nuclei in the hypothalamus and stored in the posterior pituitary. Under physiologic conditions, the release of ADH is tightly controlled. Rat studies have demonstrated that ADH is mainly released in response to changes in plasma osmolality and effective circulatory volume.[4] Plasma osmolality is tightly controlled, and small changes in osmolality trigger ADH release or suppression. In hypertonic states, osmoreceptors within the hypothalamus signal for ADH release, whereas decreased effective circulatory volume is sensed by various baroreceptors, ultimately leading to hypothalamic ADH secretion.[5]

Unlike plasma osmolality, a significant change in effective circulatory volume is required to trigger ADH release. However, once the threshold is achieved, the response is much more robust,[4] potentially surpassing the response to the osmolality stimulus. States of shock can increase vasopressin levels up to 500-fold.[6] When released into the circulation, arginine vasopressin binds to vasopressin V1a receptors, leading to vasoconstriction. Binding to basolateral vasopressin V2 receptors located on the collecting duct of the renal tubule causes the insertion of aquaporin channels into the luminal membrane, which leads to increased free water reabsorption. The net effect is the formation of a concentrated (hyperosmolar) urine and movement of solute-free water from the tubular fluid into the plasma.[7]

Urine osmolality can range from approximately 50 mOsm/kg to 1,200 mOsm/kg. A urine osmolality higher than 100 mOsm/kg implies ADH-mediated free water reabsorption and would be considered abnormally concentrated urine in a hyponatremic state.[8] A urine osmolality less than 100 mOsm/kg denotes a dilute urine and implies the absence of ADH or lack of response to ADH.[8] In the context of hyponatremia, the latter is usually seen in low-solute states and in primary polydipsia.

Urine sodium

A random urine sodium test can help evaluate kidney perfusion. A urine sodium level less than 30 mmol/L indicates a sodium-avid state in the face of decreased effective circulatory volume. This occurs in states of true volume depletion or in the hypervolemic states of heart or liver failure or nephrosis. A urine sodium level greater than 30 mmol/L is usually indicative of a sodium-replete state. Diuretic use or impaired renal tubular sodium reabsorption, for example, in Addison disease, can lead to higher urine sodium despite effective hypovolemia. In addition, glucosuria or the presence of urinary anions (as in bicarbonaturia) can also elevate urinary sodium independent of volume status.[9]

In the context of hyponatremia, a low urine sodium level is usually suggestive of decreased effective circulatory volume. A higher urine sodium level is usually seen in the syndrome of inappropriate ADH secretion (SIADH) and some cases of primary polydipsia.

Random urine potassium

Although measuring urine potassium may be important in guiding management in hyponatremia as it relates to the assessment of the clearance of electrolyte-free water, this test has no diagnostic utility in the initial evaluation of hyponatremia.

Serum ADH measurement

Measuring serum ADH is generally not pursued in the diagnostic workup of hyponatremia. While ADH measurement is offered by some laboratories, ADH is very unstable when isolated from plasma, making measurement and interpretation quite challenging.[10] Copeptin, or C-terminal proarginine vasopressin, is generated by enzymatic cleavage of the vasopressin

prohormone. It is a more stable alternative and can potentially be measured.[10] However, most commercial laboratories do not offer such testing, limiting its utility.

The results of further laboratory testing are listed in **Table 2**.

DIFFERENTIAL DIAGNOSES

2 Based on these results, which of the following is the most likely diagnosis?

- ☐ SIADH in the setting of lung pathology
- ☐ Beer potomania (low-solute intake)
- ☐ Hypovolemia
- ☐ Liver cirrhosis
- ☐ Cerebral salt wasting
- ☐ Primary polydipsia

SIADH

As reviewed above, increased plasma osmolality and decreased effective circulatory volume are the main stimuli for ADH release. SIADH occurs when ADH is produced in the absence of an osmotic or effective circulatory volume stimulus. This can occur with ectopic ADH release in certain cancers, especially lung cancer, a known paraneoplastic process.[11] SIADH can also be seen with many medications including antidepressants, anticonvulsants, and antipsychotics.[12] Disorders of the central nervous system, including but not limited to infections, trauma, and metastatic disease, can also result in SIADH.[13] It is noteworthy that nausea and pain are potent endogenous stimulants of ADH release, frequently precipitating hyponatremia in the postoperative period, particularly when intravenous fluids are administered.[14]

The urine studies in our patient are inconsistent with SIADH. The dilute urine, evident by a urine osmolality of less than 100 mOsm/kg, indicates the absence of ADH. This is the appropriate physiologic response to hypotonicity (serum osmolality of 237 mOsm/kg). Contrarily, the inappropriate release of ADH in SIADH (despite the low serum osmolality) would yield a high urine osmolality. Additionally, the urine sodium level would be expected to be higher than 30 mmol/L, appropriately indicating a non-sodium-avid state and suppression of the renin-angiotensin-aldosterone system.[15]

Hypovolemia

Hypovolemic hyponatremia is caused by ADH secretion triggered by reduced effective circulatory volume. Urine studies are expected to reveal a concentrated urine (urine osmolality > 100 mOsm/kg and usually > 300 mOsm/kg) and a low urine sodium level indicative of the sodium-avid state (except in cases of renal losses due to cerebral salt wasting or Addison disease, as detailed below). The high urine osmolality in these scenarios is reflective of ADH secretion aimed at reestablishing a depleted effective circulatory volume. In our patient, there were no clinical signs of overt volume depletion. In addition, the low urine osmolality would not support this hypothesis.[16]

TABLE 2
Further studies in our patient

Test	Results	Reference range
Blood osmolality	237 mOsm/kg	275–300
Urine osmolality	95 mOsm/kg	50–1,200
Urine sodium	22 mmol/L	14–216

Liver cirrhosis

Liver cirrhosis results in a hypervolemic state accompanied by a decreased effective circulatory volume. This results in the maladaptive release of ADH and the resultant hyponatremia commonly seen in persons with cirrhosis.[17] Urine studies will show a low urine sodium level (indicative of the sodium-avid state due to low effective circulatory volume) and an elevated urine osmolality (> 100 mOsm/kg) due to ADH secretion. A similar physiologic response occurs in advanced heart failure. Notably, hyponatremia indicates a poor prognosis in heart failure and cirrhosis.[18,19] Although the patient had elevated transaminases along with an aspartate transaminase-to-alanine transaminase ratio of 2:1, suggesting alcoholic hepatitis, there were no signs of hypervolemia or any stigmata of liver cirrhosis. Moreover, as in true hypovolemia, elevated urine osmolality along with a very low urine sodium level would be expected.

Cerebral salt wasting

Cerebral salt wasting is a potential cause of hyponatremia in patients with an underlying central nervous system pathology. It is characterized by renal sodium losses leading to hypovolemia.[20] ADH release is stimulated by hypovolemia and a decreased effective circulating volume. As such, urine osmolality in these patients is increased. In contrast to other causes of hypovolemia, urine sodium levels in cerebral salt wasting are quite elevated given that the renal sodium leak is the reason for the observed hypovolemia.[21] Our patient did not appear to have an overt central nervous system

TABLE 3
Causes of hyponatremia and their usual corresponding urine studies and urine output

Volume status	Etiology	Urine osmolality	Urine sodium	ADH-dependent	Urine output
Hypovolemic	Volume loss (nonrenal)	> 100 mOsm/Kg	< 30 mmol/L	Yes	Decreased
	Cerebral salt wasting	> 100 mOsm/Kg	> 30 mmol/L	Yes	Increased
	Diuretics	> 100 mOsm/Kg	> 30 mmol/L	Yes	Increased
Euvolemic	Syndrome of inappropriate ADH	> 100 mOsm/Kg	> 30 mmol/L	Yes	Decreased
	Low-solute state	< 100 mOsm/Kg[a]	< 30 mmol/L	No	Variable
	Primary polydipsia	< 100 mOsm/Kg	Variable	No	Increased
	Reset osmostat	Variable	Variable	No	Variable
Hypervolemic	Cirrhosis	> 100 mOsm/Kg	< 30 mmol/L	Yes	Decreased
	Heart failure	> 100 mOsm/Kg	< 30 mmol/L	Yes	Decreased
	Kidney failure	> 100 mOsm/Kg	> 30 mmol/L	No	Decreased

[a]The osmolality in a low-solute state can be higher in a concomitant hypovolemic state.

ADH = antidiuretic hormone

pathology, nor was hypovolemia evident. The low urine osmolality and low urine sodium levels would not suggest this pathology either. Important to note, cerebral salt wasting as a distinct entity vs a high-output state or special form of SIADH is the subject of considerable debate.[22] A similar physiology of renal sodium losses leading to hypovolemia occurs with Addison disease (mineralocorticoid deficiency). As in cerebral salt wasting, urine osmolality and urine sodium are elevated.

Beer potomania (low-solute state)

Normal dietary intake generates about 600 to 900 mOsm of solutes per day, mainly from protein intake. It is important to recognize that free water excretion is dependent on the presence of osmoles.[23] Normally, kidneys can dilute the urine maximally to around 50 mOsm/kg. Therefore, a person with intact maximal urine-diluting capacity (urinary osmolality 50 mOsm/kg) who consumes the usual solute diet of 600 to 900 mOsm per day can excrete 12 to 18 L of urine, and is thus capable of eliminating 12 to 18 L of free water and maintaining osmolality. In low-solute states (tea-and-toast diet or severe alcoholism), daily solute ingestion is reduced, which limits the ability of the kidneys to excrete free water.

As an example, a beer-restricted diet in which ten 12-oz cans of beer are consumed daily generates approximately 225 mOsm of solute per day. Assuming a maximally dilute urine, this limits the kidneys to excreting approximately 4.5 L of water daily. Any fluid intake exceeding this amount will lead to retention of water and thus hyponatremia. This scenario is seen during a prolonged alcohol binge, in which the carbohydrate load thwarts hunger, leading to a propensity for minimal dietary intake and limiting the solute load. Our patient's history seems to fit this process. In addition, urine studies show an expectedly dilute urine along with a low urine sodium level, owing to the low solute load and relatively high fluid intake. Correctly diagnosing these patients is crucial to their management and to avoid overcorrection of hyponatremia and its associated risks.[23]

It is not uncommon for these patients to present in a concomitant mild hypovolemic state. While the urine sodium levels will certainly be low, the urine osmolality can be somewhat higher due to ADH secretion caused by a decreased effective circulating volume. This can make the diagnosis more challenging, and for this reason a high index of suspicion and careful attention to the presenting context are critical.

Primary polydipsia

As detailed above, in a low-solute state the ability of the kidney to maximally dilute urine is impaired and, to varying degrees, fluid intake can overwhelm the kidney's capacity to excrete free water, leading to

hyponatremia. Primary polydipsia as a sole cause for hyponatremia occurs when fluid intake overwhelms the kidney's capacity for free water excretion while not limited by solute intake. This usually requires a very large amount of fluid intake, which is usually apparent from the patient's history. The urine osmolality is always low, with a variable urine sodium concentration. Notably, patients with primary polydipsia usually report concomitant polyuria, a key feature that distinguishes primary polydipsia from low-solute hyponatremia, where polyuria is not a cardinal feature.[24]

Table 3 summarizes common causes of hyponatremia and their usual corresponding urine studies and urine output.

MANAGEMENT

3 What is the next best step in the management of this patient?

- ☐ Isotonic saline (0.9% sodium chloride) administration
- ☐ Hypertonic saline (3% sodium chloride) administration
- ☐ Free water restriction
- ☐ Loop diuretic administration
- ☐ Desmopressin and 3% sodium chloride administration

Correcting hyponatremia, risk for osmotic demyelination syndrome

Osmotic demyelination syndrome describes a non-inflammatory syndrome in which there is oligodendrocyte loss and concurrent preservation of neurons and axons.[25,26] In chronic hyponatremia (> 48 hours), osmolytes shift out of brain cells to normalize brain cell volume and avoid further cellular swelling. Due to this adjustment, patients with chronic hyponatremia tend to be less symptomatic with lower levels of sodium than those who have acute hyponatremia (< 48 hours). As hyponatremia is corrected, the reverse process must occur, ie, the intracellular shift of osmolytes. Allowing enough time for this process to occur is the rationale for slowly correcting hyponatremia. Otherwise, a rapidly hypertonic extracellular environment will lead to water shifting out of brain cells along the concentration gradient and, consequently, decreased brain cell volume, apoptosis, and risk of osmotic demyelination syndrome.[27]

The rate at which hyponatremia is corrected depends on many factors, including the severity and duration of the hyponatremia, the symptoms the patient is experiencing, and the risk of osmotic demyelination syndrome. Acute hyponatremia may be (and should be) corrected rapidly. Initial serum sodium correction in patients with chronic hyponatremia (> 48 hours) should not exceed a rate of 6 to 8 mmol/L in the first 24 hours. Also, correction rates should not exceed 18 mmol/L in 48 hours in this setting. Identified factors conferring a higher risk of osmotic demyelination syndrome include having sodium levels lower than 120 mmol/L, rapid sodium correction, alcoholism, hypokalemia, being female, and having had a liver transplant.[15] Concomitant hypoxia may also be a risk factor.[28] These patients should have a more conservative correction target of 4 to 6 mmol/L per day.

Symptoms of osmotic demyelination syndrome vary by the location of the lesion and can be delayed up to 14 days after the initial insult.[29] While some patients have a full recovery, up to 35% will become fully dependent or die.[30]

Management of beer potomania (low-solute state)

Correctly diagnosing a low-solute state, in this case "beer potomania," as the cause of hyponatremia is crucial as these patients are at high risk of overcorrection and osmotic demyelination syndrome. As detailed above, free water excretion is limited by solute availability. Therefore, administration of solutes in the form of protein, saline, lactated ringers, or any osmole-containing fluid will immediately reverse this process and produce a brisk dilute urine (urine output > 150 mL/hr)[31] with a high potential of rapid overcorrection and subsequent osmotic demyelination syndrome. Our patient with beer potomania demonstrated many of the additional risk factors for osmotic demyelination syndrome detailed above.

Given the dynamic relationship of solute-and-water homeostasis in beer potomania, treatment should focus on slowly increasing the solute load (salt, protein) while closely monitoring changes in urine osmolality and urine output. Intake must be carefully monitored to avoid excessive aquaresis and rapid correction of sodium levels. A proactive approach proposed for patients with severe hyponatremia involves administering desmopressin (a selective vasopressin V2 receptor agonist) to limit the excretion of free water while 3% sodium chloride is used to slowly raise the serum sodium to precalculated daily levels.[1,32] This strategy, known as a desmopressin clamp, allows the clinician to control the sodium correction. Many times, beer potomania is diagnosed after solutes are introduced and brisk aquaresis follows. A very high hourly urine output and a fast up-trending serum sodium should alert the clinician to the diagnosis.

Rescue strategies to prevent and reverse overcorrection include electrolyte-free water infusion and possibly desmopressin administration.[1]

While formulas like the Adrogué-Madias formula[33] and online calculators (http://touchcalc.com/calculators/adrogue) can help establish the rate and amount of fluid (dextrose 5% in water or 3% sodium chloride) needed to achieve a particular serum sodium level, these situations are highly dynamic and require very frequent evaluations and adjustments based on serial trends. As such, these patients require monitoring in an intensive care setting with frequent sodium checks and therapy adjustments.

CASE CONCLUSION

The patient was treated with oral antibiotics and admitted to the intensive care unit. Brisk urine output was noticed after saline was administered in the emergency department. Serum sodium levels increased beyond the projected 8 mmol/L at the 24-hour mark. Therefore, 2 µg of desmopressin was administered and dextrose 5% in water was used to reduce the serum sodium. Subsequently, hypertonic saline was initiated along with continued desmopressin administration (2 µg every 6 hours) to safely raise the sodium levels. Once the serum sodium reached 130 mmol/L, desmopressin and hypertonic saline were discontinued. Aquaresis continued, the patient's dietary intake was subsequently liberalized, and serum sodium levels normalized within 48 hours.

TAKE-HOME POINTS

The kidney's ability to excrete free water depends on the availability (and ingestion) of solutes to be excreted. Low-solute states impair the ability of the kidneys to excrete free water, causing ADH-independent hyponatremia. When limited by a low solute intake, the kidney's capacity to excrete free water can easily be exceeded in the setting of binge drinking, resulting in severe hyponatremia. In low-solute states, the urine sodium level is low, usually with low urine osmolality. A concomitant hypovolemic state might lead to ADH secretion and more concentrated urine.

Low-solute states confer a high risk of osmotic demyelination syndrome: solute introduction restores the kidney's water-excreting capacity, which can lead to polyuria and risk for overcorrection of sodium levels. Patients with low-solute states tend to have many comorbid conditions that inherently increase the risk of osmotic demyelination syndrome (liver disease, alcoholism, concomitant electrolyte disturbances). Management of these patients requires an intensive multidisciplinary approach. Further, physicians must resist giving isotonic fluid for patients presenting with severe hyponatremia with no history or clinical signs to suggest hypovolemia.

In stable patients with severe hyponatremia and no obvious signs of hypovolemia, any fluid challenge should be preceded by a thorough and careful assessment of the situation, evaluation of serum and urinary parameters, and a rapid consultation with a nephrologist. "Doing nothing" and avoiding commission bias can prove very helpful in these situations. Treatment approaches may include the following[31]:

- Introducing enteral diet and minimizing intravenous fluids unless clinically indicated
- If needed, giving finite amounts of intravenous fluids (500 mL of 0.9% sodium chloride)
- If the patient is asymptomatic, restricting fluids and monitoring
- Measuring urine output hourly
- Checking serum sodium levels every 2 to 4 hours
- Having conservative goals of correction: 6 to 8 mmol/L at 24 hours and 14 to 16 mmol/L at 48 hours.

A proactive approach with a desmopressin clamp and hypertonic saline is recommended in severe cases. Rescue strategies should be used in case of overcorrection (or projected overcorrection) with infusion of dextrose 5% in water to lower (or control the rise of) serum sodium levels. A desmopressin clamp may also be needed in this scenario.

The overall care of the patient should not be compromised. Fluids should not be withheld if the patient needs them for specific indications, such as antibiotics, pressors, and fluids for hypotension.

DISCLOSURES

Dr. Nakhoul has disclosed consulting for Amgen, Boehringer Ingelheim, ChemoCentryx, GlaxoSmithKline, and Otsuka and teaching and speaking for ChemoCentryx. Dr. Taliercio has disclosed consulting and being an advisor or review panel participant for Otsuka. Dr. Mehdi has disclosed teaching and speaking for AstraZeneca and GlaxoSmithKline and being an advisor or review panel participant for Fresenius. Dr. Bassil reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Rafat C, Schortgen F, Gaudry S, et al.** Use of desmopressin acetate in severe hyponatremia in the intensive care unit. Clin J Am Soc Nephrol 2014; 9(2):229–237. doi:10.2215/CJN.00950113
2. **Büyükkaragöz B, Bakkaloglu SA.** Serum osmolality and hyperosmolar states. Pediatr Nephrol 2023; 38(4):1013–1025. doi:10.1007/s00467-022-05668-1
3. **Theis SR, Khandhar PB.** Pseudohyponatremia. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2023.
4. **Dunn FL, Brennan TJ, Nelson AE, Robertson GL.** The role of blood osmolality and volume in regulating vasopressin secretion in the rat. J Clin Invest 1973; 52(12):3212–3219. doi:10.1172/JCI107521
5. **Bisset GW, Chowdrey HS.** Control of release of vasopressin by neuroendocrine reflexes. Q J Exp Physiol 1988; 73(6):811–872. doi:10.1113/expphysiol.1988.sp003223
6. **Wilson MF, Brackett DJ.** Release of vasoactive hormones and circulatory changes in shock. Circ Shock 1983; 11(3):225–234. pmid:6360411
7. **Kurtzman NA, Boonjarern S.** Physiology of antidiuretic hormone and the interrelationship between the hormone and the kidney. Nephron 1975; 15(3–5):167–185. doi:10.1159/000180511
8. **Wakil A, Ng JM, Atkin SL.** Investigating hyponatraemia. BMJ 2011; 342:d1118. doi:10.1136/bmj.d1118
9. **Palmer BF, Clegg DJ.** The use of selected urine chemistries in the diagnosis of kidney disorders [published correction appears in Clin J Am Soc Nephrol 2019; 14(8):1241]. Clin J Am Soc Nephrol 2019; 14(2):306–316. doi:10.2215/CJN.10330818
10. **Pliquett RU, Obermüller N.** Endocrine testing for the syndrome of inappropriate antidiuretic hormone secretion (SIADH). In: Feingold KR, Anawalt B, Blackman MR, et al, eds. Endotext [Internet]. South Dartmouth, MA: MDText.com, Inc.; 2000. Updated December 22, 2022. https://www.ncbi.nlm.nih.gov/books/NBK279055/. Accessed March 12, 2024.
11. **Pelosof LC, Gerber DE.** Paraneoplastic syndromes: an approach to diagnosis and treatment [published correction appears in Mayo Clin Proc 2011; 86(4):364]. Mayo Clin Proc 2010; 85(9):838–854. doi:10.4065/mcp.2010.0099
12. **Shepshelovich D, Schechter A, Calvarysky B, Diker-Cohen T, Rozen-Zvi B, Gafter-Gvili A.** Medication-induced SIADH: distribution and characterization according to medication class. Br J Clin Pharmacol 2017; 83(8):1801–1807. doi:10.1111/bcp.13256
13. **Cui H, He G, Yang S, et al.** Inappropriate antidiuretic hormone secretion and cerebral salt-wasting syndromes in neurological patients. Front Neurosci 2019;13:1170. doi:10.3389/fnins.2019.01170
14. **Gowrishankar M, Lin SH, Mallie JP, Oh MS, Halperin ML.** Acute hyponatremia in the perioperative period: insights into its pathophysiology and recommendations for management. Clin Nephrol 1998; 50(6):352–360. pmid:9877108
15. **Adrogué HJ, Madias NE.** The syndrome of inappropriate antidiuresis. N Engl J Med 2023; 389(16):1499–1509. doi:10.1056/NEJMcp2210411
16. **Adrogué HJ, Tucker BM, Madias NE.** Diagnosis and management of hyponatremia: a review. JAMA 2022; 328(3):280–291. doi:10.1001/jama.2022.11176
17. **Alukal JJ, John S, Thuluvath PJ.** Hyponatremia in cirrhosis: an update. Am J Gastroenterol 2020; 115(11):1775–1785. doi:10.14309/ajg.0000000000000786
18. **Ennaifer R, Cheikh M, Romdhane H, et al.** Hyponatremia in cirrhosis: risk factors and prognostic value. Tunis Med 2016 ;94(5): 401–405. pmid:27801493
19. **Jao GT, Chiong JR.** Hyponatremia in acute decompensated heart failure: mechanisms, prognosis, and treatment options. Clin Cardiol 2010; 33(11):666–671. doi:10.1002/clc.20822
20. **Tenny S, Thorell W.** Cerebral salt wasting syndrome. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022.
21. **Mohottige D, Lehrich RW, Greenberg A.** Hypovolemic hyponatremia. Front Horm Res 2019; 52:93–103. doi:10.1159/000493240
22. **Brimioulle S, Orellana-Jimenez C, Aminian A, Vincent JL.** Hyponatremia in neurological patients: cerebral salt wasting versus inappropriate antidiuretic hormone secretion. Intensive Care Med 2008; 34(1):125–131. doi:10.1007/s00134-007-0905-7
23. **Berl T.** Impact of solute intake on urine flow and water excretion. J Am Soc Nephrol 2008; 19(6):1076–1078. doi:10.1681/ASN.2007091042
24. **Kotagiri R, Kutti Sridharan G.** Primary polydipsia. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2023.
25. **Alleman AM.** Osmotic demyelination syndrome: central pontine myelinolysis and extrapontine myelinolysis. Semin Ultrasound CT MR 2014; 35(2):153–159. doi:10.1053/j.sult.2013.09.009
26. **Popescu BF, Bunyan RF, Guo Y, Parisi JE, Lennon VA, Lucchinetti CF.** Evidence of aquaporin involvement in human central pontine myelinolysis. Acta Neuropathol Commun 2013; 1:40. doi:10.1186/2051-5960-1-40
27. **Pasantes-Morales H, Franco R, Ordaz B, Ochoa LD.** Mechanisms counteracting swelling in brain cells during hyponatremia. Arch Med Res 2002; 33(3):237–244. doi:10.1016/s0188-4409(02)00353-3
28. **Knochel JP.** Hypoxia is the cause of brain damage in hyponatremia. JAMA 1999; 281(24):2342–2343. doi:10.1001/jama.281.24.2342
29. **Singh TD, Fugate JE, Rabinstein AA.** Central pontine and extrapontine myelinolysis: a systematic review. Eur J Neurol 2014; 21(12):1443–1450. doi:10.1111/ene.12571
30. **Menger H, Jörg J.** Outcome of central pontine and extrapontine myelinolysis (n = 44). J Neurol 1999; 246(8):700–705. doi:10.1007/s004150050435
31. **Sanghvi SR, Kellerman PS, Nanovic L.** Beer potomania: an unusual cause of hyponatremia at high risk of complications from rapid correction. Am J Kidney Dis 2007; 50(4):673–680. doi:10.1053/j.ajkd.2007.07.01526.32
32. **Sterns RH, Hix JK, Silver S.** Treating profound hyponatremia: a strategy for controlled correction. Am J Kidney Dis 2010; 56(4):774–779. doi:10.1053/j.ajkd.2010.04.020
33. **Adrogué HJ, Madias NE.** Hyponatremia. N Engl J Med 2000; 342(21):1581–1589. doi:10.1056/nejm200005253422107

Address: *Ali Mehdi, MD, MEd, FACP, FASN, Department of Kidney Medicine, Medical Specialties Institute, Q7, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; mehdia@ccf.org*

Cleveland Clinic

Cleveland Clinic Ultrasound Course: Integrating POCUS into Your Practice

May 8-11, 2024

Cleveland Clinic Simulation and Advanced Skills Center | Cleveland, OH

Why Attend?

The use of ultrasound to diagnose and guide procedures is growing rapidly and you don't want to be left behind. This growth is primarily fueled by data indicating that ultrasound can improve the success rate of various procedures while decreasing complications. This course will provide you with current state-of-the-art techniques for diagnosis and guiding procedures. The skills you learn by attending this course can easily be incorporated into your current practice.

Choose from 1, 2, 3 or all 4 specialized sessions!

WEDNESDAY: Building a Point-of-Care Ultrasound Program	THURSDAY: Diagnostic POCUS Day, "Make the Diagnosis – Core Skills for POCUS Image Acquisition"	FRIDAY: Procedural POCUS Day, "Procedural Wins - Core Skills for Procedural POCUS Expertise"	SATURDAY: Hands-on Simulation Workshop Day

• **Learn directly from POCUS experts as they engage in lively lectures and roundtable discussions.**
  ◦ Machine Choice, IT Configuration, and EMR Workflows
  ◦ POCUS Training
  ◦ Quality Improvement and Credentialing & Privileging
  ◦ Billing & Coding and AI & Future Directions
• **The Wednesday session is also available via Live Stream!**
	• **Connect with instructors during learner-centered didactics and hands-on workshops!**
	  ◦ Probes and Planes (Not Airplanes!) and Artifacts and Beams (Not Lasers!) with Scan Sessions to follow
	  ◦ Morning Session: "Pump and Pipes"
	  ◦ Afternoon Session: "Evaluating the Tank"
	• **Thursday ends with an incredible opportunity to put it all together during the hands-on "Intro to Diagnosing Shock with POCUS Simulation"!**
		• **Work side-by-side with expert facilitators during interactive lectures and hands-on workshops!**
		  ◦ Basics of Procedural Ultrasound: Pt prep, Equipment, and Technique Lecture & Workshop
		  ◦ Paracentesis, Thoracentesis, and Soft Tissue Aspirations Lecture & Workshop
		  ◦ Peripheral and Central Venous Access Lecture & Workshop
		• **Wrap up Friday with the fantastic chance to put it all together during the hands-on "Putting your Procedural Ultrasound Skills into Practice: Case Based Simulation"!**
			• **Take a DEEP DIVE into BOTH Hands-on Simulation Workshops! Space is limited!**
			  ◦ "RUSH" into your Practice: Assessing Critically Ill Patients in Shock
			  ◦ Advanced Assessment of the Rapidly Decompensating Patient

Who Should Attend

This activity is designed for physicians, physician assistants, nurse practitioners, nurses, fellows, and residents in emergency medicine, internal medicine, hospital medicine, critical care, cardiology, anesthesiology, pulmonology, and radiology.

This activity is approved for *AMA PRA Category 1 Credit*™, ANCC Contact Hours, AAPA Category 1 CME Credits, American Board of Anesthesiology and American Board of Internal Medicine MOC, and ABMS Lifelong Learning CME Activity (Family Medicine and Radiology).

Register Today! **ccfcme.org/GoUltra**

Farah Ziyadeh, MD
Department of Internal Medicine, Cleveland Clinic, Cleveland, OH

Yael Mauer, MD, MPH
Department of Endocrinology and Metabolism, Cleveland Clinic, Cleveland, OH; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Management of lower-extremity venous thromboembolism: An updated review

ABSTRACT

According to the 2021 updated guidelines of the American College of Chest Physicians, the location of venous thromboembolism, the severity of symptoms, the risk of thrombus extension vs that of bleeding, and comorbidities all affect the decision to treat, the choice of antithrombotic agent, and the duration of therapy. In patients with isolated distal deep vein thrombosis without high-risk features, monitoring progression is recommended over initiating anticoagulation. However, treatment of proximal deep vein thrombosis with anticoagulation is strongly recommended by the guidelines. More evidence now supports the treatment of superficial vein thrombosis with anticoagulation in high-risk patients.

KEY POINTS

- Patients requiring anticoagulation should undergo additional risk-factor assessment to select an appropriate agent and duration of therapy.
- In patients requiring extended anticoagulation, the risks of bleeding and recurrent venous thromboembolism should be reassessed on an ongoing basis.
- In patients with isolated distal deep vein thrombosis without high-risk features, monitoring progression is recommended over starting anticoagulation.

doi:10.3949/ccjm.91a.22090

Treatment of venous thromboembolism (VTE), including deep vein thrombosis (DVT), depends on a variety of factors. The location of the VTE, severity of symptoms, risk of extension of thrombus, bleeding risk, comorbidities, and patient preferences affect the decision to treat, the choice of antithrombotic agent, and the duration of therapy, as outlined in the 2021 updated guidelines of the American College of Chest Physicians (CHEST).[1] In patients with isolated distal DVT (below the popliteal vein) without high-risk features, monitoring progression is recommended over starting anticoagulation. However, it is strongly recommended to treat proximal DVT with anticoagulation. More evidence now supports the treatment of superficial vein thrombosis with anticoagulation in high-risk patients.[1]

In this article, we review risk factors, supportive management, choice of anticoagulation therapy, and treatment considerations in special patient populations.

INCIDENCE AND RISK FACTORS

According to the US Centers for Disease Control and Prevention (CDC), approximately 900,000 people in the United States are affected by VTE each year, and 3 out of 10 will have recurrence of a clotting event within 10 years.[2] The prevalence of distal DVT, which varies widely because of different patient populations and diagnostic strategies used in studies, ranges from 23% to 59% in patients who received a diagnosis of DVT.[3]

TABLE 1
High-risk features of distal deep vein thrombosis

Severe symptoms (severe pain, throbbing pain when standing that improves with leg elevation, leg discoloration, swelling of the entire limb)
Extensive thrombosis (> 5 cm in length, involving multiple veins, > 7 mm in diameter)
Thrombosis close to the proximal veins
No reversible provoking factor (ie, no transient or persistent risk factor up to 3 months before venous thromboembolic event)
Active cancer (newly diagnosed cancer or cancer being treated with surgery, chemotherapy, radiotherapy, hormonal therapy, support therapy for terminal cancer, or combined treatments)
History of venous thromboembolism
Prolonged immobility (> 3 days)
Patient currently has COVID-19 infection

Based on information in references 1, 7–9.

TABLE 2
Risk factors for major bleeding on anticoagulation

Age greater than 75
Recent major bleeding, ie, requiring transfusion of 2 or more units of blood; retroperitoneal, spinal, or intracranial bleeding
Severe liver dysfunction (baseline abnormal prothrombin time)
Severe renal impairment (creatinine clearance rate < 30 mL/min)
Severe thrombocytopenia (platelet count < 50 × 10^9/L)
Cancer
Acute hemorrhagic stroke or cerebral lesions at high risk of bleeding
Severe uncontrolled hypertension

Based on information in references 1, 8, 11, 13, and 14.

In a population-based study, the most common risk factors for VTE included limited mobility for more than 48 hours in the past 30 days (defined as, at most, from bed to chair or bathroom), recent or current hospitalization, recent surgery, recent infection, and active malignancy.[4] The annual diagnosis rate for lower-extremity superficial vein thrombosis (SVT) was 0.64% in a prospective study. [5] The diagnosis rate increased with age, and SVT was more common in women. Patients at greater risk of developing SVT include women older than age 60 and individuals with obesity, pregnancy, smoking, infection, chronic venous insufficiency, and varicose veins.[5]

LOCATION OF THE THROMBOSIS

Isolated distal thrombosis

Isolated distal DVT ("calf DVT") is VTE below the popliteal vein.[6] The 2021 CHEST guidelines[1] recommend anticoagulation for at least 3 months for patients with a high risk of thrombus extension (**Table 1**)[1,7–9] as these patients are at greater risk of progression to proximal DVT and pulmonary embolism.[1]

In contrast, patients with a low risk of thrombus extension (ie, they do not meet the criteria in **Table 1**) should be monitored for extension with serial ultrasonography once weekly for 2 weeks, as well as for worsening of symptoms.[1] However, this is a weak recommendation with moderate-certainty evidence.[1] In patients for whom the inconvenience of weekly imaging outweighs the potential bleeding risk, anticoagulation for 3 months is a reasonable alternative.[1]

When the decision is to monitor with serial duplex venous ultrasonography, patients without extension of the thrombus require no anticoagulation, a strong recommendation with moderate-certainty evidence.[1] Proximal propagation (ie, to the popliteal vein or higher) occurs in 8% to 15% of cases of isolated distal DVT followed with duplex ultrasonography surveillance.[10] For patients with evidence of proximal extension, there is a strong recommendation to anticoagulate for 3 months.[1]

A retrospective study showed that 9 of 212 patients monitored with Doppler ultrasonography had new DVT in a distal branch of the original lesion.[7] For extension confined to distal veins or for new distal thrombosis, the recommendation is to anticoagulate for 3 months, but this is a weak recommendation with a very low certainty of evidence.[1]

Proximal deep vein thrombosis

Proximal DVT is defined as thrombus in the popliteal, femoral, or iliac veins.[7,11] The 2021 CHEST guidelines recommend treating proximal DVT with anticoagulation for at least 3 months.[1,6] Proximal DVT confers up to a 50% risk of pulmonary embolism if left untreated,[12] so treatment with anticoagulation is recommended even in the absence of symptoms ("incidental DVT").[1,11]

Use of an inferior vena cava filter should be considered only in patients deemed to have an unacceptably high bleeding risk (**Table 2**).[1,8,11,13,14] Because the filters confer significant risk (eg, occlusion, inferior vena cava strut penetration, filter embolization, movement or

fracture, and complications of insertion), it should be removed as soon as possible after anticoagulation is resumed.[1,13]

Superficial vein thrombosis

SVT is defined as thrombus involving superficial veins of the upper or lower extremities.[15] The 2021 CHEST guidelines recommend treatment of patients with SVT having high-risk features (**Table 3**)[1,15,16] with 45 days of anticoagulation (weak recommendation based on moderate-certainty evidence).[1] Patients with SVT and high-risk features should also be screened for DVT with bilateral ultrasonography due to the high likelihood of undiagnosed DVT.[15] Patients with SVT who do not have high-risk features do not require additional treatment with anticoagulation or screening for DVT. Anticoagulant therapy is generally not recommended to treat SVT associated with intra-venous therapy.[1]

It is important to note that patients with DVT and SVT should be screened for signs and symptoms of pulmonary embolism because of the risk of progression from SVT to DVT and subsequently to pulmonary embolism.[15] One study reported concomitant symptomatic pulmonary embolism in 4.7% of patients with SVT at the time of presentation.[5] Another study reported concomitant pulmonary embolism in approximately half of patients with DVT.[17]

TABLE 3
High-risk features of superficial vein thrombosis

Extensive superficial vein thrombosis (> 5 cm)
Involvement above the knee, particularly if 3 cm or less from the saphenofemoral junction
Severe symptoms
Involvement of the greater saphenous vein
History of venous thromboembolism
Active cancer
Recent surgery

Based on information in references 1, 15, and 16.

POSTTHROMBOTIC SYNDROME PREVENTION

Postthrombotic syndrome is a common complication of lower-extremity DVT, reported in 20% to 50% of patients after proximal DVT.[18,19] Previous CHEST guidelines had recommended the use of compression stockings in patients with DVT to reduce the likelihood of developing postthrombotic syndrome.[11] However, the 2021 CHEST guidelines[1] and the 2023 National Institute for Health and Care Excellence guidelines[20] no longer recommend this practice.

OUTPATIENT ANTICOAGULATION THERAPIES FOR VTE

Oral anticoagulants used in the treatment of VTE include the direct oral anticoagulants (DOACs) apixaban, rivaroxaban, edoxaban, and dabigatran, and the vitamin K antagonist warfarin. Parenteral options include low-molecular-weight heparin (LMWH) and fondaparinux. The choice of agent depends on comorbidities, renal and liver function, risk of bleeding, affordability, and patient preferences (**Table 4**).[11,21–24]

DOACs offer a predictable anticoagulation effect with fixed dosing and do not require laboratory monitoring.[21] However, they should be used with caution in patients with renal and hepatic dysfunction. They are also significantly more expensive than warfarin.[25]

Warfarin requires frequent laboratory monitoring and dosing adjustments to ensure that the international normalized ratio is within therapeutic range. It also has many drug-drug interactions, requires dietary restrictions, causes fluctuations in the international normalized ratio, and can increase the risk of bleeding or recurrent thrombosis, as well as first events in patients taking it for other indications such as atrial fibrillation.[21,22]

The 2021 CHEST guidelines recommend the use of DOACs over warfarin whenever possible, based on data showing a lower risk of major bleeding (especially intracranial hemorrhage) with DOACs vs warfarin (strong recommendation with moderate-certainty evidence).[1,21]

The 2021 CHEST guidelines recommend fondaparinux as the agent of choice for the treatment of SVT, but rivaroxaban is an acceptable alternative.[1,24] A randomized trial showed that fondaparinux was associated with a lower incidence of SVT extension compared with placebo in patients with acute symptomatic SVT of the legs.[26] The SURPRISE trial (Superficial Vein thrombosis Treated for Forty-five Days With Rivaroxaban Versus Fondaparinux) found rivaroxaban to be noninferior to fondaparinux for the treatment of SVT in terms of development of symptomatic DVT or pulmonary embolism, progression or recurrence of SVT, and all-cause mortality, and was not associated with more major bleeding.[24]

TABLE 4
Comparison of outpatient anticoagulant drugs

	Vitamin K antagonists	Direct oral anticoagulants				Parenteral anticoagulation	
	Warfarin	Dabigatran	Apixaban	Rivaroxaban	Edoxaban	Low-molecular-weight heparins	Fondaparinux
Target	Vitamin K	Thrombin	Factor Xa	Factor Xa	Factor Xa	Antithrombin III	Factor Xa
Dosing	Once daily	Twice daily	Twice daily	Once daily	Once daily	Once or twice daily	Once daily
Monitoring needed	Yes (INR)	No	No	No	No	No	No
Comorbidity-specific recommendations	Recommended for patients with antiphospholipid syndrome	Recommended for patients with active cancer with no gastrointestinal or genitourinary involvement: rivaroxaban, apixaban, or edoxaban Recommended for patients with cancer with gastrointestinal or genitourinary involvement: apixaban For patients with recent acute coronary syndrome, avoid dabigatran				Recommended for patients with active cancer and for pregnant patients	Recommended for patients with high-risk superficial vein thrombosis
Liver dysfunction considerations	Can be used in patients with increased prothrombin time or INR	Avoid in patients with increased prothrombin time or INR				Can be used in patients with increased prothrombin time or INR	Recommended for patients with high-risk superficial vein thrombosis; use with caution, monitor closely for signs of bleeding
Renal dysfunction considerations	Can be used in patients with creatinine clearance rate < 30 mL/min	For patients with creatinine clearance 30–50 mL/min, preferred agents are rivaroxaban, apixaban, or edoxaban Avoid all direct oral anticoagulants in patients with creatinine clearance rate < 30 mL/min				Use doses adjusted for renal function as recommended in product labeling	Avoid in patients with creatinine clearance rate < 30 mL/min

INR = international normalized ratio

Based on information in references 11 and 21–24.

SPECIAL PATIENT POPULATIONS

Cancer-associated thrombosis

Patients with cancer have a markedly increased risk of thromboembolism and bleeding.[27,28] In patients with cancer-associated VTE, oral factor Xa inhibitors (apixaban, edoxaban, rivaroxaban) are recommended over LMWH or vitamin K antagonists because of the oral administration of DOACs and their safety and efficacy without the need for laboratory monitoring.[1] In a recent meta-analysis of patients with cancer-associated VTE, oral factor Xa inhibitors reduced the risk of recurrent VTE similarly to LMWH, without a significantly higher likelihood of major bleeding.[27]

Patients with gastrointestinal and genitourinary malignancies may constitute an exception to the above recommendation, as there is an increased risk of bleeding in these patients with use of rivaroxaban and edoxaban when compared with LMWH,[29–31] but apixaban seems to be noninferior to LMWH, with no increased risk of major bleeding.[1,30] Thus, apixaban or LMWH is recommended in patients with high risk for mucosal bleeding.[1,30] Vitamin K antagonists are not favored in patients with cancer-associated thrombosis given the moderate-certainty evidence that LMWH is more effective in reducing recurrence of VTE, as well as the difficulty with maintaining a therapeutic range. In addition, LMWH would be easier to withhold or adjust

TABLE 5
2021 American College of Chest Physicians guidelines on duration of anticoagulation for deep vein thrombosis, based on risk factors for venous thromboembolism

Risk factors[a]	Recommendation
Major transient risk factors, occurring up to 3 months before the thrombotic event: • Surgery with general anesthesia for longer than 30 minutes • Confined to bed in hospital (only "bathroom privileges") for at least 3 days with an acute illness • Cesarean delivery	The guidelines recommend against offering extended-phase anticoagulation (strong recommendation, moderate-certainty evidence)
Minor transient risk factors, occurring up to 2 months before the thrombotic event: • Surgery with general anesthesia for less than 30 minutes • Admission to hospital for less than 3 days with an acute illness • Estrogen therapy • Pregnancy or puerperium • Confined to bed out of hospital for at least 3 days with an acute illness • Leg injury associated with reduced mobility for at least 3 days	The guidelines suggest against offering extended-phase anticoagulation (weak recommendation, moderate-certainty evidence) In patients with venous thromboembolism diagnosed in the absence of a transient provoking factor, offer extended-phase anticoagulation with a DOAC (strong recommendation, moderate-certainty evidence)
Persistent risk factors: • Active cancer (untreated, ongoing treatment or no potential curative treatment) • Inflammatory bowel disease • Antiphospholipid syndrome	In patients with antiphospholipid syndrome, vitamin K antagonists are suggested over DOACs as first-line treatment (weak recommendation with low-certainty evidence); a vitamin K antagonist can be offered for patients who can't receive or who decline DOACs (weak recommendation, moderate-certainty evidence)
Unprovoked thrombotic event (no transient or persistent risk factor identified)	The guidelines recommend offering extended-phase anticoagulation with a DOAC (strong recommendation, moderate-certainty evidence); in patients who can't receive a DOAC, extended-phase anticoagulation with a vitamin K antagonist is recommended (weak recommendation, moderate-certainty evidence)

[a]Previous venous thromboembolism is not mentioned clearly in the guidelines as affecting the duration of treatment.

DOAC = direct oral anticoagulant

Based on information in references 1 and 34.

than vitamin K antagonists for invasive interventions, if needed.[1]

Antiphospholipid syndrome-associated thrombosis

Patients with antiphospholipid syndrome are at increased risk of VTE as well as arterial thrombosis.[32] The use of DOACs to treat VTE in antiphospholipid syndrome is not well studied, but emerging data suggest a higher risk of arterial thrombosis with DOACs than with vitamin K antagonists.[32] Current recommendations favor the use of vitamin K antagonists over DOACs for VTE treatment in these patients, especially those with triple-positive antiphospholipid syndrome (presence of lupus anticoagulant, anticardiolipin, and anti-beta-2-glycoprotein 1 antibodies).[1,33] If patients experience a thrombotic event while on a therapeutic dose of warfarin, treatment options include increasing the target international normalized ratio, LMWH, and fondaparinux, or the addition of an antiplatelet agent.[1]

DURATION OF TREATMENT

When anticoagulation is indicated in patients with DVT, treatment should continue for at least 3 months after the initial thrombotic episode.[1] Anticoagulation beyond 3 months, without a specific end date, is recommended for patients at particularly high risk of recurrence (**Table 5**)[1,34] or for those with a history of prior VTE.[1] Regardless of initial risk factors, a reassessment of risk for VTE recurrence, risk of bleeding, and patient preferences should be pursued annually and at times of significant changes in health status.[1]

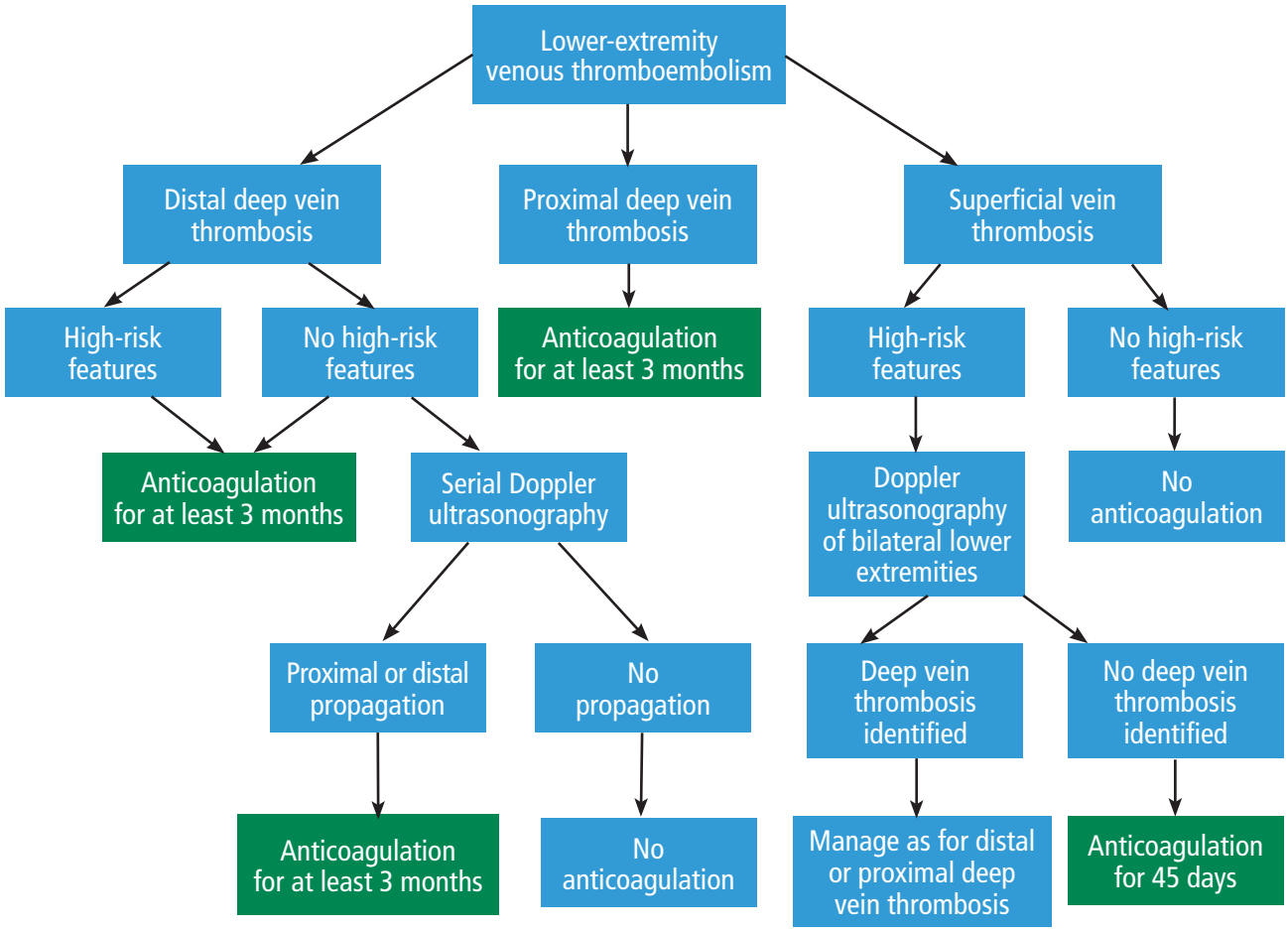


Figure 1. Approach to lower-extremity venous thromboembolism.

Based on information in references 1,15, 24, and 26.

For extended anticoagulation, a reduced dose of apixaban or rivaroxaban is recommended (weak recommendation with a very low certainty of evidence).[1]

AN ALGORITHMIC APPROACH TO MANAGEMENT OF LOWER-EXTREMITY VTE

Figure 1 summarizes the various considerations in the management of patients with distal, proximal, and superficial lower-extremity VTE.[1,15,24,26]

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Stevens SM, Woller SC, Kreuziger LB, et al.** Antithrombotic therapy for VTE disease: second update of the CHEST Guideline and Expert Panel report [published correction appears in Chest 2022; 162(1):269]. Chest 2021; 160(6):e545–e608. doi:10.1016/j.chest.2021.07.055
2. **US Centers for Disease Control and Prevention.** Data and statistics on venous thromboembolism. Updated June 28, 2023. www.cdc.gov/ncbddd/dvt/data.html. Accessed March 12, 2024.
3. **Palareti G.** How I treat isolated distal deep vein thrombosis (IDDVT). Blood 2014; 123(12):1802–1809. doi:10.1182/blood-2013-10-512616
4. **Spencer FA, Emery C, Lessard D, et al.** The Worcester Venous Thromboembolism Study: a population-based study of the clinical epidemiology of venous thromboembolism. J Gen Intern Med 2006; 21(7):722–727. doi:10.1111/j.1525-1497.2006.00458.x
5. **Frappé P, Buchmuller-Cordier A, Bertoletti L, et al.** Annual diagnosis rate of superficial vein thrombosis of the lower limbs: the STEPH community-based study [published correction appears in J Thromb Haemost 2015; 13(8):1538]. J Thromb Haemost 2014; 12(6):831–838. doi:10.1111/jth.12575

6. **Robert-Ebadi H, Righini M.** Management of distal deep vein thrombosis. Thromb Res 2017; 149:48–55. doi:10.1016/j.thromres.2016.11.009
7. **Fujioka S, Ohkubo H, Kitamura T, et al.** Risk factors for progression of distal deep vein thrombosis. Circ J 2020; 84(10):1862–1865. doi:10.1253/circj.CJ-20-0270
8. **Nieto JA, Solano R, Ruiz-Ribó MD, et al.** Fatal bleeding in patients receiving anticoagulant therapy for venous thromboembolism: findings from the RIETE registry. J Thromb Haemost 2010; 8(6):1216–1222. doi:10.1111/j.1538-7836.2010.03852.x
9. **Sartori M, Favaretto E, Cosmi B.** Relevance of immobility as a risk factor for symptomatic proximal and isolated distal deep vein thrombosis in acutely ill medical inpatients. Vasc Med 2021; 26(5):542–548. doi:10.1177/1358863X21996825
10. **Masuda EM, Kistner RL.** The case for managing calf vein thrombi with duplex surveillance and selective anticoagulation. Dis Mon 2010; 56(10):601–613. doi:10.1016/j.disamonth.2010.06.011
11. **Kearon C, Akl EA, Comerota AJ, et al.** Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines [published correction appears in Chest 2012; 142(6):1698–1704]. Chest 2012; 141(2 suppl):e419S–e496S. doi:10.1378/chest.11-2301
12. **Kearon C.** Natural history of venous thromboembolism. Circulation 2003; 107(23 suppl 1):I22–I30. doi:10.1161/01.CIR.0000078464.82671.78
13. **Duffett L, Carrier M.** Inferior vena cava filters. J Thromb Haemost 2017; 15(1):3–12. doi:10.1111/jth.13564
14. **DeYoung E, Minocha J.** Inferior vena cava filters: guidelines, best practice, and expanding indications. Semin Intervent Radiol 2016; 33(2):65–70. doi:10.1055/s-0036-1581088
15. **Beyer-Westendorf J.** Controversies in venous thromboembolism: to treat or not to treat superficial vein thrombosis. Hematology Am Soc Hematol Educ Program 2017; 2017(1):223–230. doi:10.1182/asheducation-2017.1.223
16. **Leizorovicz A, Becker F, Buchmüller A, et al.** Clinical relevance of symptomatic superficial-vein thrombosis extension: lessons from the CALISTO study. Blood 2013; 122(10):1724–1729. doi:10.1182/blood-2013-04-498014
17. **Lee JS, Moon T, Kim TH, et al.** Deep vein thrombosis in patients with pulmonary embolism: prevalance, clinical significance and outcome. Vasc Specialist Int 2016; 32(4):166–174. doi:10.5758/vsi.2016.32.4.166
18. **Galanaud JP, Monreal M, Kahn SR.** Epidemiology of the post-thrombotic syndrome. Thromb Res 2018; 164:100–109. doi:10.1016/j.thromres.2017.07.026
19. **Appelen D, van Loo E, Prins MH, Neumann MH, Kolbach DN.** Compression therapy for prevention of post-thrombotic syndrome. Cochrane Database Syst Rev 2017; 9(9):CD004174. doi:10.1002/14651858.CD004174.pub3
20. **National Institute for Health and Care Excellence (NICE).** Venous thromboembolic diseases: diagnosis, management and thrombophilia testing. London: National Institute for Health and Care Excellence (NICE); August 2, 2023. https://www.ncbi.nlm.nih.gov/books/NBK556698/. Accessed March 12, 2024.
21. **Yeh CH, Gross PL, Weitz JI.** Evolving use of new oral anticoagulants for treatment of venous thromboembolism. Blood 2014; 124(7):1020–1028. doi:10.1182/blood-2014-03-563056
22. **Witt DM, Nieuwlaat R, Clark NP, et al.** American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy. Blood Adv 2018; 2(22):3257–3291. doi:10.1182/bloodadvances.2018024893
23. **GoodRx, Inc.** Stop paying too much for prescriptions. www.goodrx.com. Accessed March 12, 2024.
24. **Beyer-Westendorf J, Schellong SM, Gerlach H, et al.** Prevention of thromboembolic complications in patients with superficial-vein thrombosis given rivaroxaban or fondaparinux: the open-label, randomised, non-inferiority SURPRISE phase 3b trial. Lancet Haematol 2017; 4(3):e105–e113. doi:10.1016/S2352-3026(17)30014-5
25. **Ortel TL, Neumann I, Ageno W, et al.** American Society of Hematology 2020 guidelines for management of venous thromboembolism: treatment of deep vein thrombosis and pulmonary embolism. Blood Adv 2020; 4(19):4693–4738. doi:10.1182/bloodadvances.2020001830
26. **Decousus H, Prandoni P, Mismetti P, et al.** Fondaparinux for the treatment of superficial-vein thrombosis in the legs. N Engl J Med 2010; 363(13):1222–1232. doi:10.1056/NEJMoa0912072
27. **Wang X, Ma Y, Hui X, et al.** Oral direct thrombin inhibitors or oral factor Xa inhibitors versus conventional anticoagulants for the treatment of deep vein thrombosis. Cochrane Database Syst Rev 2023; 4(4):CD010956. doi:10.1002/14651858.CD010956.pub3
28. **Prandoni P, Lensing AW, Piccioli A, et al.** Recurrent venous thromboembolism and bleeding complications during anticoagulant treatment in patients with cancer and venous thrombosis. Blood 2002; 100(10):3484–3488. doi:10.1182/blood-2002-01-0108
29. **Key NS, Khorana AA, Kuderer NM, et al.** Venous thromboembolism prophylaxis and treatment in patients with cancer: ASCO clinical practice guideline update. J Clin Oncol 2020; 38(5):496–520. doi:10.1200/JCO.19.01461
30. **Agnelli G, Becattini C, Meyer G, et al.** Apixaban for the treatment of venous thromboembolism associated with cancer. N Engl J Med 2020; 382(17):1599–1607. doi:10.1056/NEJMoa1915103
31. **Raskob GE, van Es N, Verhamme P, et al.** Edoxaban for the treatment of cancer-associated venous thromboembolism. N Engl J Med 2018; 378(7):615–624. doi:10.1056/NEJMoa1711948
32. **Woller SC, Stevens SM, Kaplan D, et al.** Apixaban compared with warfarin to prevent thrombosis in thrombotic antiphospholipid syndrome: a randomized trial. Blood Adv 2022; 6(6):1661–1670. doi:10.1182/bloodadvances.2021005808
33. **Zuily S, Cohen H, Isenberg D, et al.** Use of direct oral anticoagulants in patients with thrombotic antiphospholipid syndrome: guidance from the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. J Thromb Haemost 2020; 18(9):2126–2137. doi:10.1111/jth.14935
34. **Kearon C, Ageno W, Cannegieter SC, et al.** Categorization of patients as having provoked or unprovoked venous thromboembolism: guidance from the SSC of ISTH. J Thromb Haemost 2016; 14(7):1480–1483. doi:10.1111/jth.13336

Address: *Yael Mauer, MD, MPH, Cleveland Clinic Beachwood Family Health and Surgery Center, 26900 Cedar Road, Beachwood, OH 44122; mauery@ccf.org*

Cleveland Clinic

BEYOND THE PAGES:
Cleve Clin J Med Podcast

"Beyond the Pages: Cleve Clin J Med Podcast" takes you in depth into Cleveland Clinic Journal of Medicine articles. Through moderated interviews with the authors and article reviews by experts in the field, clinicians can have an even better understanding of clinical breakthroughs that are changing the practice of medicine and how to practically apply them in patient care.

Listen today!

www.ccfcme.org/CCJMpodcast

This activity has been approved for *AMA PRA Category 1 Credit*™.

Tara K. Iyer, MD, MSCP
Director, Menopause and Midlife Clinic, Division of Women's Health, Department of Medicine, Brigham and Women's Hospital, Boston, MA; Instructor of Medicine, Harvard Medical School, Boston, MA

Alexa N. Fiffick, DO, MBS, MSCP
CEO, Founder of Concierge Medicine of Westlake, Westlake, OH; Associate Director of Education, Ms.Medicine; Menopause Expert, Menopause Mandate US

Pelin Batur, MD, FACP, MSCP
Department of Subspecialty Care for Women's Health, Obstetrics and Gynecology Institute, Cleveland Clinic, Cleveland, OH; Professor, OB/GYN and Reproductive Biology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Nonhormone therapies for vasomotor symptom management

ABSTRACT

Vasomotor symptoms (VMS) are associated with adverse health consequences and can cause significant morbidity for postmenopausal women. Although hormone therapy remains the gold standard of VMS treatment in menopausal women, some women have contraindications to or may choose not to take hormone therapy. This article provides an up-to-date overview of the current evidence-based nonhormone therapies available for managing VMS. Evidence supporting various treatment options is reviewed, including lifestyle interventions, mind-body therapies, procedures, pharmacologic agents, and emerging therapies, such as neurokinin-receptor antagonists. The efficacy, safety, and clinical use of these treatments are detailed, offering insights for clinicians to make informed decisions in menopausal VMS management.

KEY POINTS

- VMS in menopausal women can lead to adverse health outcomes.
- Many complementary and alternative therapies for treating VMS lack strong scientific evidence.
- Nonhormone pharmacologic agents including some selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors, gabapentin, and oxybutynin are commonly used and effective for VMS treatment.
- Fezolinetant, a VMS medication newly approved by the US Food and Drug Administration, is a neurokinin-receptor antagonist that reduces hot flashes by modulating kisspeptin, neurokinin B, and dynorphin neurons in the hypothalamus.

doi:10.3949/ccjm.91a.23067

Vasomotor symptoms (VMS), more commonly known as hot flushes or flashes and night sweats, are the cardinal symptoms of menopause, occurring in up to 80% of postmenopausal women.[1,2] Apart from being disruptive and bothersome, VMS may independently have adverse health consequences associated with cardiovascular and metabolic changes, including increased carotid intima thickness, increased carotid and aortic calcifications, worsening lipid profiles, increased insulin resistance, and increased risk of hypertension.[3–6] Additionally, VMS have been linked to decreased bone mineral density and increased fracture incidence.[7,8]

Although hormone therapy is considered the gold standard of treatment of VMS in menopausal women, a woman may not want, or may not be a candidate (**Table 1**), to take hormone therapy for several reasons. Thus, it is important that nonhormone treatment options be made available to control symptoms, either alone or in combination with hormone therapy.

This review details various nonhormone therapies, both currently available and on the horizon, for menopausal VMS, with an emphasis on the appropriate clinical utilization, efficacy, and safety of pharmacologic agents.

NONPRESCRIPTION, COMPLEMENTARY, AND ALTERNATIVE THERAPIES

Use of complementary and alternative therapies for management of menopausal symptoms has increased over the past few decades, but concerns regarding their safety and effectiveness persist. Evidence regarding complementary and alternative therapies is often lacking, as

TABLE 1
Contraindications to hormone therapy

Contraindications	Pertinent considerations
Prior history of coronary heart disease, stroke, myocardial infarction, or unprovoked venous thromboembolism or inherited high risk of thromboembolic disease, or significantly high risk for cardiovascular disease	Relative contraindication: hormone therapy can be considered on a case-by-case basis
Unexplained vaginal bleeding	Relative contraindication: unexplained vaginal bleeding should be evaluated before hormone therapy is considered
End-stage liver disease	Relative contraindication: hormone therapy can be considered on a case-by-case basis
Prior history of estrogen-receptor-positive cancer	Absolute contraindication

many studies of these therapies have methodological deficiencies. Additionally, there are few randomized, sham, or placebo-controlled trials, which are critical in the appraisal of these therapies given the preponderance of data suggesting that placebo interventions improve VMS.[9]

The Menopause Society, formerly known as the North American Menopause Society, recommends certain evidence-based lifestyle interventions, mind-body therapies, and procedures for managing VMS.[10,11] Randomized controlled trials have demonstrated that weight loss may be effective for reducing VMS, particularly earlier in the menopause transition.[12,13] Cognitive behavioral therapy has been shown in various studies to effectively reduce the degree to which women perceive VMS as a problem.[11] Multiple studies have demonstrated that group and self-guided cognitive behavioral therapy, when compared with usual care or no active intervention, resulted in improvements in bothersome VMS, hot flash interference, and depressive symptoms.[11,14,15] Although the studies generally lacked rigorous controls, the overall body of evidence supports cognitive behavioral therapy as a recommended treatment for bothersome VMS.[11] Two separate 5-week-long randomized controlled trials demonstrated that when compared with controls, clinical hypnosis reduced the severity and frequency of VMS and also improved mood and sleep.[11,16,17]

Stellate ganglion blockade, a widely used treatment for pain management that involves injecting an anesthetic agent in the lower cervical or upper thoracic region to target the stellate ganglion, has shown potential for alleviating VMS in menopausal women. A randomized sham-controlled trial (N = 40) demonstrated a reduction in VMS intensity and frequency with stellate ganglion block, measured subjectively by patient report and objectively with ambulatory skin conductance monitors, when compared with sham controls.[18] Multiple studies have additionally reported reductions in VMS with stellate ganglion block.[19–21]

Moreover, a study in patients with breast cancer (N = 40) demonstrated comparable efficacy between stellate ganglion blockade and paroxetine 7.5 mg daily for VMS reduction.[22] While adverse events (bleeding, transient seizures) are rare and minimized with imaging guidance, they can be serious.[11] As such, larger randomized controlled trials are warranted to provide more conclusive evidence regarding the risk-benefit ratio of stellate ganglion block in VMS management.

Though complementary and alternative therapies such as trigger avoidance, cooling techniques, dietary modification, exercise, mindfulness-based interventions, acupuncture and electroacupuncture, and yoga have shown potential benefit, additional research is needed to confirm their effectiveness.[10,11] Chiropractic treatments and paced respiration have not been shown to be effective.[11] Additionally, there is currently negative, inconclusive, or insufficient evidence regarding the use of soy foods, S-equol, other soy extracts and derivatives, cannabinoids, and herbal supplements (eg, black cohosh, ashwagandha, evening primrose oil) for the reduction of VMS.[10,11] While black cohosh is not currently recommended, women who choose to take it should be counseled about its potential hepatotoxicity.

NONHORMONE PHARMACOLOGIC AGENTS

Although not as efficacious as hormone therapy, nonhormone medications remain a valuable tool for VMS relief. Pharmacologic agents found to be effective

compared with placebo for VMS treatment include selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), gabapentinoids, oxybutynin, clonidine, and a newer class of medications known as neurokinin-receptor antagonists. It is essential to note that these medications are not mutually exclusive and may be judiciously combined, while considering tolerability and effectiveness, to improve control of VMS frequency and severity. Apart from neurokinin-receptor antagonists, the precise mechanism of how each of the listed nonhormone medications reduces the burden of VMS has not yet been clearly elucidated.

SSRIs and SNRIs

SSRIs and SNRIs demonstrate mild to moderate improvement of VMS.[10,11,23,24] While limited by variability in criteria, dosing, and outcomes, large randomized, double-blind, placebo-controlled trials have found that paroxetine, escitalopram, citalopram, venlafaxine, desvenlafaxine, and duloxetine reduced hot flashes by 24% to 69% compared with placebo, with composite hot flash frequency and severity improving by 19% to 61%.[10,11,23–25] Sertraline and fluoxetine do not consistently demonstrate reductions in VMS.[24,26,27]

Given these medications are first-line treatments for a variety of mood disorders, SSRIs and SNRIs may be beneficial for patients with concurrent mood issues, such as worsening or new-onset depression or anxiety, both of which are common in peri- and postmenopausal patients.[10] As noted in **Table 2**, low doses of SSRIs and SNRIs typically control VMS compared with the higher doses that may be needed for management of mood symptoms.[10,11,23–35]

SNRIs, especially duloxetine, which is approved by the US Food and Drug Administration for the treatment of fibromyalgia and chronic musculoskeletal pain, are frequently used to treat chronic somatic pain conditions.[36–38] As such, they could be considered a good option for the treatment of VMS in patients with prominent menopause-related arthralgia. Because nonhormone medications are often used to treat VMS in breast cancer survivors, it is important to note that paroxetine and fluoxetine are potent cytochrome P450 CYP2D6 (the enzyme that converts tamoxifen to its most active metabolite) inhibitors and should not be used with tamoxifen, as they would reduce tamoxifen's bioavailability and efficacy.[10]

Although low doses of SSRIs and SNRIs are generally well-tolerated and effective in the management of hot flashes, the possible side-effect profile of these medications must be considered. The most commonly reported bothersome side effects of SSRIs and SNRIs are nausea, gastrointestinal disturbances, sleep disturbances, weight changes, sexual dysfunction, and headache.[39,40] Particularly with regard to weight and sexual dysfunction, these side effects may be dose-dependent, as a randomized placebo-controlled trial found that low-dose paroxetine (7.5 mg) did not cause weight gain or negative libido changes for up to 24 weeks.[41] Given that weight gain, sexual dysfunction, and sleep disturbances are frequently reported menopausal symptoms, it is imperative that clinicians counsel patients on these possibilities before initiating treatment.

Of note, at the comparatively higher doses of SSRIs and SNRIs used to alleviate mood symptoms, these agents can increase VMS or diaphoresis, which is often more pronounced with SNRIs than with SSRIs because of their specific norepinephrine binding and stimulation.[39,40,42] Additionally, it is crucial to counsel patients that SSRIs and SNRIs should not be abruptly discontinued, as this may lead to severe withdrawal side effects.

Gabapentinoids (gabapentin and pregabalin)

Multiple randomized controlled trials have shown that when compared with placebo, gabapentin is effective at reducing hot flash frequency by 54% and hot flash composite score (combined hot flash frequency and severity score) by 31% to 51%.[28–30]

Gabapentin is helpful in patients with a history of neuropathic pain issues, and when dosed before bedtime, can be an effective sleep aid.[10,11] The most pertinent side effects of gabapentin to consider before initiation include dizziness or coordination difficulties (thus, possible increase in fall risk), edema, drowsiness, lethargy, weight gain, nausea, and gastrointestinal disturbances.[10,11,28–31] Because fatigue and weight gain are often experienced by menopausal women, a commonly used strategy to minimize negative or compounding side effects of gabapentin is to use the lowest effective dose or nightly dosing.[11]

Current recommendations from the Menopause Society no longer support pregabalin as a treatment for reducing VMS owing to limited evidence.[11]

Oxybutynin

Evidence from several randomized controlled trials supports the effectiveness of oxybutynin in treating hot flashes, showing reduction in hot flash frequency by up to 70% to 86%.[23,24,43] Oxybutynin is an effective treatment for overactive bladder symptoms, which can increase in hypoestrogenic states. As such, it may be an ideal choice for women with prominent urinary

TABLE 2
Nonhormone pharmacologic agents currently available for management of vasomotor symptoms

Class	Medication	Dosing for VMS[a]	Clinical pearls
SSRIs	Paroxetine salt[10,11,23,24]	7.5 mg daily at bedtime	Potent cytochrome P450 CYP2D6 enzyme inhibitors; do not use with tamoxifen as SSRIs reduce tamoxifen bioavailability and efficacy
	Paroxetine[10,11,23,24]	10–25 mg daily	
	Fluoxetine[11,23,24,26]	10–30 mg daily	Paroxetine mesylate 7.5 mg was the first and only US Food and Drug Administration–approved nonhormone medication for moderate to severe menopausal VMS until the development of neurokinin-receptor antagonists
	Sertraline[11,23,24,27]	25–100 mg daily	
	Citalopram[10,11,23,24]	10–20 mg daily	Fluoxetine and sertraline are not recommended for VMS reduction owing to inconsistent data regarding efficacy in hot flash frequency and severity reduction
	Escitalopram[10,11,23–25]	10–20 mg daily	
			Sertraline has a moderate effect on the CYP2D6 enzyme
			Citalopram and escitalopram may cause QT prolongation
SNRIs	Desvenlafaxine[10,11,23,24]	100–150 mg daily	SNRIs may increase blood pressure, use with caution in patients with hypertension
	Venlafaxine[10,11,23,24]	37.5–75 mg daily	Venlafaxine is the most well studied SNRI in combination with tamoxifen
	Duloxetine[11,23,25]	30–60 mg daily	
			Duloxetine has a moderate effect on the CYP2D6 enzyme
Gabapentinoid	Gabapentin[10,11,28–31]	300–2,400 mg daily (divided doses)	Consider for patients with a history of neuropathic pain or sleep concerns
			Consider nightly dosing (starting dose of 100–300 mg at bedtime) to minimize any adverse effects of daytime fatigue
Antimuscarinic	Oxybutynin[11,24,31,32]	2.5–5 mg twice a day (immediate release), up to 15 mg/day (extended release)	Consider for patients with concurrent overactive bladder or hyperhidrosis
			Use caution in older adults (≥ 65 years); avoid altogether in patients ≥ 65 years taking concomitant anticholinergic medications
Alpha-2 adrenergic agonist	Clonidine[11,32,33]	0.05–0.1 mg once or twice a day	Consider for patients with hypertension, especially if improved blood pressure control is desired
			Avoid in older adult patients (≥ 65 years)
			Less often used and no longer recommended by the Menopause Society owing to modest efficacy vs placebo and side-effect profile
Neurokinin-receptor antagonist	Fezolinetant[11,34,35]	45 mg daily	Exercise caution in patients taking concomitant CYP1A2 enzyme inhibitors, which increase potency of fezolinetant
			Check transaminase levels at baseline, 3 months, 6 months, and 9 months

[a]Based on clinical efficacy demonstrated in randomized controlled trials and the Menopause Society recommendations.[10,11]

SNRI = serotonin-norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitors; VMS = vasomotor symptoms

conditions and VMS. Common side effects include dry mouth and eyes, urinary retention, dizziness, drowsiness, constipation, vision changes, and nausea.[43,44]

Anticholinergics, including oxybutynin, are noted on the American Geriatrics Society Beers Criteria list as potentially inappropriate medications in adults ages 65 and older owing to an association with impaired cognitive and physical functioning, risk of dementia, and risk of delirium.[32] Multiple case-control studies have linked oxybutynin to an increased incidence of cognitive impairment, consistent with mounting evidence indicating that a high anticholinergic burden elevates the risk of cognitive decline and potentially worsens long-term neurocognitive outcomes.[45–47] While caution should be exercised in the use of oxybutynin in the general population, the use of more than 1 medication with anticholinergic properties should be avoided in older adults.[32]

Of note, extended-release oxybutynin, though potentially more tolerable than immediate-release formulations and effective for VMS management, has been predominantly investigated at a 15-mg daily dose for reducing hot flashes and night sweats.[48] Considering the efficacy of lower doses of immediate-release oxybutynin, ranging from 2.5 to 5 mg twice daily, it is reasonable to contemplate lower-dose, extended-release formulations for VMS reduction.

Clonidine

Multiple studies demonstrate modest improvement in hot flashes with clonidine.[10,11,23,24,33] One randomized, double-blind, placebo-controlled trial demonstrated a 26% decrease in hot flash frequency (P = .045 clonidine vs placebo) in patients with breast cancer. One randomized, double-blind, placebo-controlled trial demonstrated a 38% decrease in hot flash frequency in postmenopausal patients with breast cancer using tamoxifen.[49]

Common side effects of clonidine include fatigue and weakness, headache, dry eyes and mouth, hypotension, dizziness or lightheadedness, and sedation.[11,24] Rebound hypertension and withdrawal symptoms may also occur with abrupt discontinuation of clonidine.[11,23,50] Given the high risk of adverse effects, such as depression of the central nervous system, bradycardia, and orthostatic hypotension, clonidine is included in the 2015 American Geriatrics Society Beers Criteria and it is generally not recommended in patients 65 or older.[32] Additionally, given the significant side-effect burden and lower comparative efficacy with this medication, the Menopause Society has removed it as a recommended nonhormone treatment for menopause.[11]

Neurokinin-receptor antagonists

It has been postulated that VMS are directly caused by estrogen decline or deficiency given that estrogen therapy often eliminates VMS.[51,52] However, this is not the case for all women,[53] and unconjugated serum estrogen levels do not differ between symptomatic and asymptomatic women.[54] Kisspeptin, neurokinin B, and dynorphin (KNDy) neurons are present in the thermoregulatory zone of the hypothalamus, and are noted to be hypertrophied in postmenopausal women.[11,34,54,55] Evidence shows that these neurons play a role in VMS etiology.[55] KNDy neurons are inhibited by estrogen and activated by neurokinin.[55] Therefore, blockade of KNDy neurons is a proposed target for VMS treatment.

Neurokinin-receptor antagonists are a novel group of medications that directly target the thermoregulatory center in the hypothalamus through modulation of KNDy neurons and are currently being studied for VMS relief.

Fezolinetant, a neurokinin-3–receptor antagonist, was found to be safe, well-tolerated, and efficacious for the treatment of moderate to severe VMS and was approved by the US Food and Drug Administration at a dose of 45 mg daily in May 2023.[35] SKYLIGHT 2 was a randomized, double-blind, placebo-controlled, 12-week, phase 3 trial with re-randomization for a 40-week active treatment extension in women ages 40 to 65 experiencing a minimum average of 7 moderate to severe VMS episodes per day.[34] Fezolinetant 45 mg reduced VMS frequency by more than 50% compared with placebo (average 2 to 3 fewer VMS episodes per day) with rapid onset of effect by week 1 and full effect by week 4 that was sustained through week 52.[34] At week 12, VMS frequency was reduced by 93% with fezolinetant and 46% with placebo.[34,56] The 45-mg dose of fezolinetant also demonstrated clinically meaningful improvements in sleep measures.[34]

The most common side effects of fezolinetant in clinical studies included abdominal pain, diarrhea, headache, nausea, and gastrointestinal disturbances.[34,35] Pooled clinical trial data found that approximately 2.3% of patients exposed to fezolinetant 45 mg experienced transaminase elevations.[35] As such, checking alanine aminotransferase and aspartate aminotransferase levels is recommended at baseline, 3 months, 6 months, and 9 months when using this medication.[35]

Contraindications for use of this medication, listed on the package insert, include known cirrhosis, severe renal impairment, and concurrent use with CYP1A2 inhibitors.[35] Given that CYP1A2 inhibitors can significantly increase the potency of fezolinetant, it is

important to assess whether patients are using these pharmacologic agents before starting concomitant medications. Pertinent drugs to consider include caffeine, certain SSRIs (such as fluvoxamine), fluoroquinolone antibiotics, and some estradiol formulations. Of note, although caffeine is considered a weak to moderate CYP1A2 inhibitor, caffeine consumption was not limited in participants of fezolinetant clinical studies and thus caffeine can be used judiciously.[34] Additionally, smoking (a moderate CYP1A2 inducer) does not seem to significantly impact clinical exposure of fezolinetant in concomitant users.[34,35]

Elinzanetant, which acts as an antagonist in both the neurokinin-1 and neurokinin-3 receptors, is not yet commercially available. SWITCH-1 was a multicenter, multicountry, double-blind, phase 2b, adaptive, dose-range–finding study evaluating the safety and efficacy of elinzanetant for VMS management. It found that elinzanetant 120 mg yielded statistically significant reductions vs placebo in VMS frequency and severity at 4 weeks (difference in least square means [SE] −3.93 [1.02]; $P < .001$) and 12 weeks (−2.95 [1.15]; $P = .01$).[57] Clinically meaningful improvements in sleep and quality-of-life measures were also seen.[57] Pending further study, this medication is expected to be available sometime after 2025.

CONCLUSION

Menopausal VMS are often overlooked and undertreated. It is imperative for healthcare professionals to evaluate for and manage VMS in women, ensuring that all available options are presented as viable choices for those experiencing distressing symptoms. Although menopausal hormone therapy remains the gold standard of care for VMS in women under age 60 or within 10 years of menopause without contraindications, clinicians have many nonhormone options to use in conjunction with or instead of menopausal hormone therapy.[58]

The existing literature provides compelling evidence for the efficacy of nonhormone therapies in managing VMS when hormone-based options are not an option or are undesired. Given the wide range of symptoms resulting from ovarian hormone cessation in menopause, clinicians must consider the possible exacerbating ramifications of each pharmacologic agent on other menopausal symptoms when selecting a treatment for VMS. Recently, emerging therapies such as neurokinin-receptor antagonists have shown promise in reducing VMS with few adverse effects. Clinicians should individualize treatment based on patient needs, history, response, and preferences.

Despite the availability of numerous nonhormone and nonpharmacologic options for VMS treatment, many patients still face significant symptom burden owing to limitations in treatment tolerability, efficacy, and access. As such, there remains a pressing need for more effective and safe treatment options for menopausal VMS management.

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Gold EB, Colvin A, Avis N, et al.** Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: Study of Women's Health Across the Nation. Am J Public Health 2006; 96(7):1226–1235. doi:10.2105/AJPH.2005.066936
2. **Nappi RE, Kroll R, Siddiqui E, et al.** Global cross-sectional survey of women with vasomotor symptoms associated with menopause: prevalence and quality of life burden. Menopause 2021; 28(8): 875–882. doi:10.1097/GME.0000000000001793
3. **Thurston RC, El Khoudary SR, Sutton-Tyrrell K, et al.** Vasomotor symptoms and lipid profiles in women transitioning through menopause. Obstet Gynecol 2012; 119(4):753–761. doi:10.1097/AOG.0b013e31824a09ec
4. **Jackson EA, El Khoudary SR, Crawford SL, et al.** Hot flash frequency and blood pressure: data from the Study of Women's Health Across the Nation. J Womens Health (Larchmt) 2016; 25(12):1204–1209. doi:10.1089/jwh.2015.5670
5. **Thurston RC, Chang Y, Barinas-Mitchell E, et al.** Menopausal hot flashes and carotid intima media thickness among midlife women. Stroke 2016; 47(12):2910–2915. doi:10.1161/STROKEAHA.116.014674
6. **Thurston RC, El Khoudary SR, Sutton-Tyrrell K, et al.** Vasomotor symptoms and insulin resistance in the Study of Women's Health Across the Nation. J Clin Endocrinol Metab 2012; 97(10):3487–3494. doi:10.1210/jc.2012-1410
7. **Gast GC, Grobbee DE, Pop VJ, et al.** Vasomotor symptoms are associated with a lower bone mineral density. Menopause 2009; 16(2):231–238. doi:10.1097/gme.0b013e318185e25b
8. **Crandall CJ, Aragaki A, Cauley JA, et al.** Associations of menopausal vasomotor symptoms with fracture incidence. J Clin Endocrinol Metab 2015; 100(2):524–534. doi:10.1210/jc.2014-3062
9. **Li L, Xu L, Wu J, Dong L, Lv Y, Zheng Q.** Quantitative analysis of placebo response and factors associated with menopausal hot flashes. Menopause 2017; 24(8):932–937. doi:10.1097/GME.0000000000000858
10. **The North American Menopause Society Position Statement Advisory Panel.** Nonhormonal management of menopause-associated vasomotor symptoms: 2015 position statement of The North American Menopause Society. Menopause 2015; 22(11):1155–1174. doi:10.1097/GME.0000000000000546
11. **The North American Menopause Society Position Statement Advisory Panel.** The 2023 Nonhormone Therapy Position Statement of The North American Menopause Society Advisory Panel. The 2023 nonhormone therapy position statement of The North American Menopause Society. Menopause 2023; 30(6):573–590. doi:10.1097/GME.0000000000002200

12. **Thurston RC, Ewing LJ, Low CA, Christie AJ, Levine MD.** Behavioral weight loss for the management of menopausal hot flashes: a pilot study. Menopause 2015; 22(1):59–65. doi:10.1097/GME.0000000000000274
13. **Huang AJ, Subak LL, Wing R, et al.** An intensive behavioral weight loss intervention and hot flushes in women [published correction appears in Arch Intern Med 2010; 170(17):1601]. Arch Intern Med 2010; 170(13):1161–1167. doi:10.1001/archinternmed.2010.162
14. **Green SM, Donegan E, Frey BN, et al.** Cognitive behavior therapy for menopausal symptoms (CBT-Meno): a randomized controlled trial. Menopause 2019; 26(9):972–980. doi:10.1097/GME.0000000000001363
15. **Hardy C, Griffiths A, Norton S, Hunter MS.** Self help cognitive behavior therapy for working women with problematic hot flushes and night sweats (MENOS@Work): a multicenter randomized controlled trial. Menopause 2018; 25(5):508–519. doi:10.1097/GME.0000000000001048
16. **Elkins G, Marcus J, Stearns V, et al.** Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors. J Clin Oncol 2008; 26(31):5022–5026. doi:10.1200/JCO.2008.16.6389
17. **Elkins GR, Fisher WI, Johnson AK, Carpenter JS, Keith TZ.** Clinical hypnosis in the treatment of postmenopausal hot flashes: a randomized controlled trial. Menopause 2013; 20(3):291–298. doi:10.1097/gme.0b013e31826ce3ed
18. **Walega DR, Rubin LH, Banuvar S, Shulman LP, Maki PM.** Effects of stellate ganglion block on vasomotor symptoms: findings from a randomized controlled clinical trial in postmenopausal women. Menopause 2014; 21(8):807–814. doi:10.1097/GME.0000000000000194
19. **Pachman DR, Barton D, Carns PE, et al.** Pilot evaluation of a stellate ganglion block for the treatment of hot flashes. Support Care Cancer 2011; 19(7):941–947. doi:10.1007/s00520-010-0907-9
20. **Haest K, Kumar A, Van Calster B, et al.** Stellate ganglion block for the management of hot flashes and sleep disturbances in breast cancer survivors: an uncontrolled experimental study with 24 weeks of follow-up. Ann Oncol 2012; 23(6):1449–1454. doi:10.1093/annonc/mdr478
21. **van Gastel P, Kallewaard J-W, van der Zanden M, de Boer H.** Stellate-ganglion block as a treatment for severe postmenopausal flushing. Climacteric 2013; 16(1):41–47. doi:10.3109/13697137.2012.709889
22. **Rahimzadeh P, Imani F, Nafissi N, Ebrahimi B, Faiz SHR.** Comparison of the effects of stellate ganglion block and paroxetine on hot flashes and sleep disturbance in breast cancer survivors. Cancer Manag Res 2018; 10:4831–4837. doi:10.2147/CMAR.S173511
23. **Biglia N, Bounous VE, De Seta F, Lello S, Nappi RE, Paoletti AM.** Non-hormonal strategies for managing menopausal symptoms in cancer survivors: an update. Ecancermedicalscience 2019; 13:909. doi:10.3332/ecancer.2019.909
24. **Sahni S, Lobo-Romero A, Smith T.** Contemporary non-hormonal therapies for the management of vasomotor symptoms associated with menopause: a literature review. touchREV Endocrinol 2021; 17(2):133–137. doi:10.17925/EE.2021.17.2.133
25. **Biglia N, Bounous VE, Susini T, et al.** Duloxetine and escitalopram for hot flushes: efficacy and compliance in breast cancer survivors. Eur J Cancer Care (Engl) 2018; 27(1):10.1111/ecc.12484. doi:10.1111/ecc.12484
26. **Loprinzi CL, Sloan JA, Perez EA, et al.** Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol 2002; 20(6): 1578–1583. doi:10.1200/JCO.2002.20.6.1578
27. **Grady D, Cohen B, Tice J, Kristof M, Olyaie A, Sawaya GF.** Ineffectiveness of sertraline for treatment of menopausal hot flushes: a randomized controlled trial. Obstet Gynecol 2007; 109(4):823–830. doi:10.1097/01.AOG.0000258278.73505.fa
28. **Guttuso T Jr, Kurlan R, McDermott MP, Kieburtz K.** Gabapentin's effects on hot flashes in postmenopausal women: a randomized controlled trial. Obstet Gynecol 2003; 101(2):337–345. doi:10.1016/s0029-7844(02)02712-6
29. **Butt DA, Lock M, Lewis JE, Ross S, Moineddin R.** Gabapentin for the treatment of menopausal hot flashes: a randomized controlled trial. Menopause 2008; 15(2):310–318. doi:10.1097/gme.0b013e3180dca175
30. **Pandya KJ, Morrow GR, Roscoe JA, et al.** Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. Lancet 2005; 366(9488):818–824. doi:10.1016/S0140-6736(05)67215-7
31. **Biglia N, Sgandurra P, Peano E, et al.** Non-hormonal treatment of hot flushes in breast cancer survivors: gabapentin vs. vitamin E. Climacteric 2009; 12(4):310–318. doi:10.1080/13697130902736921
32. **American Geriatrics Society 2015 Beers Criteria Update Expert Panel.** American Geriatrics Society 2015 updated Beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015; 63(11):2227–2246. doi:10.1111/jgs.13702
33. **Pandya KJ, Raubertas RF, Flynn PJ, et al.** Oral clonidine in postmenopausal patients with breast cancer experiencing tamoxifen-induced hot flashes: a University of Rochester Cancer Center Community Clinical Oncology Program study. Ann Intern Med 2000; 132(10):788–793. doi:10.7326/0003-4819-132-10-200005160-00004
34. **Johnson KA, Martin N, Nappi RE, et al.** Efficacy and safety of fezolinetant in moderate to severe vasomotor symptoms associated with menopause: a phase 3 RCT. J Clin Endocrinol Metab 2023; 108(8):1981–1997. doi:10.1210/clinem/dgad058
35. **Astellas Pharma US, Inc.** VEOZAH (fezolinetant) tablets, for oral use (package insert). https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216578s000lbl.pdf. Accessed March 6, 2024.
36. **Okifuji A, Gao J, Bokat C, Hare BD.** Management of fibromyalgia syndrome in 2016. Pain Manag 2016; 6(4):383–400. doi:10.2217/pmt-2016-006
37. **Ma X, Zhou S, Sun W, et al.** Efficacy and safety of duloxetine in chronic musculoskeletal pain: a systematic review and meta-analysis. BMC Musculoskelet Disord 2023; 24(1):394. doi:10.1186/s12891-023-06488-6
38. **Smith HS, Smith EJ, Smith BR.** Duloxetine in the management of chronic musculoskeletal pain. Ther Clin Risk Manag 2012; 8:267–277. doi:10.2147/TCRM.S17428
39. **Cascade E, Kalali AH, Kennedy SH.** Real-world data on SSRI antidepressant side effects. Psychiatry (Edgmont) 2009; 6(2):16–18. pmid:19724743
40. **Santarsieri D, Schwartz TL.** Antidepressant efficacy and side-effect burden: a quick guide for clinicians. Drugs Context 2015; 4:212290. doi:10.7573/dic.212290
41. **Portman DJ, Kaunitz AM, Kazempour K, Mekonnen H, Bhaskar S, Lippman J.** Effects of low-dose paroxetine 7.5 mg on weight and sexual function during treatment of vasomotor symptoms associated with menopause. Menopause 2014; 21(10):1082–1090. doi:10.1097/GME.0000000000000210
42. **Thompson SR, Compton LE, Fang ML, Chen J-L.** Pharmacologic treatment of antidepressant-induced excessive sweating: a systematic review. Arch Clin Psych 2021; 48(1):57–65. doi:10.15761/0101-60830000000279
43. **Leon-Ferre RA, Novotny PJ, Wolfe EG, et al.** Oxybutynin vs placebo for hot flashes in women with or without breast cancer: a randomized, double-blind clinical trial (ACCRU SC-1603). JNCI Cancer Spectr 2019; 4(1):pkz088. doi:10.1093/jncics/pkz088
44. **Jannsen Pharmaceutical.** DITROPAN XL® (oxybutynin chloride) Extended release tablets for oral use (package insert). https://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/DITROPAN+XL-pi.pdf. Accessed March 13, 2024.
45. **Coupland CAC, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J.** Anticholinergic drug exposure and the risk of dementia: a nested case-control study. JAMA Intern Med 2019; 179(8):1084–1093. doi:10.1001/jamainternmed.2019.0677
46. **Malcher MF, Droupy S, Berr C, et al.** Dementia associated with anticholinergic drugs used for overactive bladder: a nested case-control study using the French National Medical-Administrative Database. J Urol 2022; 208(4):863–871. doi:10.1097/JU.0000000000002804

47. **Richardson K, Fox C, Maidment I, et al.** Anticholinergic drugs and risk of dementia: case-control study. BMJ (Clin Res Ed) 2018; 361:k1315. doi:10.1136/bmj.k1315
48. **Simon JA, Gaines T, LaGuardia KD; Extended-Release Oxybutynin Therapy for VMS Study Group.** Extended-release oxybutynin therapy for vasomotor symptoms in women: a randomized clinical trial. Menopause 2016; 23(11):1214–1221. doi:10.1097/GME.0000000000000773
49. **Boekhout AH, Vincent AD, Dalesio OB, et al.** Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomized, double-blind, placebo-controlled trial. J Clin Oncol 2011; 29(29):3862–3868. doi:10.1200/JCO.2010.33.1298
50. **Shionogi Pharma, Inc.** KAPVAY (clonidine hydrochloride) extended-release tablets, oral (package insert). https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022331s001s002lbl.pdf. Accessed March 13, 2024.
51. **Kenemans P, Barentsen R, Van de Weijer P.** Practical HRT. 2nd ed. Zeist, The Netherlands: Medical Forum International; 1996.
52. **Johnson SR.** Menopause and hormone replacement therapy. Med Clin North Am 1998; 82(2):297–320. doi:10.1016/s0025-7125(05)70608-8
53. **Thurston RC, Joffe H.** Vasomotor symptoms and menopause: findings from the Study of Women's Health across the Nation. Obstet Gynecol Clin North Am 2011; 38(3):489–501. doi:10.1016/j.ogc.2011.05.006
54. **Hutton JD, Jacobs HS, Murray MA, James VH.** Relation between plasma oestrone and oestradiol and climacteric symptoms. Lancet 1978; 1(8066):678–681. doi:10.1016/s0140-6736(78)90796-1
55. **Trower M, Anderson RA, Ballantyne E, Joffe H, Kerr M, Pawsey S.** Effects of NT-814, a dual neurokinin 1 and 3 receptor antagonist, on vasomotor symptoms in postmenopausal women: a placebo-controlled, randomized trial. Menopause 2020; 27(5):498–505. doi:10.1097/GME.0000000000001500
56. **Depypere H, Timmerman D, Donders G, et al.** Treatment of menopausal vasomotor symptoms with fezolinetant, a neurokinin 3 receptor antagonist: a phase 2a trial. J Clin Endocrinol Metab 2019; 104(12):5893–5905. doi:10.1210/jc.2019-00677
57. **Simon JA, Anderson RA, Ballantyne E, et al.** Efficacy and safety of elinzanetant, a selective neurokinin-1,3 receptor antagonist for vasomotor symptoms: a dose-finding clinical trial (SWITCH-1). Menopause 2023; 30(3):239–246. doi:10.1097/GME.0000000000002138
58. **The North American Menopause Society 2022 Hormone Therapy Position Statement Advisory Panel.** The 2022 hormone therapy position statement of the North American Menopause Society. Menopause 2022; 29(7):767–794. doi:10.1097/GME.0000000000002028

Address: *Tara K. Iyer, MD, MSCP, Division of Women's Health, Department of Medicine, Brigham and Women's Hospital, 1620 Tremont Street, 3rd Floor, Boston, MA 02120; tiyer@bwh.harvard.edu*

Noura Nachawi, MD
Department of Metabolism, Endocrinology & Diabetes, University of Michigan, Ann Arbor, MI; Assistant Professor, University of Michigan, Ann Arbor, MI

Dingfeng Li, MD
Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic, Cleveland, OH; Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

M. Cecilia Lansang, MD, MPH
Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic, Cleveland, OH; Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Glucocorticoid-induced adrenal insufficiency and glucocorticoid withdrawal syndrome: Two sides of the same coin

ABSTRACT

Diseases of the adrenal glands can lead to primary adrenal insufficiency, and suppression of the hypothalamic-pituitary-adrenal axis can cause secondary adrenal insufficiency (adrenal suppression). The most common cause of adrenal suppression is exogenous steroids, a condition recently termed *glucocorticoid-induced adrenal insufficiency* (GIAI). Similarly, weaning from high doses of glucocorticoids or giving insufficient glucocorticoid replacement after curative surgery for endogenous hypercortisolism (Cushing syndrome) can lead to glucocorticoid withdrawal syndrome, which overlaps with GIAI.

KEY POINTS

- GIAI is common in patients treated with glucocorticoids.
- GIAI may go unrecognized when caused by non-oral formulations of glucocorticoids: intra-articular, epidural, inhaled, and even topical.
- When tapering high doses of glucocorticoids, patients can develop symptoms of glucocorticoid withdrawal similar to those of GIAI.
- Patients with GIAI are a vulnerable population with a poor baseline quality of life. Lack of awareness of GIAI among patients and physicians often leads to worse clinical outcomes and quality of life.

doi:10.3949/ccjm.91a.23039

Glucocorticoid-induced adrenal insufficiency (GIAI) is a well-known side effect of glucocorticoid therapy, and clinicians usually expect it in patients who receive systemic (oral, intravenous, and intramuscular) glucocorticoids in doses equivalent to more than 5 mg of prednisone for at least 3 weeks.[1] However, glucocorticoids given through other routes can also suppress the adrenal glands.

Unfamiliarity with GIAI, especially when caused by nonsystemic formulations of glucocorticoids, can lead to delay in diagnosis or misdiagnosis and lack of proper patient education. This lack of awareness often leads to failure to implement an adrenal action plan and underuse of injectable glucocorticoids at home or, in cases of adrenal crisis, in the emergency room.[2] Ultimately, gaps in care in managing adrenal suppression often worsen clinical outcomes and quality of life in this vulnerable patient population, who tend to have a poor quality of life at baseline.[3]

This review highlights the differences between primary adrenal insufficiency, secondary adrenal insufficiency (including GIAI), and glucocorticoid withdrawal syndrome.

DEFINITION AND TYPES OF ADRENAL INSUFFICIENCY

The adrenal cortex produces 3 main types of hormones[4]:

TABLE 1
Common causes of primary adrenal insufficiency

Autoimmune
Isolated
Autoimmune polyglandular syndrome type 1
Autoimmune polyglandular syndrome type 2
Adrenal infection
Tuberculosis
Human immunodeficiency virus
Cytomegalovirus
Fungal infections: candidiasis, histoplasmosis, paracoccidioidomycosis
Syphilis
African trypanosomiasis
Adrenal metastases
Breast, lung, colon, stomach cancers or lymphoma
Adrenal hemorrhage
Trauma
Anticoagulation
Antiphospholipid syndrome
Congenital adrenal hyperplasia
21-hydroxylase deficiency
11-hydroxylase deficiency
3B-hydroxysteroid dehydrogenase II deficiency
Drug-induced primary adrenal insufficiency
Adrenal enzyme inhibitors: mitotane, ketoconazole, metyrapone, etomidate
Drugs that accelerate cortisol metabolism: fluconazole, phenytoin, rifampin, barbiturates
Immune checkpoint inhibitors
Anti-PD-1 (programmed cell death protein 1) monoclonal antibodies: pembrolizumab, nivolumab
CTLA-4 (cytotoxic T-lymphocyte antigen 4) inhibitor: ipilimumab
Others
Adrenoleukodystrophy and adrenomyeloneuropathy
Familial glucocorticoid deficiency
Familial glucocorticoid resistance

- Glucocorticoids (primarily cortisol) from the zona fasciculata
- Mineralocorticoids (aldosterone, deoxycorticosterone) from the zona glomerulosa
- Androgens and their precursors (androstenedione, dihydroepiandrostenedione, dihydroepiandrostenedione sulfate, testosterone, and 11-oxygenated 19-carbon androgens) from the zona reticularis.

Adrenal insufficiency is the inability of the adrenal cortex to synthesize and produce glucocorticoids, mineralocorticoids, or both.

Primary adrenal insufficiency

Diseases of the adrenal cortex can lead to primary adrenal insufficiency, with insufficient production of glucocorticoids, mineralocorticoids, or both. The prevalence of primary adrenal insufficiency in the United States is not well documented. However, it is rising in Europe, where it has been reported to be as high as 22.1 per 100,000 population.[5,6]

Autoimmune adrenalitis (also known as Addison disease, for Thomas Addison,[7] who first described it in 1855) is the most common cause of primary adrenal insufficiency in developed countries.[8] Other causes include tuberculosis, human immunodeficiency virus infection, trauma, and use of immune checkpoint inhibitors (**Table 1**).

Secondary adrenal insufficiency

Secondary adrenal insufficiency occurs when the hypothalamus does not produce enough corticotropin-releasing hormone or the anterior pituitary gland does not produce enough adrenocorticotropic hormone, so that the adrenal cortex is not stimulated and does not produce enough glucocorticoids. Mineralocorticoid secretion, however, is usually preserved, as the renin-angiotensin-aldosterone system, involving the cardiovascular and renal systems, is not affected.[9] Therefore, patients with secondary adrenal insufficiency are less likely to have hypotension than those with primary adrenal insufficiency.

Adrenal insufficiency caused by suppressed corticotropin-releasing hormone is sometimes called *tertiary adrenal insufficiency*. However, this term remains controversial. Here, we will use *secondary adrenal insufficiency* for both pituitary and hypothalamic causes of adrenal insufficiency.

Secondary adrenal insufficiency is more common than primary, with an estimated prevalence of up to 28 per 100,000 people.[10] Common causes include pituitary tumors, other tumors metastasizing to the pituitary gland, and head trauma (**Table 2**).

Other important causes are the many drugs that can affect the hypothalamic-pituitary-adrenal axis (HPAA) at different levels (**Figure 1**). The drugs that primary care clinicians most often encounter are immune checkpoint inhibitors, opioids, and glucocorticoids. Secondary adrenal insufficiency caused by emerging immunotherapies such as monoclonal antibody targeting programmed cell death protein 1 (PD-1; nivolumab and pembrolizumab) and monoclonal antibody targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4; ipilimumab) is also common, more so when these agents are used in combination or sequence.[11] Of note, these

medicines can also cause primary adrenal insufficiency, though infrequently.[12]

Opioids are believed to suppress the adrenal glands by binding to receptors in the hypothalamus and pituitary, exerting tonic inhibition on the HPAA.[13] Opioid-induced adrenal insufficiency is estimated to affect approximately 15% of patients treated with opioids for at least 3 to 6 months.[14] Li et al[15] reported that 9 (9%) of 102 patients who were receiving more than 20 morphine milligram equivalents per day developed adrenal insufficiency. All were treated with glucocorticoid replacement while weaning off opioids until their HPAA recovered, which occurred within 1 to 14 months of stopping the opioid. Glucocorticoid replacement improved pain, quality of life, and physical function.[15]

THE DEEP SLEEP OF ADRENAL GLANDS: ADRENAL SUPPRESSION AND GIAI

Glucocorticoids are powerful anti-inflammatory agents used to treat autoimmune and other conditions. However, long-term use in supraphysiologic doses can suppress the HPAA and consequently cause GIAI.

GIAI is a fairly new term and has been used by some authors interchangeably with *adrenal suppression*.[16] Other authors use the term more specifically to describe symptoms in patients with HPAA suppression who receive inadequate treatment with glucocorticoids during stressful situations.[17] The rest of the discussion will focus on GIAI, given that exogenous glucocorticoid use is the most common cause of adrenal suppression.

In a systematic review and meta-analysis of 73 studies, the median prevalence of GIAI was 37% in patients receiving any form of glucocorticoids.[18] In another meta-analysis, the median prevalence was 48.7% in those receiving oral glucocorticoids and 52.2% in those receiving intra-articular injections.[19]

Excessive glucocorticoids, whether endogenous due to adrenal lesions secreting excessive cortisol or from an exogenous source, bind to receptors in the hypothalamus and pituitary, triggering negative feedback on adrenocorticotropic hormone release. Chronic suppression of adrenocorticotropic hormone eventually leads to atrophy of the zona fasciculata but not the zona glomerulosa, resulting in impaired cortisol secretion but intact mineralocorticoid secretion.[20]

Risk factors for GIAI

Although high-quality evidence is lacking, available data suggest that many factors affect the risk of GIAI, including glucocorticoid dose, duration, formulation, frequency and timing of administration, pharmacokinetics, interaction with other medications, and cushingoid features.[16]

TABLE 2
Common causes of secondary adrenal insufficiency

Pituitary tumors
Pituitary tumors replacing normal corticotropic cells
Adrenocorticotropic hormone deficiency after tumor resection or radiation treatment
Nonpituitary tumors
Meningioma
Craniopharyngioma
Sellar or suprasellar metastases (lung, colon, and breast cancer)
Pituitary infiltration
Granulomatosis with polyangiitis
Sarcoidosis
Amyloidosis
Hemochromatosis
Lymphoma
Autoimmune
Lymphocytic hypophysitis
Isolated (usually with pregnancy)
Associated with other autoimmune disease (thyroid, vitiligo, type 1 diabetes, pernicious anemia)
Sheehan syndrome
Infarction in the pituitary gland due to excessive postpartum hemorrhage
Pituitary apoplexy
Acute hemorrhage in the pituitary adenoma
Head trauma
Severe head trauma leading to fracture of the skull base and injury in the pituitary gland
Drug-induced central adrenal insufficiency
See **Figure 1**
Rare congenital causes
Mutations of *TBX19* (T-box transcription factor 19) and *PCSK1* kexin (proprotein convertase subtilisin) genes
Mutations of *POMC* (proopiomelanocortin) gene

Glucocorticoid dose and duration. In studies in patients with asthma,[19] GIAI occurred in 2.4% of those treated with low doses of systemic glucocorticoids, 8.5% of those receiving medium doses, and 21.5% of those receiving high doses. Short-term use (< 1 month) resulted in GIAI in 1.4%, medium-term use (1 month to 1 year) resulted in GIAI in 11.9%, and long-term use (> 1 year) resulted in GIAI in 27.4%. The patterns were similar in patients treated only with inhaled glucocorticoids. However, other studies have found no correlations between glucocorticoid dose or duration and risk of GIAI.[18]

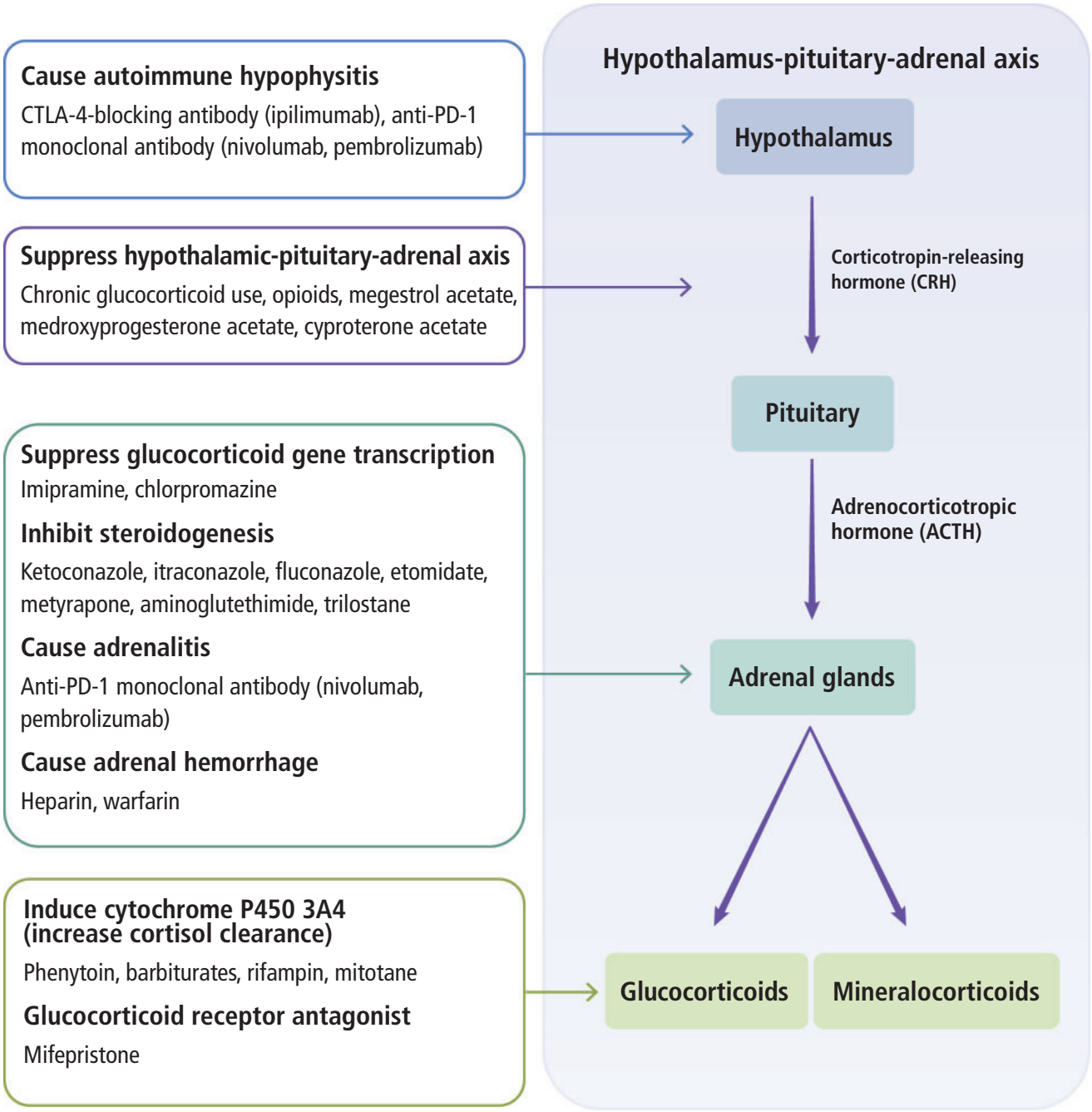


Figure 1. How various drugs can cause secondary adrenal insufficiency.

CTLA-4 = cytotoxic T-lymphocyte antigen 4; PD-1 = programmed cell death protein 1

TABLE 3
Risk factors for glucocorticoid-induced adrenal insufficiency

Route of administration	Reported risk	Factors that increase the risk	Factors that decrease the risk
Inhaled	Dose- and duration-dependent[41] 20.3% in patients treated for > 1 year[19]	High doses (any glucocorticoid > 0.8 mg/day or fluticasone propionate > 0.75 mg/day)[42] Concurrent use of intranasal or oral glucocorticoids[43,44] Use of spacer device to deliver more medication to the lower airways[45] Higher lung volumes[45]	Beclomethasone dipropionate, budesonide, and triamcinolone acetonide are less likely to suppress the HPAA compared with fluticasone propionate[42] Ciclesonide has the lowest risk of HPAA suppression[46] Lower lung volumes[45]
Intranasal	Low (≤ 4.2%)[19,46,47]	Long-term use (> 12 months)[46]	Short-term use[46]
Intra-articular injections	52.2%[19] GIAI usually occurs 1 to 8 weeks after injection[48] After single and repeated injections[49]	Higher doses[49] Patients with inflammatory disease[49] Administration in bilateral joints simultaneously[48]	Patients with degenerative disease[49]
Epidural injections	52.2%[19]	Higher doses[50] Longer-acting glucocorticoids (eg, methylprednisolone, triamcinolone)[51]	Lower doses[50] Shorter-acting glucocorticoids[51]
Topical	4.7%[19,52] Shampoo formulations are not linked to GIAI[53]	Disruption of skin barrier[52,54] Long-term use (> 12 months)[52,55] Higher-potency topical glucocorticoids (eg, betamethasone dipropionate, clobetasol propionate)[52,55,56] Higher doses Application to larger body surface[52,54] Use of occlusive bandage[52,54] Application on the eyelids, scrotum, and mucosal surfaces[52,54]	Lower-potency topical glucocorticoids (eg, dexamethasone cream 0.1%, hydrocortisone 0.5%, hydrocortisone 1%, hydrocortisone 2.5%, methylprednisolone 1%)[55]

GIAI = glucocorticoid-induced adrenal insufficiency; HPAA = hypothalamic-pituitary-adrenal axis

Based on information in references 19 and 41–56.

Formulation. Dexamethasone is 25 times more potent than hydrocortisone, and prednisone is 4 times more potent. Duration of effect is more than 36 hours for dexamethasone, 18 to 36 hours for prednisone, and 8 to 12 hours for hydrocortisone.[21,22] At equivalent doses (0.75 mg of dexamethasone is equivalent to 5 mg of prednisone or 20 mg of hydrocortisone),[21,22] dexamethasone has stronger suppressive effects on the HPAA compared with hydrocortisone. However, studies have not shown any difference in HPAA suppression in patients treated with equivalent doses of prednisone compared with dexamethasone.[23,24]

Frequency and timing of administration. Pulse therapy with high-dose glucocorticoids (eg, intravenous methylprednisolone 250–500 mg weekly for 6–12 weeks)[25,26] and alternate single-day dosing are less likely to cause GIAI[27,28] compared with bedtime dosing and frequent dosing (more than once daily).[29–31] GIAI after short bursts of glucocorticoids (7–14 days) has been infrequently reported,[28,32,33] particularly in patients with chronic obstructive pulmonary disease who receive frequent short bursts of glucocorticoids[34] and patients with malignancies who receive bursts of dexamethasone to mitigate chemotherapy-related nausea.[35]

Interactions with other medications. Concomitant use of glucocorticoids and hepatic cytochrome P450 3A4 inhibitors (eg, protease inhibitors, azoles, clarithromycin, erythromycin) increases the levels of active metabolites of glucocorticoids, and consequently, the risk of GIAI.[36,37] This happens with all glucocorticoid formulations metabolized by cytochrome P450 3A4 regardless of route of administration: oral, injectable, intra-articular, and even inhaled and intranasal formulations.[38–40] Primary care clinicians should be aware of these interactions when

they suspect GIAI, especially in patients with chronic obstructive pulmonary disease or human immunodeficiency virus infection.

Cushingoid features. A cushingoid appearance usually indicates that the glucocorticoid dose is excessive. Some authors have indicated that patients with cushingoid features while on glucocorticoids are at a very high risk for GIAI.[16]

Unrecognized sources of exogenous glucocorticoids

Inhaled glucocorticoids bind to receptors in the lungs, mouth, and oropharynx, leading to systemic exposure and possibly HPAA suppression.[21] **Table 3** summarizes the reported risk of GIAI after exposure to the different formulations and factors that can increase or decrease the risk.[19,41–56]

Intra-articular and epidural injections. Systemic absorption of intra-articular glucocorticoids has been widely described.[57,58] Similarly, HPAA suppression after epidural corticosteroid injections has been reported with multiple formulations, doses, and frequencies (after both single and recurrent doses).[59]

Some patients do not know that these injections contain steroids and therefore may not report this exposure if they present with GIAI symptoms.[60] Serum and urine testing for synthetic steroids are important tools when GIAI is suspected.[61] Urine screening for synthetic glucocorticoids (liquid chromatography-tandem mass spectrometry with stable isotope dilution analysis) is reported to detect prednisone and prednisolone for up to 40 days after epidural injections and for up to 62 days after triamcinolone epidural injections.[60]

Topical formulations. Several studies reported GIAI induced by topical cutaneous glucocorticoids.[19,52]

Eye drops. GIAI due to ophthalmic glucocorticoids has been reported in adult, pediatric, and animal studies.[62,63]

Locally active enteral formulations. Rectal glucocorticoids and oral budesonide are used to treat inflammatory bowel disease. The risk of GIAI is dose- and duration-dependent in patients taking oral budesonide, being higher when patients take more than 6 mg daily for at least 8 weeks.[64] GIAI has been reported in patients using prednisolone enemas,[65] whereas beclomethasone dipropionate enemas seem to be safer.[66]

Other medications with glucocorticoid activity

Megestrol acetate is a synthetic progestin with glucocorticoid-like activity commonly used as an appetite stimulant in patients with malignancy and anorexia. Several reports have highlighted the incidence of adrenal insufficiency, Cushing syndrome, or both in patients treated with megestrol acetate,[67,68] specifically, when megestrol acetate is combined with dexamethasone.[35]

Medroxyprogesterone acetate, another progestin that binds glucocorticoid receptors,[69,70] is used to treat endometrial cancer, endometriosis, and abnormal uterine bleeding, and as a contraceptive, and is reported to cause HPAA suppression.[71]

GLUCOCORTICOID WITHDRAWAL SYNDROME

Excessive endogenous hormone secretion or exogenous administration often leads to tolerance (decreased response to the elevated hormones and the need for even higher levels to achieve the same effect) followed by physiologic and psychologic dependence.[1] In this situation, gradually tapering or abruptly stopping the glucocorticoids can induce glucocorticoid withdrawal syndrome,[1] even while patients are still receiving supraphysiologic doses of glucocorticoids.

Glucocorticoid withdrawal syndrome manifests as a spectrum of nonspecific symptoms and is mediated by multiple mechanisms. Chronic suppression of corticotropin-releasing hormone after stopping or tapering from glucocorticoids leads to adrenal insufficiency, adrenal crisis, depressive mood changes,[72] hypersomnia, and lethargy.[73,74] Prolonged suppression of proopiomelanocortin-related peptides causes myalgia, arthralgia, fever, and headache.[1] Depressed central noradrenergic and dopaminergic systems cause nonspecific withdrawal symptoms along with anorexia, nausea, vomiting, and weight loss.[1] Loss of glucocorticoid's suppressive effect on calcium absorption results in hypercalcemia and hyperphosphatemia.[1]

These symptoms can develop at any time—during glucocorticoid taper (while the patient is still on supraphysiologic doses), after completely stopping glucocorticoids, and even after there is biochemical evidence of HPAA recovery.[1]

Long-term treatment with supraphysiologic doses of glucocorticoids often leads to HPAA suppression and adrenal insufficiency. At the same time, tolerance to and dependence on high doses of glucocorticoids causes glucocorticoid withdrawal syndrome when attempting to taper or discontinue these drugs. Therefore, adrenal insufficiency and glucocorticoid withdrawal syndrome share similar clinical features (**Table 4**); however, they are completely different clinical entities that often overlap until the HPAA recovers. Results of biochemical testing including early morning cortisol levels and the corticotropin stimulation test can be normal or suboptimal, and hence, not helpful in making this diagnosis.[75]

TABLE 4
Adrenal insufficiency, glucocorticoid-induced adrenal insufficiency, and glucocorticoid withdrawal syndrome

	Adrenal insufficiency	Glucocorticoid-induced adrenal insufficiency	Glucocorticoid withdrawal syndrome
Diagnosis	Clinical symptoms and biochemical testing: Low 8 AM cortisol (< 4.8 µg/dL)[a] Abnormal response to corticotropin stimulation test (cortisol peak < 12.6 µg/dL at 30 minutes and 60 minutes)[a] Variable adrenocorticotropic hormone (for primary adrenal insufficiency > 63.3 pg/mL, for secondary adrenal insufficiency < 7.2 pg/mL)[b]	After abrupt discontinuation or quick taper of exogenous glucocorticoid or Cushing syndrome: Low 8 AM cortisol (< 4.8 µg/dL)[a] Low adrenocorticotropic hormone (< 7.2 pg/mL)[b] Low dehydroepiandrosterone sulfate[c] Abnormal response to corticotropin stimulation test (cortisol peak < 12.6 µg/dL at 30 and 60 minutes)[a]	Clinical symptoms of adrenal insufficiency with or without cushingoid features while gradually tapering or after abrupt discontinuation of glucocorticoid No laboratory test to diagnose
Mechanism	Lack of glucocorticoid secretion from adrenal cortex due to either adrenal etiology (primary adrenal insufficiency) or pituitary or hypothalamic etiology (secondary adrenal insufficiency)	HPAA suppression due to excessive endogenous or exogenous glucocorticoid, leading to atrophy of adrenal cortex	Tolerance of and dependence on supraphysiologic doses of glucocorticoid
Prevention	Replace with physiologic doses of glucocorticoid	Gradually taper glucocorticoid until completely stopped	Use the lowest effective supraphysiologic glucocorticoid dose when indicated
Treatment	Replace with physiologic doses of glucocorticoid	Gradually taper glucocorticoid until completely stopped Consider stress-dose glucocorticoid under stressors	No effective treatment: empirically increase glucocorticoid to prolong HPAA suppression

[a]Cortisol values per the Elecsys Cortisol II assay.
[b]Adrenocorticotropic hormone values per the Electro Chemiluminescence Immunoassay.
[c]Dehydroepiandrosterone sulfate normal values (µg/dL) per the Electro Chemiluminescence Immunoassay for females, by age:
15–19 years 65.1–368.0; 20–24 years 148–407; 25–34 years 98.8–340; 35–44 years 60.9–337; 45–54 years 35.4–256; 55–64 years 18.9–205; 65–74 years < 247; 75–99 years 12–154.

For males, by age:
15–19 years 70.2–492; 20–24 years 211–492; 25–34 years 160–449; 35–44 years 88.9–427; 45–54 years 44.3–331; 55–64 years 51.7–295; 65–74 years 33.6–249; 75–99 years 16.2–123.

HPAA = hypothalamic-pituitary-adrenal axis

Glucocorticoid withdrawal syndrome after successful treatment of Cushing syndrome

Evidence on glucocorticoid withdrawal syndrome in patients with GIAI caused by exogenous glucocorticoid use is lacking. However, several studies have looked into glucocorticoid withdrawal syndrome in patients with GIAI caused by adrenal lesions secreting excessive endogenous cortisol (adrenocorticotropic hormone-independent Cushing syndrome). Up to 99% of patients with Cushing syndrome have HPAA suppression.[76] Patients with Cushing syndrome can develop tolerance to and dependence on excessive endogenous cortisol, and hence, suffer from glucocorticoid withdrawal syndrome postoperatively.[76] After resection, glucocorticoid taper is indicated until the HPAA recovers.

Postoperative glucocorticoid withdrawal syndrome is usually characterized by biochemical evidence of HPAA suppression, with many signs and symptoms consistent with cortisol deficiency despite the use of supraphysiologic doses of glucocorticoids. Common symptoms include myalgias, arthralgias, fatigue, weakness, sleep disturbance, and mood changes. In a recent prospective observational study, myalgias, arthralgias, and weakness got progressively worse 5 to 12 weeks after surgery.[77] Glucocorticoid withdrawal syndrome can be difficult to differentiate from adrenal

TABLE 5
Approach to glucocorticoid taper in patients with glucocorticoid-induced adrenal insufficiency and after surgery for Cushing syndrome

Average daily prednisone dose
> 40 mg/day: decrease by 10 mg weekly until 40 mg daily
20–40 mg/day: decrease by 5 mg weekly until 20 mg daily
10–20 mg/day: decrease by 1–2.5 mg weekly until 10 mg daily
5–10 mg/day: decrease by 1 mg weekly until < 5 mg daily
< 5 mg/day: switch to equivalent dose of hydrocortisone (eg, 10 mg in the morning and 5 mg in the early afternoon); hold hydrocortisone for 24 hours and retest HPAA

Testing for HPAA recovery
If patient has been on prednisone 5 mg/day, switch to equivalent dose of hydrocortisone, wait for 2–4 weeks, and hold hydrocortisone for 24 hours before testing

Check 8 AM serum cortisol:
If < 10 µg/dL,[a] continue current dose of hydrocortisone and retest in 4–8 weeks
If ≥ 10 µg/dL, perform 250-µg corticotropin stimulation test:
- If suboptimal (cortisol peak < 12.6 µg/dL at 30 minutes and 60 minutes), consider stopping daily glucocorticoid replacement if patient has no withdrawal symptoms, but continue the sick-day rule (using stress-dose glucocorticoid) until repeating corticotropin stimulation test
- If optimal (peak cortisol ≥ 12.6 µg/dL), stop glucocorticoid if patient is comfortable

If 8 AM serum cortisol ≥ 12.6 µg/dL, consider stopping glucocorticoid if patient is ready in terms of withdrawal symptoms, or performing 250-µg corticotropin stimulation test or tapering glucocorticoid dose

Frequency of testing:
- If the results of tests are abnormal, recheck every 2–3 months
- If no recovery within 1 year, reassess every 3–6 months

Things to consider
- If glucocorticoid withdrawal syndrome develops at any point, increase the glucocorticoid dose to the most recent dose on which the patient did not have glucocorticoid withdrawal syndrome; consider decrements every other week rather than weekly
- If patient is on dexamethasone, consider switching to prednisone
- If patient is on twice-daily prednisone dosing, consider switching to equivalent dose of prednisone in the morning once daily

[a]Values per the Elecsys Cortisol II assay.

HPAA = hypothalamic-pituitary-adrenal axis

Based in part on information in reference 81.

insufficiency, which complicates glucocorticoid dosing and tapering regimens.

In a retrospective study of the postoperative course of 81 patients with adrenocorticotropic hormone-independent Cushing syndrome,[78] glucocorticoid withdrawal syndrome was most common when the 8 AM serum cortisol level 24 hours after the last glucocorticoid dose was less than 5 µg/dL, whereas no withdrawal symptoms were reported when it was higher than 10 µg/dL.

ASSESSING AND EXPEDITING HPAA RECOVERY IN GIAI

Currently, there is no consensus on the best approach to assessing HPAA recovery in patients with GIAI and those who have undergone surgery for Cushing syndrome. However, several factors related to the patient's characteristics, glucocorticoid course of therapy, and biochemical testing could be used to estimate the recovery of the HPAA and help clinicians with their approach to patients with GIAI.

Studies have looked at recovery of the HPAA after successful surgery for endogenous adrenocorticotropic hormone-independent Cushing syndrome, and we could extrapolate some of their conclusions to GIAI.[78] Slower HPAA recovery is expected in patients treated with higher doses of glucocorticoids, women, patients with lower body mass index, and patients with cushingoid features. Faster recovery (in weeks to months) is reported in patients treated with high doses of oral glucocorticoids for less than 1 month.[19] HPAA recovery could take up to 6 to 12 months in patients treated with glucocorticoids for more than 12 months.[19,79] Future studies are needed to prove the hypothesis.

An observational study by Pofi et al[79] involving 776 patients suggested a cutoff of 3.6 µg/dL (using the Roche Modular System) between baseline cortisol and

30-minute cortisol levels after a 250-µg corticotropin stimulation test to predict recovery of the HPAA. If the change in cortisol level is less than 3.6 µg/dL and the random cortisol level is less than 7.2 µg/dL after 1 year, patients are less likely to recover HPAA function.[79]

Switching from a longer-acting glucocorticoid (eg, dexamethasone, prednisone) to a shorter-acting one (eg, hydrocortisone) has been hypothesized to expedite HPAA recovery, but evidence remains inadequate to recommend one glucocorticoid vs others for HPAA recovery.[16,80]

Corticosteroid taper in patients with GIAI and after surgery for Cushing syndrome

Clinicians should work in multidisciplinary teams and closely monitor conditions that could possibly worsen or relapse due to lowering glucocorticoid doses. Glucocorticoids should be tapered when appropriate to safely induce HPAA recovery while at the same time avoiding glucocorticoid withdrawal syndrome or adrenal crisis.

Based on available literature and expert opinion,[81] we suggest the approach to tapering glucocorticoids in patients with GIAI outlined in **Table 5**.

TAKE-HOME POINTS

Primary care clinicians should be aware of the high incidence of GIAI in patients who are treated with formulations of glucocorticoids other than oral forms. Glucocorticoid withdrawal syndrome develops due to dependance on supraphysiologic doses. Its symptoms closely resemble those of GIAI.

Primary care clinicians are encouraged to taper glucocorticoids when possible and test for HPAA recovery. If patients develop symptoms of glucocorticoid withdrawal syndrome while tapering, clinicians could consider increasing the glucocorticoid dose slightly and reattempting a slower taper.

DISCLOSURES

Dr. Li has disclosed conducting research for BridgeBio Pharma. Dr. Lansang has disclosed receiving research funding support from Abbott, serving as a research principal investigator for Abbott and Dexcom, and conducting research for Xeris. Dr. Nachawi reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

REFERENCES

1. **Hochberg Z, Pacak K, Chrousos GP.** Endocrine withdrawal syndromes. Endocr Rev 2003; 24(4):523–538. doi:10.1210/er.2001-0014
2. **Li D, Genere N, Behnken E, et al.** Determinants of self-reported health outcomes in adrenal insufficiency: a multisite survey study. J Clin Endocrinol Metab 2021; 106(3):e1408–e1419. doi:10.1210/clinem/dgaa668
3. **Li D, Brand S, Hamidi O, et al.** Quality of life and its determinants in patients with adrenal insufficiency: a survey study at 3 centers in the United States. J Clin Endocrinol Metab 2022; 107(7): e2851–e2861. doi:10.1210/clinem/dgac175
4. **Melmed S, Polonsky KS, Larsen PR, Kronenberg HM, eds.** Williams Textbook of Endocrinology. 13th ed. Bucharest, Romania: Elsevier; 2016.
5. **Olafsson AS, Sigurjonsdottir HA.** Increasing prevalence of Addison disease: results from a nationwide study. Endocr Pract 2016; 22(1):30–35. doi:10.4158/EP15754.OR
6. **Løvås K, Husebye ES.** High prevalence and increasing incidence of Addison's disease in western Norway. Clin Endocrinol (Oxf) 2002; 56(6):787–791.doi:10.1046/j.1365-2265.2002.t01-1-01552.x
7. **Addison T.** On the constitutional and local effects of disease of the supra-renal capsules / by Thomas Addison. London, UK: Wellcome Collection; 1855. https://wellcomecollection.org/works/xsmzqpdw. Accessed March 14, 2024.
8. **Erichsen MM, Løvås K, Skinningsrud B, et al.** Clinical, immunological, and genetic features of autoimmune primary adrenal insufficiency: observations from a Norwegian registry. J Clin Endocrinol Metab 2009; 94(12):4882–4890. doi:10.1210/jc.2009-1368
9. **Bancos I, Hahner S, Tomlinson J, Arlt W.** Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol 2015; 3(3):216–226. doi:10.1016/S2213-8587(14)70142-1
10. **Arlt W, Allolio B.** Adrenal insufficiency. Lancet 2003; 361(9372):1881–1893. doi:10.1016/S0140-6736(03)13492-7
11. **Iglesias P, Sánchez JC, Díez JJ.** Isolated ACTH deficiency induced by cancer immunotherapy: a systematic review. Pituitary 2021; 24(4):630–643. doi:10.1007/s11102-021-01141-8
12. **Grouthier V, Lebrun-Vignes B, Moey M, et al.** Immune checkpoint inhibitor-associated primary adrenal insufficiency: WHO VigiBase Report analysis. Oncologist 2020; 25(8):696–701. doi:10.1634/theoncologist.2019-0555
13. **Donegan D, Bancos I.** Opioid-induced adrenal insufficiency. Mayo Clin Proc 2018; 93(7):937–944. doi:10.1016/j.mayocp.2018.04.010
14. **de Vries F, Bruin M, Lobatto DJ, et al.** Opioids and their endocrine effects: a systematic review and meta-analysis. J Clin Endocrinol Metab 2020; 105(3):1020–1029. doi:10.1210/clinem/dgz022
15. **Li T, Cunningham JL, Gilliam WP, Loukianova L, Donegan DM, Bancos I.** Prevalence of opioid-induced adrenal insufficiency in patients taking chronic opioids. J Clin Endocrinol Metab 2020; 105(10):e3766–e3775. doi:10.1210/clinem/dgaa499
16. **Prete A, Bancos I.** Glucocorticoid induced adrenal insufficiency [published correction appears in BMJ 2021; 374:n1936]. BMJ 2021; 374:n1380. doi:10.1136/bmj.n1380
17. **Borresen SW, Klose M, Glintborg D, Watt T, Andersen MS, Feldt-Rasmussen U.** Approach to the patient with glucocorticoid-induced adrenal insufficiency. J Clin Endocrinol Metab 2022; 107(7):2065–2076. doi:10.1210/clinem/dgac151
18. **Joseph RM, Hunter AL, Ray DW, Dixon WG.** Systemic glucocorticoid therapy and adrenal insufficiency in adults: a systematic review. Semin Arthritis Rheum 2016; 46(1):133–141. doi:10.1016/j.semarthrit.2016.03.001
19. **Broersen LH, Pereira AM, Jørgensen JO, Dekkers OM.** Adrenal insufficiency in corticosteroids use: systematic review and meta-analysis. J Clin Endocrinol Metab 2015; 100(6):2171–2180. doi:10.1210/jc.2015-1218
20. **Crowley RK, Argese N, Tomlinson JW, Stewart PM.** Central hypoadrenalism. J Clin Endocrinol Metab 2014; 99(11):4027–4036. doi:10.1210/jc.2014-2476
21. **Williams DM.** Clinical pharmacology of corticosteroids. Respir Care 2018; 63(6):655–670. doi:10.4187/respcare.06314
22. **Meikle AW, Tyler FH.** Potency and duration of action of glucocorticoids. Effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. Am J Med 1977; 63(2):200–207. doi:10.1016/0002-9343(77)90233-9
23. **Kuperman H, Odone Filho V, Cristofani LM, Assis de Almeida MT, Setian N, Damiani D.** Evaluation of adrenal reserve in children with acute lymphocytic leukemia treated with prednisone or dexamethasone. Horm Res Paediatr 2012; 78(2):73–80. doi:10.1159/000339830

24. **Grossmann C, Scholz T, Rochel M, et al.** Transactivation via the human glucocorticoid and mineralocorticoid receptor by therapeutically used steroids in CV-1 cells: a comparison of their glucocorticoid and mineralocorticoid properties. Eur J Endocrinol 2004; 151(3):397–406. doi:10.1530/eje.0.1510397
25. **Jespersen S, Nygaard B, Kristensen LØ.** Methylprednisolone pulse treatment of Graves' ophthalmopathy is not associated with secondary adrenocortical insufficiency. Eur Thyroid J 2015; 4(4): 222–225. doi:10.1159/000440834
26. **Giotaki Z, Fountas A, Tsirouki T, Bargiota A, Tigas S, Tsatsoulis A.** Adrenal reserve following treatment of Graves' orbitopathy with intravenous glucocorticoids. Thyroid 2015; 25(4):462–463. doi:10.1089/thy.2014.0533
27. **Ackerman GL, Nolsn CM.** Adrenocortical responsiveness after alternate-day corticosteroid therapy. N Engl J Med 1968; 278(8):405–409. doi:10.1056/NEJM196802222780801
28. **Carter ME, James VH.** Effect of alternate-day, single-dose, corticosteroid therapy on pituitary-adrenal function. Ann Rheum Dis 1972; 31(5):379–383. doi:10.1136/ard.31.5.379
29. **Jasani MK, Boyle JA, Greig WR, et al.** Corticosteroid-induced suppression of the hypothalamo-pituitary-adrenal axis: observations on patients given oral corticosteroids for rheumatoid arthritis. Q J Med 1967; 36(143):261–276. pmid:6049762
30. **Nichols T, Nugent CA, Tyler FH.** Diurnal variation in suppression of adrenal function by glucocorticoids. J Clin Endocrinol Metab 1965; 25:343–349. doi:10.1210/jcem-25-3-343
31. **Grant SD, Forsham PH, DiRaimondo VC.** Suppression of 17-hydroxycorticosteroids in plasma and urine by single and divided doses of triamcinolone. N Engl J Med 1965; 273(21):1115–1118. doi:10.1056/NEJM196511182732101
32. **Brigell DF, Fang VS, Rosenfield RL.** Recovery of responses to ovine corticotropin-releasing hormone after withdrawal of a short course of glucocorticoid. J Clin Endocrinol Metab 1992; 74(5):1036–1039. doi:10.1210/jcem.74.5.1314844
33. **Lević Z, Micić D, Nikolić J, et al.** Short-term high dose steroid therapy does not affect the hypothalamic-pituitary-adrenal axis in relapsing multiple sclerosis patients. Clinical assessment by the insulin tolerance test. J Endocrinol Invest 1996; 19(1):30–34. doi:10.1007/BF03347855
34. **Fleishaker DL, Mukherjee A, Whaley FS, Daniel S, Zeiher BG.** Safety and pharmacodynamic dose response of short-term prednisone in healthy adult subjects: a dose ranging, randomized, placebo-controlled, crossover study. BMC Musculoskelet Disord 2016; 17:293. doi:10.1186/s12891-016-1135-3
35. **Han HS, Park JC, Park SY, et al.** A prospective multicenter study evaluating secondary adrenal suppression after antiemetic dexamethasone therapy in cancer patients receiving chemotherapy: a Korean South West Oncology Group study. Oncologist 2015; 20(12):1432–1439. doi:10.1634/theoncologist.2015-0211
36. **Lebrun-Vignes B, Archer VC, Diquet B, et al.** Effect of itraconazole on the pharmacokinetics of prednisolone and methylprednisolone and cortisol secretion in healthy subjects. Br J Clin Pharmacol 2001; 51(5):443–450. doi:10.1046/j.1365-2125.2001.01372.x
37. **Busse KH, Formentini E, Alfaro RM, Kovacs JA, Penzak SR.** Influence of antiretroviral drugs on the pharmacokinetics of prednisolone in HIV-infected individuals. J Acquir Immune Defic Syndr 2008; 48(5):561–566. doi:10.1097/QAI.0b013e31817bebeb
38. **Yombi JC, Maiter D, Belkhir L, Nzeusseu A, Vandercam B.** Iatrogenic Cushing's syndrome and secondary adrenal insufficiency after a single intra-articular administration of triamcinolone acetonide in HIV-infected patients treated with ritonavir. Clin Rheumatol 2008; 27(suppl 2):S79–S82. doi:10.1007/s10067-008-1022-x
39. **Foisy MM, Yakiwchuk EM, Chiu I, Singh AE.** Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV Med 2008; 9(6):389–396. doi:10.1111/j.1468-1293.2008.00579.x
40. **Saberi P, Phengrasamy T, Nguyen DP.** Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: a review of pharmacokinetics, case reports and clinical management. HIV Med 2013; 14(9):519–529. doi:10.1111/hiv.12039
41. **Lasky-Su J.** Inhaled corticosteroid use for asthma is linked to adrenal suppression. Nat Med 2022; 28(4):645–646. doi:10.1038/s41591-022-01732-3
42. **Lipworth BJ.** Systemic adverse effects of inhaled corticosteroid therapy: a systematic review and meta-analysis. Arch Intern Med 1999; 159(9):941–955. doi:10.1001/archinte.159.9.941
43. **Zöllner EW, Lombard C, Galal U, Hough S, Irusen E, Weinberg E.** Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled and nasal corticosteroids—more common than expected? J Pediatr Endocrinol Metab 2011; 24(7–8):529–534. doi:10.1515/jpem.2011.198
44. **Zöllner EW, Lombard CJ, Galal U, Hough FS, Irusen EM, Weinberg E.** Hypothalamic–pituitary-adrenal axis suppression in asthmatic school children. Pediatrics 2012; 130(6):e1512–1519. doi:10.1542/peds.2012-1147
45. **Lipworth B, Kuo C, Jabbal S.** Adrenal suppression with inhaled corticosteroids: the seed and the soil. Lancet Respir Med 2018; 6(6):e19. doi:10.1016/S2213-2600(18)30148-6
46. **Derendorf H, Nave R, Drollmann A, Cerasoli F, Wurst W.** Relevance of pharmacokinetics and pharmacodynamics of inhaled corticosteroids to asthma. Eur Respir J 2006; 28(5):1042–1050. doi:10.1183/09031936.00074905
47. **Sampieri G, Namavarian A, Lee JJW, Hamour AF, Lee JM.** Hypothalamic-pituitary-adrenal axis suppression and intranasal corticosteroid use: a systematic review and meta-analysis. Int Forum Allergy Rhinol 2022; 12(1):11–27. doi:10.1002/alr.22863
48. **Habib G, Khazin F, Jabbour A, et al.** Simultaneous bilateral knee injection of methylprednisolone acetate and the hypothalamic-pituitary adrenal axis: a single-blind case-control study. J Investig Med 2014; 62(3):621–626. doi:10.2310/JIM.0000000000000048
49. **Mader R, Lavi I, Luboshitzky R.** Evaluation of the pituitary-adrenal axis function following single intraarticular injection of methylprednisolone. Arthritis Rheum 2005; 52(3):924–928. doi:10.1002/art.20884
50. **Sim SE, Hong HJ, Roh K, Seo J, Moon HS.** Relationship between epidural steroid dose and suppression of hypothalamus-pituitary-adrenal axis. Pain Physician 2020; 23(4S):S283–S294. pmid:32942788
51. **Friedly JL, Comstock BA, Heagerty PJ, et al.** Systemic effects of epidural steroid injections for spinal stenosis. Pain 2018; 159(5): 876–883. doi:10.1097/j.pain.0000000000001158
52. **Böckle BC, Jara D, Nindl W, Aberer W, Sepp NT.** Adrenal insufficiency as a result of long-term misuse of topical corticosteroids. Dermatology 2014; 228(4):289–293. doi:10.1159/000358427
53. **Andres P, Poncet M, Farzaneh S, Soto P.** Short-term safety assessment of clobetasol propionate 0.05% shampoo: hypothalamic-pituitary-adrenal axis suppression, atrophogenicity, and ocular safety in subjects with scalp psoriasis. J Drugs Dermatol 2006; 5(4):328–332. pmid:16673799
54. **Hengge UR, Ruzicka T, Schwartz RA, Cork MJ.** Adverse effects of topical glucocorticosteroids. J Am Acad Dermatol 2006; 54(1):1–15. doi:10.1016/j.jaad.2005.01.010
55. **Weston WL, Fennessey PV, Morelli J, et al.** Comparison of hypothalamus-pituitary-adrenal axis suppression from superpotent topical steroids by standard endocrine function testing and gas chromatographic mass spectrometry. J Invest Dermatol 1988; 90(4):532–535. doi:10.1111/1523-1747.ep12461062
56. **Walsh P, Aeling JL, Huff L, Weston WL.** Hypothalamus-pituitary-adrenal axis suppression by superpotent topical steroids. J Am Acad Dermatol 1993; 29(3):501–503. doi:10.1016/s0190-9622(08)82011-7
57. **Armstrong RD, English J, Gibson T, Chakraborty J, Marks V.** Serum methylprednisolone levels following intra-articular injection of methylprednisolone acetate. Ann Rheum Dis 1981; 40(6):571–574. doi:10.1136/ard.40.6.571
58. **Derendorf H, Möllmann H, Grüner A, Haack D, Gyselby G.** Pharmacokinetics and pharmacodynamics of glucocorticoid suspensions after intra-articular administration. Clin Pharmacol Ther 1986; 39(3):313–317. doi:10.1038/clpt.1986.45
59. **Lee MS, Moon HS.** Safety of epidural steroids: a review. Anesth Pain Med (Seoul) 2021; 16(1):16–27. doi:10.17085/apm.21002
60. **Lansang MC, Farmer T, Kennedy L.** Diagnosing the unrecognized systemic absorption of intra-articular and epidural steroid injections. Endocr Pract 2009; 15(3):225–228. doi:10.4158/EP.15.3.225

61. **Cizza G, Nieman LK, Doppman JL, et al.** Factitious Cushing syndrome. J Clin Endocrinol Metab 1996; 81(10):3573–3577. doi:10.1210/jcem.81.10.8855803
62. **Kröger L, Kotaniemi K, Jääskeläinen J.** Topical treatment of uveitis resulting in adrenal insufficiency. Acta Paediatr 2009; 98(3): 584–585. doi:10.1111/j.1651-2227.2008.01091.x
63. **Roberts SM, Lavach JD, Macy DW, Severin GA.** Effect of ophthalmic prednisolone acetate on the canine adrenal gland and hepatic function. Am J Vet Res 1984; 45(9):1711–1714. pmid:6497127
64. **Löfberg R, Rutgeerts P, Malchow H, et al.** Budesonide prolongs time to relapse in ileal and ileocaecal Crohn's disease. A placebo controlled one year study. Gut 1996; 39(1):82–86. doi:10.1136/gut.39.1.82
65. **Luman W, Gray RS, Pendek R, Palmer KR.** Prednisolone metasulphobenzoate foam retention enemas suppress the hypothalamo-pituitary-adrenal axis. Aliment Pharmacol Ther 1994; 8(2):255–258. doi:10.1111/j.1365-2036.1994.tb00284.x
66. **Kumana CR, Seaton T, Meghji M, Castelli M, Benson R, Sivakumaran T.** Beclomethasone dipropionate enemas for treating inflammatory bowel disease without producing Cushing's syndrome or hypothalamic pituitary adrenal suppression. Lancet 1982; 1(8272):579–583. doi:10.1016/s0140-6736(82)91747-0
67. **González Villarroel P, Fernández Pérez I, Páramo C, et al.** Megestrol acetate-induced adrenal insufficiency. Clin Transl Oncol 2008; 10(4):235–237. doi:10.1007/s12094-008-0188-7
68. **Mehta K, Weiss I, Goldberg MD.** Megace mystery: a case of central adrenal insufficiency. Case Rep Endocrinol 2015; 2015:147265. doi:10.1155/2015/147265
69. **Thomas CP, Liu KZ, Vats HS.** Medroxyprogesterone acetate binds the glucocorticoid receptor to stimulate alpha-ENaC and sgk1 expression in renal collecting duct epithelia. Am J Physiol Renal Physiol 2006; 290(2):F306–F312. doi:10.1152/ajprenal.00062.2005
70. **Kontula K, Paavonen T, Luukkainen T, Andersson LC.** Binding of progestins to the glucocorticoid receptor. Correlation to their glucocorticoid-like effects on in vitro functions of human mononuclear leukocytes. Biochem Pharmacol 1983; 32(9):1511–1518. doi:10.1016/0006-2952(83)90474-4
71. **Malik KJ, Wakelin K, Dean S, Cove DH, Wood PJ.** Cushing's syndrome and hypothalamic-pituitary-adrenal axis suppression induced by medroxyprogesterone acetate. Ann Clin Biochem 1996; 33(pt 3):187–189. doi:10.1177/000456329603300302
72. **Kling MA, Roy A, Doran AR, et al.** Cerebrospinal fluid immunoreactive corticotropin-releasing hormone and adrenocorticotropin secretion in Cushing's disease and major depression: potential clinical implications. J Clin Endocrinol Metab 1991; 72(2):260–271. doi:10.1210/jcem-72-2-260
73. **Gold PW, Chrousos GP.** The endocrinology of melancholic and atypical depression: relation to neurocircuitry and somatic consequences. Proc Assoc Am Physicians 1999; 111(1):22–34. doi:10.1046/j.1525-1381.1999.09423.x
74. **Opp M, Obál F Jr, Krueger JM.** Corticotropin-releasing factor attenuates interleukin 1-induced sleep and fever in rabbits. Am J Physiol 1989; 257(3 pt 2):R528–R535. doi:10.1152/ajpregu.1989.257.3.R528
75. **Dixon RB, Christy NP.** On the various forms of corticosteroid withdrawal syndrome. Am J Med 1980; 68(2):224–230. doi:10.1016/0002-9343(80)90358-7
76. **Di Dalmazi G, Berr CM, Fassnacht M, Beuschlein F, Reincke M.** Adrenal function after adrenalectomy for subclinical hypercortisolism and Cushing's syndrome: a systematic review of the literature. J Clin Endocrinol Metab 2014; 99(8):2637–2645. doi:10.1210/jc.2014-1401
77. **Zhang CD, Li D, Singh S, et al.** Glucocorticoid withdrawal syndrome following surgical remission of endogenous hypercortisolism: a longitudinal observational study. Eur J Endocrinol 2023; 188(7): 592–602. doi:10.1093/ejendo/lvad073
78. **Hurtado MD, Cortes T, Natt N, Young WF Jr, Bancos I.** Extensive clinical experience: hypothalamic-pituitary-adrenal axis recovery after adrenalectomy for corticotropin-independent cortisol excess. Clin Endocrinol (Oxf) 2018; 89(6):721–733. doi:10.1111/cen.13803
79. **Pofi R, Feliciano C, Sbardella E, et al.** The short synacthen (corticotropin) test can be used to predict recovery of hypothalamo-pituitary-adrenal axis function. J Clin Endocrinol Metab 2018; 103(8):3050–3059. doi:10.1210/jc.2018-00529
80. **Sagar R, Mackie S, Morgan AW, Stewart P, Abbas A.** Evaluating tertiary adrenal insufficiency in rheumatology patients on long-term systemic glucocorticoid treatment. Clin Endocrinol (Oxf) 2021; 94(3):361–370. doi:10.1111/cen.14405
81. **He X, Findling JW, Auchus RJ.** Glucocorticoid withdrawal syndrome following treatment of endogenous Cushing syndrome. Pituitary 2022; 25(3):393–403. doi:10.1007/s11102-022-01218-y

Address: *Noura Nachawi, MD, 24 Frank Lloyd Wright Drive, Ste 1300, Lobby C, Ann Arbor, MI 48105; nachawin@med.umich.edu*

How to earn *AMA PRA Category 1 Credit*™ and ABIM MOC points

AMA/PRA Category 1 Credit™

To read articles as CME activities and claim credit, go to www.ccjm.org, click on the "CME/MOC" menu, and then "Articles." Find the articles that you want to read as CME activities and click on the appropriate links. After reading an article, click on the link to complete the activity. You will be asked to log in to your MyCME account (or to create an account). Upon logging in, select "CME," complete the activity evaluation, and print your certificate.

Call 216-444-2661 or e-mail ccjm@ccf.org with questions.

Maintenance of Certification (MOC) Points

All *Cleveland Clinic Journal of Medicine* CME activities are eligible for ABIM MOC points. Physicians may claim MOC points in addition to CME credit.

Follow the instructions for completing and claiming credit for CME activities.

When you log into your MyCME account, select "CME & MOC" and enter your ABIM identification number and your date of birth. The system will store this information after you enter it the first time.

Complete the quiz and evaluation and print your CME certificate.

April 2024 CME/MOC activity:

Estimated time to complete the activity: up to 1 hour

Nonhormone therapies for vasomotor symptom management

Release date: April 1, 2024
Expiration date: March 31, 2025

FINANCIAL DISCLOSURES: In accordance with the Standards for Integrity and Independence issued by the Accreditation Council for Continuing Medical Education (ACCME), The Cleveland Clinic Center for Continuing Education mitigates all relevant conflicts of interest to ensure CE activities are free of commercial bias.

AUTHOR AND STAFF DISCLOSURES: Authors' potential conflicts of interest are disclosed within their articles. *Cleveland Clinic Journal of Medicine's* staff disclose the following financial relationships that may be relevant to their editorial roles: Dr. Brian F. Mandell (Editor in Chief) reports teaching and speaking for Genentech; and consulting for Horizon Pharma. Dr. Kristin Highland (Associate Editor) has disclosed financial interests (consulting, research, teaching, and speaking) with Actelion Pharmaceuticals, Bayer Healthcare, Boehringer Ingelheim, Eiger Biopharmaceuticals, Gententech, Gossamer Bio, Lilly, Reata Pharmaceuticals, United Therapeutics, and Viela Bio. Dr. Christian Nasr (Associate Editor) reports service on advisory committees or review panels for Exelixis, Horizon Pharma, Neurogastrx, and Nevro Corp.; and consulting for Siemens.

DISCLAIMER: The information in these educational activities is provided for general medical education purposes only and is not meant to substitute for the independent medical judgment of a physician relative to diagnostic and treatment options of a specific patient's medical condition. The viewpoints expressed in these CME activities are those of the authors. They do not represent an endorsement by The Cleveland Clinic Foundation. In no event will The Cleveland Clinic Foundation be liable for any decision made or action taken in reliance upon the information provided through these CME activities.

CME ACCREDITATION:
In support of improving patient care, Cleveland Clinic Center for Continuing Education is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

The Cleveland Clinic Center for Continuing Education designates this journal-based CME activity for a maximum of *1.0 AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Participants claiming CME credit from this activity may submit the credit hours to the American Osteopathic Association for Category 2 credit.

AMERICAN BOARD OF INTERNAL MEDICINE (ABIM):
Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1.0 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Please Note: To receive MOC you must select the MOC option during the online credit claiming process and complete the required steps. ABIM MOC points will be reported within 30 days of claiming credit.