CME | MOC

Cleveland Clinic
100 YEARS
EST. 1921

CLEVELAND CLINIC JOURNAL OF MEDICINE

Expanding our perspective on anaphylactic reactions

NPO-after-midnight orders: When are they appropriate?

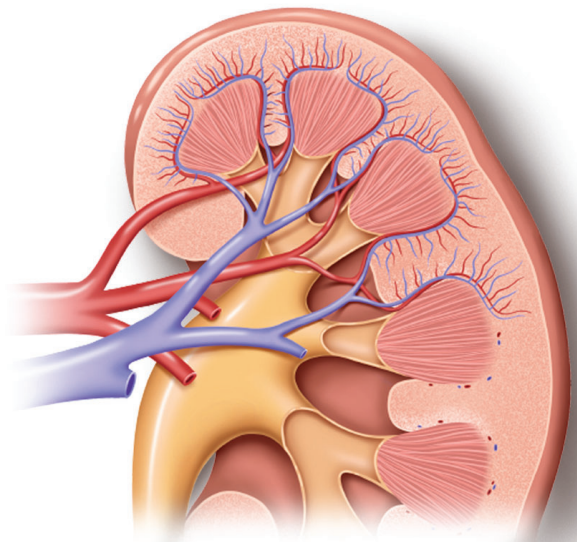**Hypertrichosis and topical corticosteroid use**

Soft tissue sarcoma: Recognition and prompt referral

Recurrent anemia in chronic lymphocytic leukemia

Vitamin A: A vitamin to keep in mind

Highlights from the anaphylaxis practice parameter update

Extraosseous calcification in kidney disease

CCF
©2022

CLEVELAND CLINIC JOURNAL OF MEDICINE

PRINTED WITH SOY INK   AMM | Association of Medical Media   BPA WORLDWIDE

2022

FEBRUARY

HVTI'S PERSONAL HEALTHCARE LEADERSHIP DEVELOPMENT SERIES
February 2
Live stream

HVTI'S PERSONAL HEALTHCARE LEADERSHIP DEVELOPMENT SERIES
February 16
Live stream

BREAST CANCER UPDATE: REVIEW OF BREAST CANCER SYMPOSIA
February 23
Live stream

VALVE DISEASE, STRUCTURAL INTERVENTIONS, AND DIASTOLOGY/ IMAGING SUMMIT
February 25
Live stream

BASIC AND CLINICAL IMMUNOLOGY FOR THE BUSY CLINICIAN
February 26
Live stream

MARCH

HVTI'S PERSONAL HEALTHCARE LEADERSHIP DEVELOPMENT SERIES
March 2
Live stream

MANAGEMENT OF CHECKPOINT INHIBITOR-RELATED TOXICITY
March 3–4
Live stream

PAIN MANAGEMENT SYMPOSIUM
March 5–9
Orlando, FL

HEALTHCARE DELIVERY AND IMPLEMENTATION SCIENCE CENTER SPEAKER SERIES
March 8
Live stream

HVTI'S PERSONAL HEALTHCARE LEADERSHIP DEVELOPMENT SERIES
March 16
Live stream

MULTIDISCIPLINARY HEAD AND NECK CANCER UPDATE
March 18–19
Fort Lauderdale, FL

APRIL

EASE YOUR WAY INTO THE ESOPHAGUS
April 1
Cleveland, OH

IBD MASTER CLASS: THE CLEVELAND CLINIC MEDICAL AND SURGICAL TEAM APPROACH TO COMPLEX IBD
April 4–5
Live stream

COMPREHENSIVE CARE FOR THE LIFETIME TREATMENT OF ADULT CONGENITAL HEART DISEASE
April 22–23
Chicago, IL

MAY

DIABETES DAY
May 5
Live stream

HEART, VASCULAR, AND THORACIC INSTITUTE ADVANCED PRACTICE PROVIDER SYMPOSIUM
May 20–21
Live stream

JUNE

MEDICAL DERMATOLOGY THERAPY UPDATE
June 1–3
Cleveland, OH

INTENSIVE REVIEW OF INTERNAL MEDICINE
June 13–17
Live stream

JULY

CLEVELAND SPINE REVIEW: HANDS-ON 2022
July 20–25
Cleveland, OH

AUGUST

NEUROLOGY UPDATE: A COMPREHENSIVE REVIEW FOR THE CLINICIAN
August 5–7
Washington, DC

INTERPROFESSIONAL APPROACH TO MANAGEMENT OF CRITICALLY ILL LIVER PATIENTS
August 15–16
Cleveland, OH, and live stream

SEPTEMBER

PRIMARY CARE WOMEN'S HEALTH: ESSENTIALS AND BEYOND
September 8–9
Cleveland, OH

RESTORING NEUROLOGICAL FUNCTION: THE CROSSROADS OF NEUROLOGY, PSYCHIATRY, AND NEUROSURGERY
September 16
Warrensville Heights, OH

DECEMBER

MASTERING THE MITRAL VALVE
December 2–3
New York, NY

SHAPING THE MANAGEMENT OF PARKINSON DISEASE: DEBATING THE MOST CONTROVERSIAL ISSUES AND DISCUSSING THE LATEST BREAKTHROUGHS
December 3–4
Lake Tahoe, NV

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

TABLE OF CONTENTS

CCF ©2022

Upcoming Features

■ **Evaluating breast cancer risk**

■ **When is testing needed for penicillin allergy?**

■ **Anemia of chronic kidney disease**

CLEVELAND CLINIC JOURNAL OF MEDICINE

Cleveland Clinic

**Healthcare Delivery &
Implementation Science Center**
Speaker Series

Evaluation of Interventions at the Transition of Care from Hospital to Home

Tuesday, March 8, Noon – 1:30 pm | Virtual

Sunil Kripalani, MD, MSc, SFHM, FACP
Professor of Medicine
Director, Center for Clinical Quality and Implementation Research
Director, Center for Health Services Research
Vanderbilt University Medical Center

Cleveland Clinic Faculty

Anita Misra-Hebert, MD, MPH, FACP
Director, Healthcare Delivery and
Implementation Science Center

Valerie Chepp, PhD
Qualitative Methodologist,
Healthcare Delivery and
Implementation Science Center

Amy O'Linn, DO, SFHM, FACP
Enterprise Readmission
Reduction, Physician Lead

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

LEARNING OBJECTIVES
› Discuss how a learning health system structure can advance research on transitions of care from hospital to home
› Discuss results of recent research completed to evaluate readmission risk prediction as well as a post-discharge home visit program in the Cleveland Clinic Health System
› Discuss appropriate methods to capture implementation outcomes for inpatient-based transitional care interventions

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

22-EDU-2635059

Anaphylaxis: Expanding our perspective

This month in our "Guidelines to Practice" series, Weller and Hsieh review the 2020 practice parameter update on anaphylaxis.[1,2] I suspect that most of us have a Frank Netter-like caricatured image of the patient with anaphylaxis (aka anaphylactic shock): mottled skin with some flush, swollen lips, some urticaria, hypotensive, tachycardic with wheezing heard on lung exam on the verge of cardiovascular collapse. But as highlighted by Weller and Hsieh, this is an extreme presentation on the spectrum of severity of anaphylaxis.

As the use of infused new protein-based medications increases across all specialties, we are spending more time reading package inserts and using drug databases to familiarize ourselves with the possible adverse effects of the medications. And we often find anaphylaxis listed as a rare but reported side effect. But as Weller and Hsieh point out, anaphylaxis is not always the extreme scenario we learned about in medical school. Rather, there is a range of far milder allergic infusion reactions that are nonetheless anaphylaxis.

This is not to minimize the potential impact of these reactions on patients and on what we should think about before prescribing these medications. While corticosteroid and antihistamine pretreatment is understandably provided before infusion of medications that have a perceived or recognized risk of hypersensitivity reactions, we still lack studies clearly demonstrating that these protocols reduce the occurrence of anaphylaxis.

Instructive from reading the summary of the practice update is the strong recommendation for the administration of epinephrine, and the reminder that some patients experience biphasic anaphylaxis—a potentially serious delayed occurrence warranting prolonged observation of some patients after the initial anaphylactic event has resolved. Interestingly, administration of glucocorticoids at the time of the initial allergic reaction does not seem to prevent this second reaction.

For those of us who don't deal with severe allergic reactions on a daily basis, but do care for patients at risk of having one as a result of our therapeutic interventions, the paper by Weller and Hsieh is worth reading.

Brian F. Mandell, MD, PhD
Editor in Chief

1. **Weller KN, Hsieh FH**. Anaphylaxis: Highlights from the practice parameter update. Cleve Clin J Med 2022; 89(2):106–111. doi:10.3949/ccjm.89a.21076
2. **Shaker MS, Wallace DV, Golden DBK, et al**. Anaphylaxis–a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis. J Allergy Clin Immunol 2020; 145(4):1082–1123. doi:10.1016/j.jaci.2020.01.017

Cleveland Clinic | Comprehensive COVID Care

Participate in an interdisciplinary educational resource for the care of COVID-19 patients

Learn best practices in current therapy and rapidly evolving management strategies for COVID-19 patients

Review new safety protocols and procedures that ensure the safety of caregivers and patients in a COVID-19 environment

Attain key concepts pertinent to inpatient management of COVID and Non-COVID medical care for physicians preparing for redeployment

Access Just-in-Time care management guides for quick and easy referencesvon diagnosis and strategies for patient care treatment.

Participate Today! **healthcareedu.ccf.org**

Cleveland Clinic

Improve Your Virtual Patient Visit Skills

As staffing shortages and concerns about exposure to COVID-19 continue, patients are eager to visit their doctor virtually. But not all physicians are comfortable conducting virtual visits.

You can take advantage of a free series of self-directed on-line modules to help you build your virtual patient visit skills.

The free course offers:

- brief introduction to virtual visits

- guidance for demonstrating communication and empathy

- best practices for taking a patient history

- instructions for conducting a physical examination, based on organ system

To help you master the content, the free course includes many video demonstrations and knowledge checks throughout.

Visit clevelandclinic.org/virtual-training

With the exception of the physical examination module, these activities have been approved for *AMA PRA Category 1 Credit™*.

OUR PEER-REVIEWERS FOR 2021

We thank those who reviewed manuscripts submitted to the *Cleveland Clinic Journal of Medicine* in 2021. Reviewing papers for the *Journal*—both for specialty content and for relevance to our readership—is an arduous task that involves considerable time and effort. Our publication decisions depend in no small part on the timely efforts of reviewers, and we are indebted to them for contributing their expertise this past year.

—Brian F. Mandell, MD, PhD, Editor in Chief

Abraham, Jame
Aggarwal, Avneep
Akindipe, Olufemi
Albert, Chonyang
Al-Jaghbeer, Mohammed
Almeida, Francisco Aécio
Alvarez-Tostado, Javier
Aneja, Ashish
Angel, Jonathan B.
Anthony, John Scott
Arce, Karla M.
Aronica, Mark A.
Aronowitz, Paul
Ashton, Rendell
Attaway, Amy
Auron, Moises
Aziz, Peter
Azok, Joseph Thomas
Bajic, Petar
Barbastefano, Juan
Barnett, Brian
Basali, Diana
Batur, Pelin
Bautista, Jan
Benedetto, Paul X.
Bernstein, Eden
Bhugra, Priyanka
Bjelac, Jaclyn
Blaha, Steven C.
Bolash, Robert
Brizendine, Kyle
Bungo, Brandon
Burkey, Brian
Callahan, Sean J.
Camporota, Luigi
Chatterjee, Soumya
Chen, Jennifer C.
Cherian, Neil
Cho, Leslie S.
Chute, Deborah

Cohn, Steven L.
Correia, Natalie
Courson, Jeff
Cove, Matthew
Cozza, MD, Kelly L.
Crone, Timothy
Cummings, Kenneth C.
Donroe, Joseph
Duggal, Abhijit
Duran Crane, Alejandro
Eghtesad, Bijan
El Hage, Lea
El Khoudary, Samar R.
Eltelbany, Ahmed
Emerman, Charles
Emery, Michael
Erwin, Angelika
Estela Cubells, José Ramón
Fares, Maan
Fernandez, James
Feyda, George
Fix, Oren K.
Franco, Kathleen N.
Gambir, Harvir Singh
Ganesh, Santosh Yatam
Garg, Divyani
Gebel, James
George, Pravin
Gilligan, Timothy
Gomes, Marcelo
Goraya, Shazia T.
Grant, Jelani K.
Graves, Kencee
Gutierrez, James F.
Hanks, Justin
Hatipoglu, Umur
Hayden, Stephen P.
Highland, Kristin
Hoogwerf, Byron J.
Howard-McNatt, Marissa

Huff, J. Stephen
Inkster, Michelle D.
Jacob, Ceena Neena
Jhaveri, Stacie
John, Binu
Jones, Danita
Kalaycio, Matt E.
Kapoor, Aanchal
Kashyap, Sangeeta R.
Kaur, Jasmeet
Keller, David L.
Keskinen, Rosemary S.
Khetarpal, Shilpi
Khorana, Alok
Kohli, Ruhail
Kransdorf, Lisa N.
Krishnan, Sudhir
Kruse, Megan
Kung, Simon
Laffin, Luke J.
Lagman, Ruth L.
Lamarre, Eric
Latson, Larry
Lehman, Bethany
Lehman, Julia S.
Lever, Harry M.
Levitin, Abraham
Li, James T.
Licata, Angelo
Lichtenberg, Robert
Lichtin, Alan E.
Lipman, Jeremy
Littlejohn, Emily
Long, Donald E.
Long, Margaret E.
Longworth, David L.
Lum, Jessica
Lynch, Gwendolyn F.
Mansour, John
Mauer, Yael

Mayock, Robert T.
Mazzoni, Sandra
Mehdi, Ali
Mesko, Nathan
Mintz, Bruce
Montane, Bryce
Morren, John
Mucha, Simon
Mummadi, Srinivas R.
Nasr, Christian
Natowicz, Marvin
Nielsen, Craig D.
Noble, Mark
Olansky, Leann
Ott, Susan M.
Paladugu, Srikanth
Parker, Marcie
Pederson, Holly
Peixoto, Aldo
Perry, Julian D.
Piliang, Melissa P.
Poterucha, John J.
Prendergast, Bernard
Press, Valerie
Radford, Diane M.
Reed, Grant
Reid, Ian Reginald
Remer, Erick M.
Ribeiro Neto, Manuel
Richardville, Kyle
Rodriguez, L. Leonardo
Rogers, Nick
Rome, Ellen S.
Rothberg, Michael
Ruggieri, Paul M.
Rutecki, Gregory
Sahni, Sabrina
Sandler, Courtney W.
Schwartz, Robert A.
Sears, Steven

Sekar, Arjun
Seth, Abhishek
Shrestha, Nabin K.
Silberzweig, Jeffrey Ira
Silver, Bernard J.
Simon, James F.
Singh, Tanveer
Soeters, Peter
Sooriakumaran, Prasanna
Stanton-Hicks, Ursula
Stevens, Tyler
Stone, Neil
Strasburg, Jessica M.
Sullivan, Daniel M.
Taege, Alan J.
Taylor, James S.
Thacker, Holly
Theil, Karl S.
Tough DeSapri, Kristi
Tuck, Matthew
Unwala, Rashmi
Wahner-Roedler, Dietlind
Walsh, R. Matthew
Wang, Ming-Hsien
Wang, Tom Kai Ming
Wang, Xiangling
Warren, Christine B.
Watts, Gregory
Whitsett, Maureen
Williams, Susan E.
Wong, Christina
Young, James B.
Zein, Joe
Zickuhr, Lisa
Zimrin, Ann B.
Zuccaro, Jr., Gregory

Tyler Chapman, DO
Assistant Professor of Medicine, Penn State Health, Milton S. Hershey Medical Center, Hershey, PA

Elizabeth Sinz, MD, MEd
Professor of Anesthesiology and Perioperative Medicine, Penn State Health, Milton S. Hershey Medical Center, Hershey, PA

Brian McGillen, MD, FACP, SFHM
Associate Professor of Medicine, Penn State Health, Milton S. Hershey Medical Center, Hershey, PA

ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Does my hospitalized patient need an NPO-after-midnight order preoperatively?

A *69-year-old man with osteopenia is brought to the emergency department after falling while walking on his driveway. He suffered no loss of consciousness. Initial evaluation reveals a right intertrochanteric hip fracture, and he is admitted to the hospital medicine service. On admission, the nocturnist is asked to place an order for nothing by mouth (NPO) after midnight, as the patient will be an "add-on" for surgery the next day. The next day, the patient is taken to the operating room at 3:45 pm, almost 16 hours after the order disallowing food or drink was placed.*

A: Not every inpatient awaiting surgery under general anesthesia requires an order for nothing by mouth (NPO) after midnight, and it is important for internists to be aware of recommendations on this matter.

Ordering NPO after midnight has been a common practice to lower the risk of aspiration of gastric contents during general anesthesia, which is due in part to suppression of laryngeal reflexes from anesthesia.[1,2] Unfortunately, delays, cancellations, and postponements of surgical procedures are common, and disallowing oral intake for prolonged periods in these situations may lead to patient harm and frustration. A recent review by Black et al[3] reported that orders for NPO after midnight were low-value patient care, a practice that is not evidence-based practice and that causes significant patient dissatisfaction.

Further, the use of midnight as the cutoff for oral intake is arbitrary, chosen more for the convenience of the operating room schedule and the ordering provider rather than the patient. A 2003 Cochrane review[4] concluded that there was no support for lengthier fasting periods such as the standard NPO after midnight

when compared with shortened fluid fasts. In fact, the American Society of Anesthesiologists (ASA) guidelines for preoperative fasting allow light meals up to 6 hours and clear liquids up to 2 hours before elective procedures utilizing general anesthesia.[5] These guidelines are similar to those of the European Society of Anaesthesiology and Intensive Care (ESAIC).[6]

■ CONSIDERATIONS BEFORE ORDERING NPO AFTER MIDNIGHT

When placing a preoperative NPO order, the following should be considered:
- Orders for NPO after midnight should be used sparingly
- Providers should be aware of the potential harms of prolonged fasting
- When patients are expected to undergo inpatient procedures, communication between providers is key to ensure preoperative recommendations from all teams are followed
- Major society guidelines should serve as a backbone for the development of protocols that utilize dietary modifications and briefer periods of fasting before elective procedures
- Allowing clear liquids 2 hours or a light breakfast 6 hours before administration of anesthesia is preferred.

■ ELECTIVE OR SEMI-URGENT PROCEDURES

We suggest that institutions utilize published guidelines as a basis to implement multidisciplinary protocols incorporating brief, evidence-based fasting periods before elective surgical procedures. Furthermore, given the potential harm to the patient of prolonged fasting, an individualized approach should be made regarding NPO-after-midnight orders, including patients undergoing semi-urgent procedures.

Disallowing oral intake for prolonged periods may lead to patient harm and frustration

The benefits of a patient-centered approach avoiding prolonged fasting when appropriate is well-cited. In a study of bariatric surgery patients, Nossaman et al[7] reported that instituting a policy allowing patients access to water up to 2 hours before surgery resulted in shorter hospital length of stay compared with patients in a post hoc analysis before the policy was instituted. Interestingly, no perioperative aspiration events were reported in either group.[7]

■ PATIENTS AT HIGH RISK OF ASPIRATION

Prolonged fasting became a standard in the mid-1900s, when catastrophic surgical complications were reported in obstetric patients who aspirated during labor.[8] Although this practice has incorrectly been extrapolated to nearly all surgical and radiologic procedures, patients in labor, patients with obesity, those with a history of esophageal surgery, and those with gastrointestinal obstruction are at highest risk of aspiration[1] and thus may require a prolonged fast. Clinicians should be able to identify these patients early in the hospital course when taking a careful history.

■ THE BOTTOM LINE

Although the practice of prolonged preoperative fasting has been considered the best way to prevent aspiration, overutilization of NPO-after-midnight orders represents low-value care, and it violates at least 3 of the 6 healthcare quality domains (safety, efficacy, and patient-centeredness) without leading to improved outcomes. Furthermore, prolonged fasting is an obstacle to maintaining appropriate hydration preoperatively, thus making it more difficult to optimize hemodynamics after induction of general anesthesia.[9] Unfortunately, the evidence-based guidelines for perioperative dietary allowance published by the ASA and ESAIC are not widely adopted as standard of care for inpatients in need of nonelective procedures.[5,6]

Evidence shows that more liberal NPO policies do not increase cases of aspiration or surgical case cancellation.[10] In the case of the patient in the opening scenario, it would be prudent for the nocturnist to order an early breakfast of clear liquids after a discussion with colleagues in orthopedic surgery and anesthesiology. This should not interfere with the patient's surgery, even if the surgery occurs earlier than originally anticipated.

An optimal approach to NPO in hospitalized patients awaiting surgery would be for overnight nursing staff to be able to confirm operating room scheduling before leaving their shift. Scheduling of add-on surgeries should be refined in patient-centered ways, as this is a root cause leading to the practice of ordering NPO after midnight. This would help ensure that patients receive their meals appropriately. This approach would best be developed through systemic solution planning that would include representatives from nursing (operating room and bedside staff), hospital medicine, surgical and procedural specialties, and anesthesiology. ■

■ DISCLOSURES

■ REFERENCES

1. **Nason KS**. Acute intraoperative pulmonary aspiration. Thorac Surg Clin 2015; 25(3):301–307. doi:10.1016/j.thorsurg.2015.04.011
2. **Merchant RN, Chima N, Ljungqvist O, Kok JNJ**. Preoperative fasting practices across three anesthesia societies: survey of practitioners. JMIR Perioper Med 2020; 3(1):e15905. doi:10.2196/15905
3. **Black MK, Lupa MC, Lemley LW, Dreesen EB, Deaton AM, Wardrop RM 3rd**. Things we do for no reason™: NPO after midnight. J Hosp Med 2021; 16(6):368–370. doi:10.12788/jhm.3537
4. **Brady M, Kinn S, Stuart P**. Preoperative fasting for adults to prevent perioperative complications. Cochrane Database Syst Rev 2003; (4):CD004423. doi:10.1002/14651858.CD004423
5. **Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: an updated report by the American Society of Anesthesiologists Task Force on Preoperative Fasting and the Use of Pharmacologic Agents to Reduce the Risk of Pulmonary Aspiration**. Anesthesiology 2017; 126(3):376–393. doi:10.1097/ALN.0000000000001452
6. **Smith I, Kranke P, Murat I, et al**. Perioperative fasting in adults and children: guidelines from the European Society of Anaesthesiology. Eur J Anaesthesiol 2011; 28(8):556–569. doi:10.1097/EJA.0b013e3283495ba1
7. **Nossaman VE, Richardson WS, Wooldridge JB Jr, Nossaman BD**. Duration of Nil Per Os is causal in hospital length of stay following laparoscopic bariatric surgery. Surg Endosc 2017; 31(4):1901–1905. doi:10.1007/s00464-016-5191-4
8. **Mendelson CL**. The aspiration of stomach contents into the lungs during obstetric anesthesia. Am J Obstet Gynecol 1946; 52:191–205. doi:10.1016/s0002-9378(16)39829-5
9. **Li Y, He R, Ying X, Hahn RG**. Dehydration, hemodynamics and fluid volume optimization after induction of general anesthesia. Clinics (Sao Paulo) 2014; 69(12):809–816. doi:10.6061/clinics/2014(12)04
10. **Murphy GS, Ault ML, Wong HY, Szokol JW**. The effect of a new NPO policy on operating room utilization. J Clin Anesth 2000; 12(1):48–51. doi:10.1016/s0952-8180(99)00139-7

Address: Tyler Chapman, DO, Department of Internal Medicine, Penn State Health, Milton S. Hershey Medical Center, 500 University Drive, Hershey, PA 17036; tchapman@pennstatehealth.psu.edu

Yuya Ando, MD
Department of Internal Medicine, Division of Gastroenterology, Self-Defense Forces Central Hospital, Tokyo, Japan; Department of Family Medicine, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan

Sachiko Ono, MPH, PhD
Department of Eat-loss Medicine, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

Yosuke Ono, MD, PhD
Department of General Medicine, National Defense Medical College, Saitama, Japan

Yoshinori Miura, MD, PhD
Department of Dermatology, Self-Defense Forces Central Hospital, Tokyo, Japan

Hypertrichosis and topical corticosteroid use
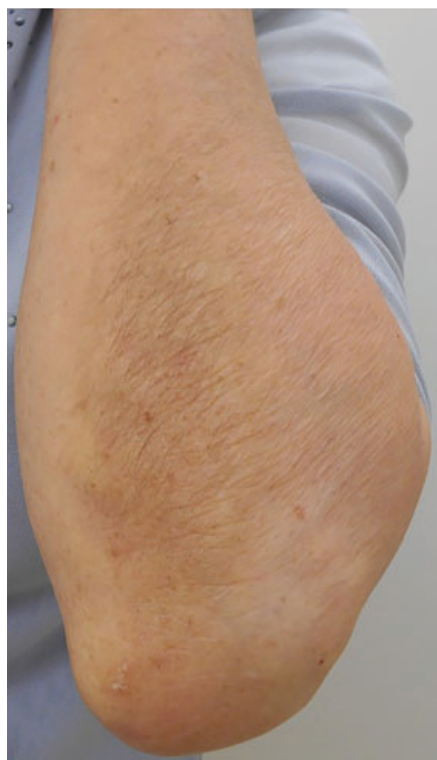
Figure 1. Thick hair growth on the patient's left forearm.

Figure 2. Arrows point to striae atrophicae on the patient's left forearm. Hair growth on the right forearm is normal.

Hypertrichosis is an adverse effect of topical corticosteroids

An 80-year-old woman with mild dementia presented to our clinic with a chief complaint of recent hair growth on her left forearm. On examination, the hair was thick and restricted to the ulnar side of the left forearm (**Figure 1**). The left forearm also had striae atrophicae (**Figure 2**).

The patient's medical history revealed that 2 years earlier she had been prescribed the topical steroid betamethasone butyrate propionate for treatment of xerotic dermatitis, which

had subsided within a short period. However, she had continued to apply the corticosteroid to her left arm for more than 2 years after the dermatitis had subsided, and she was still using it at the time of presentation.

The hair on the left forearm was significantly longer and denser than on the right forearm. The abnormal hair growth occurred where the topical steroid was applied. Because these findings were unilateral, we excluded conditions such as hirsutism, ovarian hyperthecosis, androgen-secreting ovarian and adrenal tumors, and Cushing disease, and we diagnosed her with hypertrichosis caused by long-term use of steroid ointment.

DIFFERENTIAL DIAGNOSIS OF HYPERTRICHOSIS

Hypertrichosis is an abnormal amount of hair growth that can be distributed anywhere on the body. Regarding the differential diagnosis, it is important to separate hypertrichosis from hirsutism, which is defined as abnormal hair growth on the skin of females in androgen-influenced areas that are considered characteristic for hair growth in males, such as the mustache region.[1]

Race and ethnicity also affect the differential diagnosis of hypertrichosis. For instance, regardless of the serum androgen concentration in women of reproductive age, East Asian and Native American women usually have less body hair, while women of Mediterranean ethnicities have many more body hair.

Furthermore, hypertrichosis is not a malignant condition, whereas hirsutism implies an underlying hormonal disorder because it is most frequently caused by polycystic ovary syndrome.[2] Idiopathic hirsutism is the appearance of hirsutism in females without abnormal serum androgen concentrations, menstrual disorders, or other clinical disorders.[3]

In addition, endocrine disorders associated with excessive androgen production such as congenital adrenal hyperplasia, androgen-secreting tumors, and ovarian hyperthecosis can cause hirsutism. Drugs such as danazol and any type of androgen therapy are also associated with excessive hair growth. Hypertrichosis can also be caused by topical minoxidil for alopecia areata and prostaglandin analog therapy.[4]

TOPICAL CORTICOSTEROIDS AND HYPERTRICHOSIS

Although topical corticosteroids are considered safer than systemic corticosteroids, they can cause local cutaneous and systemic adverse effects. The most common local side effects are atrophy, striae, rosacea, perioral dermatitis, acne, and purpura, while hypertrichosis, pigment alteration, delayed wound-healing, and exacerbation of skin infection are less common.[5] Widespread use of high-potency topical corticosteroids or chronic topical corticosteroid use can cause suppression of the hypothalamic-pituitary axis.[5] Less frequent but important systemic effects of these drugs are hyperglycemia, glaucoma, and adrenal insufficiency.[6]

CASE CONCLUSION

Our patient had been using betamethasone butyrate propionate ointment, which is available in Japan but not in the United States. It is a dermatologic corticosteroid categorized as a potent (group III) drug by the World Health Organization Anatomical Therapeutic Chemical classification system,[7] which classifies topical steroids from group I (weak) to group IV (very potent).

We considered that the patient's localized use of this topical corticosteroid for more than 2 years led to the hypertrichosis and striae atrophicae on her left forearm. We tapered the dose of topical corticosteroid, and consequently, the amount of hair decreased considerably.

The key to successful topical corticosteroid use is accurate prescription and good communication with patients. Clinicians should caution patients that excessive use and overuse of topical corticosteroids can lead to hypertrichosis as a cutaneous adverse effect. ■

DISCLOSURES

REFERENCES

1. **Carmina E, Koyama T, Chang L, Stanczyk FZ, Lobo RA**. Does ethnicity influence the prevalence of adrenal hyperandrogenism and insulin resistance in polycystic ovary syndrome? Am J Obstet Gynecol 1992; 167(6):1807–1812. doi:10.1016/0002-9378(92)91779-a
2. **Carmina E, Rosato F, Jannì A, Rizzo M, Longo RA**. Extensive clinical experience: relative prevalence of different androgen excess disorders in 950 women referred because of clinical hyperandrogenism. J Clin Endocrinol Metab 2006; 91(1):2–6. doi:10.1210/jc.2005-1457
3. **Azziz R, Carmina E, Sawaya ME**. Idiopathic hirsutism. Endocr Rev 2000; 21(4):347–362. doi:10.1210/edrv.21.4.0401
4. **Alm A, Grierson I, Shields MB**. Side effects associated with prostaglandin analog therapy. Surv Ophthalmol 2008; 53[Suppl1]:S93–S105. doi:10.1016/j.survophthal.2008.08.004
5. **Coondoo A, Phiske M, Verma S, Lahiri K**. Side-effects of topical steroids: a long overdue revisit. Indian Dermatol Online J 2014; 5(4):416–425. doi:10.4103/2229-5178.142483
6. **Hengge UR, Ruzicka T, Schwartz RA, Cork MJ**. Adverse effects of topical glucocorticosteroids. J Am Acad Dermatol 2006; 54(1):1–18. doi:10.1016/j.jaad.2005.01.010
7. **World Health Organization**. WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index. https://www.whocc.no/atc_ddd_index/?code=D07AC01. Accessed January 20, 2022.

Address: Yosuke Ono, Department of General Medicine, National Defense Medical College, 3-2 Namiki, Tokorozawa, Saitama 359-8513, Japan; onoyousuke1979@yahoo.co.jp

Amir Hossain Gahanbani Ardakani, BSc, MBBS
Department of Orthopaedic Oncology, Royal National Orthopaedic
Hospital, Stanmore, UK

Alex Woollard, BM, BSc, PhD, FRCS (Plast)
Department of Plastic Surgery, Royal National Orthopaedic
Hospital, Stanmore, UK; Royal Free Hospital, London, UK

Howard Ware, MBBS, FRCS (Tr&Orth)
Department of Orthopaedic Surgery, Cleveland Clinic,
London, UK

Panagiotis Gikas, MBBS Hons, MD (Res), PhD, FRCS (Tr&Orth)
Department of Orthopaedic Oncology, Royal National Orthopaedic Hospital, Stanmore, UK

Soft tissue sarcoma: Recognizing a rare disease

ABSTRACT

The recognition of a malignant soft tissue mass can be challenging, given the rarity of soft tissue sarcoma and the extensive overlap between benign and malignant presentations. Awareness of the signs and symptoms of soft tissue sarcoma in primary care practice ensures prompt referral to a sarcoma center for appropriate assessment and treatment to optimize outcomes.

KEY POINTS

The rarity of soft tissue sarcoma, its heterogeneity, and overlap of symptoms with benign conditions are challenges to timely diagnosis.

A smaller tumor at diagnosis (< 5 cm) is associated with better prognosis.

Patients suspected of having a soft tissue sarcoma require prompt referral to a sarcoma center for assessment and treatment.

THE FINDING OF A SOFT TISSUE MASS on the trunk or limbs can be the source of anxiety and distress for patients, and a diagnostic challenge for clinicians. While in most cases the masses are benign,[1] early recognition of the signs and symptoms of soft tissue sarcoma (STS) and prompt referral to a center with expertise in STS are essential to ensure effective multidisciplinary team management and optimize outcome.

■ THE EPIDEMIOLOGY OF SOFT TISSUE SARCOMA

STS is rare. About 3,300 cases per year are reported in the United Kingdom,[2] and 13,500 new cases were reported in the United States in 2021, with 5,300 deaths, for an incidence rate of 15 to 35 per 1 million of the adult population.[3]

In the United States, the average overall 5-year survival rate for STS is approximately 65%.[3] The rate is 81% for patients who present with localized STS vs 15% for those who present with distant metastases.[3] Survival rates vary depending on tumor type, size, grade, response to treatment, and some patient demographic factors. Almost half of patients who present with intermediate-grade or high-grade tumors develop metastatic disease, although this rate is highly dependent on the presenting site and timing of diagnosis.[4]

STS accounts for only 1% of all adult cancer diagnoses,[5] and primary care physicians are likely to diagnose only 1 patient with STS in their entire career. But STS is also an important and often overlooked cause of death in patients ages 14 to 29,[5,6] and it represents 7% to 10% of all childhood cancers.[7] Therefore,

TABLE 1

Clinical features of soft tissue masses that require urgent investigation

Increasing size

Size greater than 5 cm (ie, golf-ball size)

Deeper-lying mass (deep to fascia)

Firmer than surrounding tissue

Patient has potential risk factors (previous radiotherapy, chronic lymphedema, inherited syndrome such as Gardner syndrome, Li-Fraumeni syndrome, and von Recklinghausen disease)

Local symptoms and signs of infiltration

With or without pain (large painless lumps should raise concern)

The greater the number of clinical features, the greater the risk of malignancy.

The average 5-year survival for a patient with an STS is approximately 65%

lumps and bumps presenting in all age groups should be viewed with a degree of caution.

■ CHALLENGES TO CLINICAL RECOGNITION OF SOFT TISSUE SARCOMA

STS is a heterogeneous group of tumors of mesenchymal cell origin that can occur anywhere in the body, affecting the extremities in 50% of cases, the trunk and retroperitoneum in 40%, and the head and neck in 10%.[3]

Awareness of STS is low among both the general public and healthcare providers. The wide range in presentation sites, lesion size, and patient ages and the overlap of symptoms with those of benign conditions make this diagnosis challenging. Lumps may often be dismissed or misdiagnosed as harmless cysts or fatty tissue. A UK survey found that patients with STS were significantly more likely to be treated for another condition or advised that their symptoms were not serious.[8] In 2006, Grimer et al[9] published a sarcoma database review that included a plea for greater recognition of potential malignant lumps and bumps, especially those larger than a golf ball (5 cm). This led to a campaign to raise public awareness of STS in the United Kingdom.[10] But despite attempts to increase recognition of STS, the typical size at presentation (10 cm) has changed very little.

■ FEATURES THAT GUIDE THE DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a soft tissue mass can include infections such as abscess, benign lesions such as ganglion, lipoma, and schwannoma, trauma (myositis ossificans), other cancers, and secondary cancers. Infections tend to present with a fluctuant mass along with systemic symptoms of fevers and night sweats. A thorough history and physical examination can usually narrow the differential diagnosis and guide further investigation.

A detailed examination of a lump includes its site, size, shape, contour, color, consistency, tenderness, tethering, transillumination, and fluctuance. Specific examination findings such as transillumination (ganglion), bruits or palpable thrills (hemangiomas, arteriovenous malformations), variability in size (ganglion, hemangiomas), a "doughy" softer consistency (lipoma), and a positive Tinel sign (schwannoma) may help to narrow the diagnosis further.[1]

STS tends to present as a large, painless, unexplained mass anywhere in the body that has been increasing in size. The belief that only painful masses are worrisome is wrong. The UK guidelines[5] suggest that a lump that is larger than 5 cm, exhibits growth, is deep in the body, and is painful should be considered malignant until proven otherwise (**Table 1**). Increasing size is the best individual indicator of a greater risk of malignancy.[5] A mass growing slowly over a period of weeks to months, painful or not, should raise more concern than a painful mass growing rapidly over a period of days. No change in the size of a tumor over a longer time period favors a benign diagnosis.

Adding to the diagnostic challenges is a lack of known risk factors for STS. In most cases, there is no identifiable underlying cause. The risk of developing sporadic STS is increased in patients with a history of previous radiotherapy and chronic lymphedema. Certain genetic mutations, particularly chromosomal translocations, and inherited syndromes such as Gardner syndrome, Li-Fraumeni syndrome, and von Recklinghausen disease can also predispose patients to STS.[11] Systemic signs such as weight loss, fatigue, fevers, chills, and night sweats are uncommon.[1]

Late diagnosis affects the prognosis

Studies have found an almost linear relationship between the increasing lesion size and poorer prognosis that is independent of other factors, even for patients without metastatic disease at diagnosis.[9] This is particularly true of tumors larger than 5 cm, emphasizing the point that a smaller tumor at diagnosis and treatment is associated with better prognosis.[9] A smaller lump is easier to remove and reduces the surgical and long-term functional impact on the local anatomical area. Other factors associated with worse clinical outcomes are high-grade histology, positive margins after resection, and patient age over 60.

Unfortunately, in the United Kingdom, the average wait for a patient from noticing symptoms to referral and subsequent investigations is 92 weeks. By the time of diagnosis, the average tumor size is 10 cm or larger.[9,12] According to guidelines, a patient with a concerning lump or mass that is increasing in size, larger than 5 cm, in the deep fascia, and painful should be referred immediately to a sarcoma center for further evaluation, even if the risk of malignancy is only 3% to 4%.[5,13] Early referral is important to improve the outcomes.

■ WHICH DIAGNOSTIC TESTS ARE PREFERABLE?

Ultrasonography

A patient suspected of having STS should initially undergo ultrasonography. Blood tests provide no benefit in the diagnosis of STS and thus are not recommended. Ultrasonography is proven to be cost effective, with a high negative predictive value for soft tissue masses.[14,15] The diagnostic specificity is further increased if the procedure is performed by an experienced musculoskeletal radiologist.

The National Institute of Clinical Excellence (NICE) recommends that all adults be referred for ultrasonography within 2 weeks of presentation and within 48 hours in pediatric patients. Referral can made to a sarcoma center. If ultrasonography raises suspicion of STS or is inconclusive, the patient must be referred to a sarcoma center.[5] Features that raise concern are increased size, irregular margins, heterogeneity (ie, tissue existing where it should not), and architectural distortion. Outgrowth of blood supply with concomitant central necrosis seen on color Doppler ultrasonography is usually indicative of a higher-grade sarcoma.[16] If requesting ultrasonography in the primary care setting could introduce delay, then urgent referral to a sarcoma center is recommended.

The most common soft tissue lesions diagnosed from an initial workup are lipomas, ie, benign tumors of fat cells. Both ultrasonography and magnetic resonance imaging (MRI) have a high sensitivity and specificity for this diagnosis. Studies have shown that ultrasonography has an overall sensitivity of 86% and a specificity of 96% in the diagnosis of lipomas.[17]

The role of magnetic resonance imaging

If the diagnosis remains uncertain or if there are concerning features, then the most sensitive and specific imaging modality available is MRI. MRI with contrast enhancement is preferred over noncontrast MRI to assess characteristics of the mass. Obtaining contrast MRI results first helps save time and reduces the need for repeated investigations. MRI is considered the technical standard for localizing and staging STS as it enables accurate analysis of the soft tissue structure as well as its relationship to surrounding local structures. It is often used for biopsy and surgical planning.[15,18] MRI has a very high negative predictive value (100%) for distinguishing a benign lipoma from a malignant lipoma.[19]

The role of biopsy

The standard diagnostic approach must also include biopsy, in most cases multiple percutaneous core needle specimens obtained under ultrasonographic guidance.[5] In some cases, incisional or excisional (open) biopsy may be required. Biopsy should be performed by a team composed of a tumor-trained orthopedic surgeon, radiologist, and pathologist to ensure that optimal samples are taken and analyzed without compromising the final surgical treatment and unnecessary contamination of healthy tissue. Poorly performed biopsies can lead to a higher risk of adverse outcomes and expenses.[20]

A high degree of suspicion for STS based on the biopsy results should trigger prompt referral to a sarcoma center for triple assessment of clinical history, imaging, and biopsy, all of

Delayed diagnosis is a common reason for malpractice claims related to sarcoma care

which should be done on the same day.[5] And if STS is diagnosed, these centers have multidisciplinary teams trained to maximize long-term survival, minimize local recurrence, optimize function, and minimize morbidity, and they also have resources to perform additional staging studies to identify distant spread of proven STS. This additional information helps tailor treatment to the individual patient.

■ AVOIDING A 'WHOOPS PROCEDURE'

The term "whoops procedure" describes when a mass assumed to be benign is resected and the final pathologic diagnosis comes back, unexpectedly, as sarcoma or other pathology. At one sarcoma center, approximately three-quarters of referrals originated from a whoops procedure undertaken in a primary or secondary care unit.[21] Misdiagnosis occurs most often in soft tissue tumors that are smaller than 5 cm, painless, and superficial to the fascia.[22] A retrospective review of almost 400 cases found that a lack of appropriate preoperative workup, including imaging and biopsy, was responsible for whoops procedures.[23] In short, they are essentially a result of low awareness among practitioners for the presence of a potential STS.

Whoops procedures have been shown to cause the following:

- Lower rates of local control and limb salvage
- A shorter mean time to recurrence and subsequent metastasis
- An increase in wound complications and amputation rate
- A higher rate of postoperative wound complications and greater need for flap coverage
- Overall poorer functional outcomes.[21,24]

To avoid a whoops procedure, a patient with a suspected soft tissue lump of unknown pathology should be referred to a sarcoma center for appropriate imaging and assessment. Appropriate biopsy procedures also dramatically reduce the degree of mismanagement and overall harm to patients.

■ LITIGATION AND COST

Medical malpractice claims related to STS care have been increasing in both the United Kingdom and the United States, and common reasons are poor awareness, lack of knowledge, false reassurance, and late referrals.[25,26] In one review, litigation rates dramatically fell if a patient had been referred to a sarcoma center.[26]

In the United States, the mean indemnity payment favoring the patient was approximately $2.30 million (£1.7 million) in 2020, with delay in diagnosis being the main reason (86%).[25] These cases were mostly filed against the primary care physicians.[23] Thus, educating practitioners and raising awareness of STS in order to prompt early referral are keys to providing better care and reducing malpractice claims.

■ TAKE-HOME MESSAGE

Effective management of patients with suspected STS requires practitioners to be aware of the signs and symptoms and to know the appropriate testing procedures. Referring patients with known or suspected STS to a sarcoma center, which has knowledgeable multidisciplinary teams and is equipped for accurate diagnosis and subsequent management, will ensure the most optimal outcomes. It is important to not delay a referral. Early referrals can also reduce the number and devastating impact of the so-called whoops procedures. ■

■ DISCLOSURES

Features that raise concern for a malignant soft tissue mass include increasing size, irregular margins, and architectural distortion

■ REFERENCES

1. **Mayerson JL, Scharschmidt TJ, Lewis VO, Morris CD**. Diagnosis and management of soft-tissue masses. J Am Acad Orthop Surg 2014; 22(11):742–750. doi:10.5435/JAAOS-22-11-742

2. **Cancer Research UK**. Soft tissue sarcoma statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/soft-tissue-sarcoma. Accessed January 20, 2022.

3. **American Cancer Society**. Key statistics for soft tissue sarcomas. https://www.cancer.org/cancer/soft-tissue-sarcoma/about/key-statistics.html. Accessed January 20, 2022.

4. **Coindre JM, Terrier P, Guillou L, et al**. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer 2001; 91(10):1914–1926. doi:10.1002/1097-0142(20010515)91:10<1914::aid-cncr1214>3.0.co;2-3

5. **Dangoor A, Seddon B, Gerrand C, Grimer R, Whelan J, Judson I**. UK guidelines for the management of soft tissue sarcomas. Clin Sarcoma Res 2016; 6:20. doi:10.1186/s13569-016-0060-4

6. **Geraci M, Birch JM, Alston RD, Moran A, Eden TO**. Cancer mortality in 13 to 29-year-olds in England and Wales, 1981–2005. Br J Cancer 2007; 97(11):1588–1594. doi:10.1038/sj.bjc.6604080

7. **Birch JM, Alston RD, Quinn M, Kelsey AM**. Incidence of malignant disease by morphological type, in young persons aged 12–24 years in England, 1979–1997. Eur J Cancer 2003; 39(18):2622–2631. doi:10.1016/j.ejca.2003.08.006

8. **Younger E, Husson O, Bennister L, et al**. Age-related sarcoma patient experience: results from a national survey in England. BMC Cancer 2018; 18(1):991. doi:10.1186/s12885-018-4866-8

9. **Grimer RJ**. Size matters for sarcomas! Ann R Coll Surg Engl 2006; 88(6):519–524. doi:10.1308/003588406X130651

10. **Sarcoma UK**. Impact of sarcoma: National Sarcoma Survey 2020. https://sarcoma.org.uk/sites/default/files/resources/impact_of_sarcoma_2020_national_sarcoma_survey_-_technical_report_-_accessible.pdf

11. **American Cancer Society**. Risk factors for soft tissue sarcomas. https://www.cancer.org/cancer/soft-tissue-sarcoma/causes-risks-prevention/risk-factors.html. Accessed January 20, 2022.

12. **Sarcoma UK**. Soft tissue sarcoma. https://sarcoma.org.uk/sarcoma-types/soft-tissue-sarcoma. Accessed January 20, 2022.

13. **Grimer R, Judson I, Peake D, Seddon B**. Guidelines for the management of soft tissue sarcomas. Sarcoma 2010; 2010:506182. doi:10.1155/2010/506182

14. **Farfalli GL, Aponte-Tinao LA, Rasumoff A, Ayerza MA, Muscolo DL**. Intraoperative ultrasound assistance for excision of impalpable musculoskeletal soft tissue tumors. Orthopedics 2011; 34(9):e570–e573. doi:10.3928/01477447-20110714-03

15. **Church DJ, Krumme J, Kotwal S**. Evaluating soft-tissue lumps and bumps. Mo Med 2017; 114(4):289–294. pmid:30228613

16. **Aga P, Singh R, Parihar A, Parashari U**. Imaging spectrum in soft tissue sarcomas. Indian J Surg Oncol 2011; 2(4):271–279. doi:10.1007/s13193-011-0095-1

17. **Rahmani G, McCarthy P, Bergin D**. The diagnostic accuracy of ultrasonography for soft tissue lipomas: a systematic review. Acta Radiol Open 2017; 6(6):2058460117716704. doi:10.1177/2058460117716704

18. **Ostlere S, Graham R**. Imaging of soft tissue masses. Imaging 2005; 17(3)268–284. doi:10.1259/imaging/74338804

19. **Coran A, Ortolan P, Attar S, et al**. Magnetic resonance imaging assessment of lipomatous soft-tissue tumors. In Vivo 2017; 31(3):387–395. doi:10.21873/invivo.11071

20. **Mankin HJ, Lange TA, Spanier SS**. The hazards of biopsy in patients with malignant primary bone and soft-tissue tumors. J Bone Joint Surg Am 1982; 64(8):1121–1127. pmid:7130225

21. **Koulaxouzidis G, Schwarzkopf E, Bannasch H, Stark GB**. Is revisional surgery mandatory when an unexpected sarcoma diagnosis is made following primary surgery? World J Surg Oncol 2015; 13:306. doi:10.1186/s12957-015-0719-y

22. **Tedesco NS, Henshaw RM**. Unplanned resection of sarcoma. J Am Acad Orthop Surg 2016; 24(3):150–159. doi:10.5435/JAAOS-D-15-00074

23. **Mesko NW, Wilson RJ, Lawrenz JM, et al**. Pre-operative evaluation prior to soft tissue sarcoma excision—why can't we get it right? Eur J Surg Oncol 2018; 44(2):243–250. doi:10.1016/j.ejso.2017.11.001

24. **Venkatesan M, Richards CJ, McCulloch TA, et al**. Inadvertent surgical resection of soft tissue sarcomas. Eur J Surg Oncol 2012; 38(4):346–351. doi:10.1016/j.ejso.2011.12.011

25. **Hwang R, Park HY, Sheppard W, Bernthal NM**. Delayed diagnosis is the primary cause of sarcoma litigation: analysis of malpractice claims in the United States. Clin Orthop Relat Res 2020; 478(10):2239–2253. doi:10.1097/CORR.0000000000001340

26. **Harrison WD, Sargazi N, Yin Q, Chandrasekar CR**. Delayed diagnosis in primary care—the main cause of sarcoma litigation in the United Kingdom. J Surg Oncol 2016; 113(4):361–363. doi:10.1002/jso.24149

Address: Amir Hossain Gahanbani Ardakani, BSc, MBBS, Department of Orthopaedic Oncology, Royal National Orthopaedic Hospital, Brockley Hill, Stanmore, London HA7 4LP UK; amir.ardakani1@nhs.net

Korey Bartolomeo, DO
Department of Kidney Medicine, Glickman Urological & Kidney Institute, Cleveland Clinic, Cleveland, OH

Xin Yee Tan, MD
Department of Kidney Medicine, Glickman Urological & Kidney Institute, Cleveland Clinic, Cleveland, OH

Richard Fatica, MD
Vice-chair, Department of Kidney Medicine, Glickman Urological & Kidney Institute, Cleveland Clinic; Clinical Assistant Professor, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Extraosseous calcification in kidney disease

ABSTRACT

A consequence of chronic and end-stage kidney disease is a higher risk of calcium deposition in sites other than the bones. The authors of this review outline current understanding of the pathogenesis, presentation, diagnosis, and treatment of this group of disorders.

KEY POINTS

Extraosseous calcification is a broad term that encompasses vascular calcification, soft tissue calcification, and calciphylaxis, all of which are seen in patients with end-stage kidney disease.

The pathogenesis of extraosseous calcification is an active process involving a complex interplay of abnormal electrolyte levels, cell differentiation, and dysregulation of many biochemical pathways.

Vascular calcification is predominantly diagnosed incidentally, while soft tissue calcification and calciphylaxis are diagnosed on the basis of radiographic and clinical presentation, sometimes requiring biopsy.

Management is based on low-quality evidence and includes maintaining a neutral calcium balance, correcting hyperphosphatemia, and controlling comorbidities. Surgical and other nonmedical therapies may help somewhat in managing calciphylaxis and soft tissue manifestations.

C HRONIC KIDNEY DISEASE, DEFINED as an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2 or structural kidney damage sustained over 3 months, is increasing in prevalence worldwide. It is estimated to affect between 2% and 17% of all adults, and the United States is at the high end of this prevalence range.[1]

As chronic kidney disease progresses, it leads to higher rates of bone mineral disease, a systemic disorder involving the following:

- Abnormalities in serum calcium, phosphate, parathyroid hormone (PTH), and vitamin D levels
- Disorders of bone metabolism (renal osteodystrophy)
- Calcium deposition in both vascular and soft tissues.[2]

Patients with end-stage kidney disease are at high risk of complications from disorders of bone metabolism, which are strongly associated with increased rates of cardiovascular and all-cause mortality.[3–6]

■ NAMES AND PRESENTATIONS

Extraosseous tissue calcification can involve both vascular tissues (arteries and heart valves) and soft tissues. A variety of terms have been used to describe it, based on the location and the type of tissue involved (**Table 1**), but subclassifying it precisely and studying its prevalence are challenging because its presentation is heterogeneous.

■ REGULATION OF CALCIUM AND PHOSPHATE

Serum calcium and phosphate levels are kept under tight control by regulatory hormones

TABLE 1

Common terms used to describe calcification

Soft tissue calcification

Dystrophic calcification: occurring in damaged or degenerated tissue in the setting of normal metabolic factors

Metastatic calcification: occurring in otherwise normal tissue, secondary to deranged metabolic factors, as in hypercalcemia

Calciphylaxis (calcific uremic arteriopathy): ischemic skin lesions characterized by calcium deposition and thrombosis in the dermis and subcutaneous adipose tissue, most commonly associated with advanced kidney disease

Calcinosis cutis universalis: diffuse involvement of subcutaneous and fibrous structures, most commonly in association with autoimmune disorders

Tumoral calcinosis: massive deposition of calcium-phosphorus crystals in periarticular areas

Calcinosis circumscripta: localized or isolated calcification; term sometimes used if calciphylaxis involvement is limited to an extremity

Vascular calcification

Atherosclerotic (intimal) calcification: inflammatory vaso-occlusive calcification of intima as a result of endothelial dysfunction

Monckeberg arterial calcification: medial calcification deposition in small and medium arteries without luminal narrowing

Infantile calcification: extensive calcification of medium and large arteries due to *ENPP1* gene mutation

released by various organs, with complex feedback mechanisms (**Figure 1**).

Interestingly, both calcium and phosphate are regulated by the same hormone, ie, PTH.[7,8] When serum calcium levels are low and serum phosphate levels are high, the parathyroid glands release more PTH, which acts in several organs to raise the calcium and, on the whole, to lower the phosphate levels.

In the kidney, PTH directly increases calcium reabsorption in the distal tubule and loop of Henle and increases phosphate excretion by inhibiting its reabsorption in the proximal tubule.[9,10] Also in the kidney, PTH upregulates production of 1 alpha-hydroxylase, leading to increased conversion of active vitamin D (1,25-dihydroxycholecalciferol) from its precursor, 25-hydroxycholecalciferol. In turn, in the intestine, active vitamin D increases the absorption of calcium and to a lesser degree phosphate, and in the bone, it

has direct actions on both osteoblasts and osteocytes, promoting maturation, expression of skeletal hormones such as fibroblast growth factor 23 (FGF-23), and proper mineralization.[11,12]

FGF-23 is an important skeletal hormone that lowers phosphate levels by promoting its wasting (ie, suppressing its reabsorption) in the kidney, suppressing its absorption in the intestine, and, in a negative feedback loop, lowering both PTH and 1,25-dihydroxycholecalciferol production.[13] Klotho, a protein that has multiple effects in many tissues, facilitates binding of FGF-23 to FGF receptor 1 in the kidney, leading to fewer phosphate receptors in the proximal convoluted tubules, more phosphate excreted in the urine, and lower serum phosphate levels.[14] The net effect of these interactions is homeostatic balance in serum calcium and phosphate levels.

■ CALCIUM-PHOSPHATE AXIS DERANGEMENTS

In chronic kidney disease, nephrons are progressively lost. Among the ill effects is a higher phosphate level, which in turn upregulates production of FGF-23 by the osteocytes and osteoblasts and leads to bone mineral disease (**Figure 1**). Bone mineral disease can begin early in the course of chronic kidney disease,[15] when the eGFR may still be as high as 69 mL/min/1.73 m^2. Meanwhile, klotho production is downregulated, so that less FGF-23 binds to its receptor in the kidney,[16,17] less 1 alpha-hydroxylase and active vitamin D are produced, and more phosphate is reabsorbed in the proximal convoluted tubule.[18,19]

As chronic kidney disease progresses to its end stage, FGF-23 levels keep getting higher, and the elevation is accompanied by other calcium-phosphate axis derangements such as excess PTH release, decreased 1,25-dihydroxycholecalciferol, and increased sclerostin (an inhibitor of bone formation).[20,21] Together, these derangements lead to the clinical manifestations described below.

Vascular calcification

Vascular calcification is an active process involving de-differentiation of vascular smooth muscle cells. It begins with amorphous development of calcium phosphate nanocrystals in con-
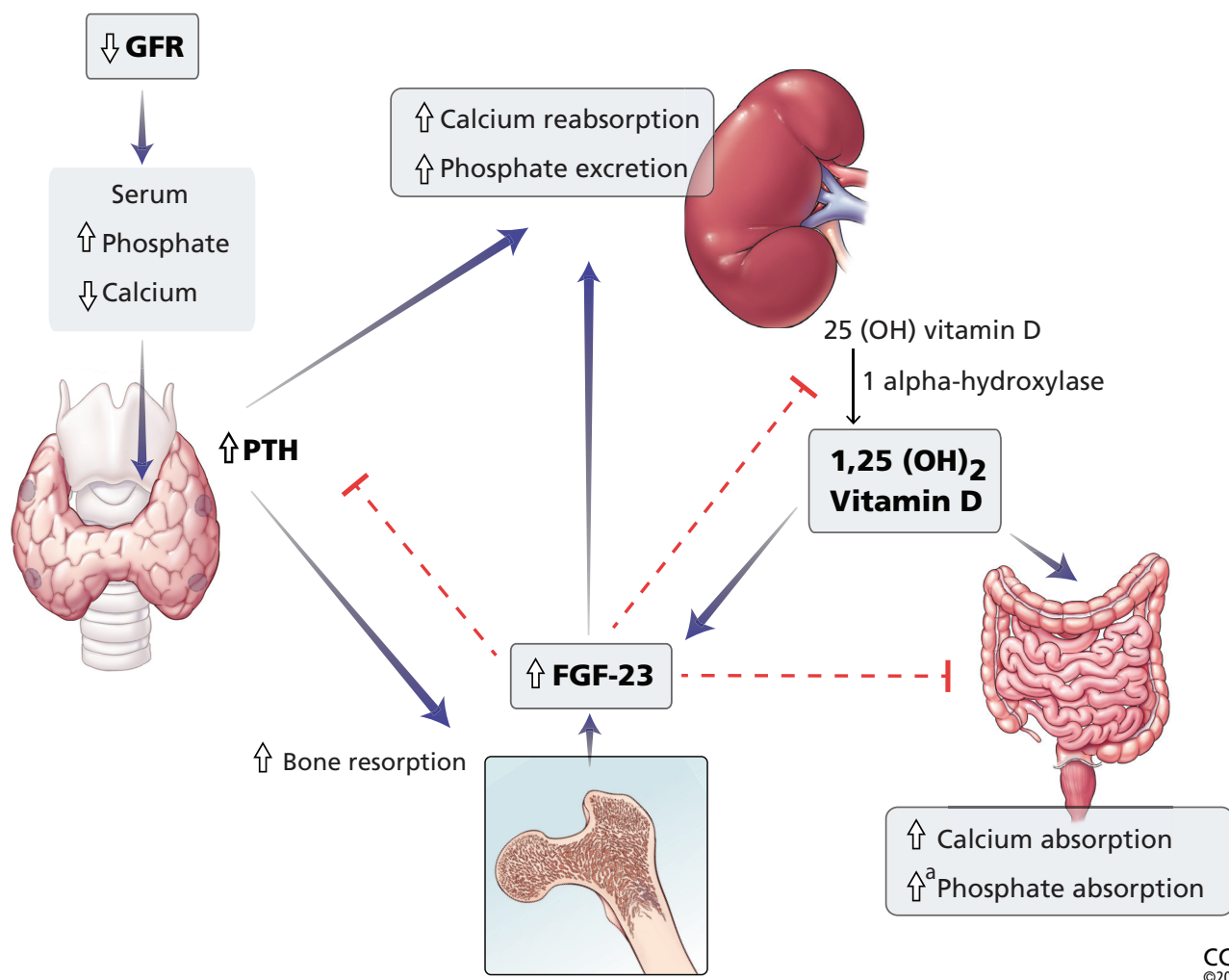
Figure 1. Calcium and phosphate metabolism in chronic kidney disease. Decreased glomerular filtration rate (GFR) leads to changes in serum calcium and phosphate, triggering release of parathyroid hormone (PTH) from the parathyroid glands and fibroblast growth factor 23 (FGF-23) from osteoblasts and osteocytes. These hormones have complex downstream effects on the kidney, gut, and bone, both from direct effects on the tissue and from indirect effects through modulation of enzyme activity in vitamin D conversion.

[a] Minimally increased.

25(OH) vitamin D = 25-hydroxycholecalciferol; 1,25(OH)$_2$ vitamin D = 1,25-dihydroxycholecalciferol

junction with other calcium-regulatory proteins in the wall of the artery.[22] Deposition of these nanocrystals can begin in the intima of the artery near sites of cholesterol buildup, either progressing into the media or beginning in the media itself, the latter of which is most specific to kidney disease.

In end-stage kidney disease, progression of vascular calcification occurs earlier than in normal aging and is likely driven by hyperphosphatemia, a positive calcium balance,

inflammation, and dysregulation between pro-calcification and anticalcification regulatory factors. An in-depth discussion of the pathogenesis of vascular calcification is beyond the scope of this paper and can be found elsewhere.[23]

Soft tissue calcification

Soft tissue calcification is fairly common in chronic and end-stage kidney disease, but only a small number of patients develop tu-

Figure 2. Calciphylaxis in a 51-year-old man with end-stage kidney disease.

From reference 27.

Calciphylaxis is intensely painful, unlike the other presentations

moral calcinosis, characterized by massive calcium phosphate deposition in periarticular locations predisposed to microtrauma.

Tumoral calcinosis is well described in families, with autosomal-recessive inheritance stemming from a number of genes, including loss-of-function mutation of *FGF23* and missense mutation of *alpha-Klotho*, contributing to the hyperphosphatemia.[24] Hyperphosphatemia is likely a necessary contributor to these familial forms of tumoral calcinosis, but it may also explain their presence in chronic and end-stage kidney disease, stemming from local tissue production or from exogenous phosphate retention.[25,26]

■ PRESENTATION AND DIAGNOSIS

Calciphylaxis is intensely painful, unlike other presentations (**Figure 2**).[27] It is most commonly seen in adipose-dense tissues but can develop centrally and in appendicular areas, including the genital regions. Skin lesions can vary from induration to ulceration with eschar formation.[28] Its diagnosis is predominantly clinical. A skin biopsy to the depth of the subcutaneous tissue can aid diagnosis but poses significant procedural risks that include pain intensification, poor healing, and secondary infection.[29]

Soft tissue calcifications, in contrast, are usually painless, unless radicular symptoms develop from mass effect. Instead, there is typically a decrease in range of motion of the affected joints,[30] of which (in descending order of frequency) the hip, elbow, shoulder, foot, and wrist are most commonly affected (**Figure 3**).[31] Soft tissue calcifications tend to be formally diagnosed based on the location of the calcium deposition, in addition to morphologic descriptions to rule out cancer mimickers.

Vascular calcification. Traditional risk factors that predict atherosclerotic calcification do not fully explain the high prevalence of vascular calcification in patients with chronic and end-stage kidney disease. Additional potentially modifiable risk factors related to kidney disease or its treatment have been shown to accelerate calcification (**Table 2**).[32]

■ MEDICAL THERAPY

Most of the research has focused on therapies directed at vascular calcification, given its clinical implications with cardiovascular disease in end-stage kidney disease.

Dietary phosphate restriction, phosphate binders

Given the central role of elevated phosphate and FGF-23 in the pathogenesis of extraosseous calcification, controlling serum phosphate levels, first through dietary phosphate restriction and then with intestinal phosphate binders, is a logical and low-cost management choice in preventing vascular calcification.

The most commonly used phosphate intestinal binders are calcium-based (eg, calcium carbonate, calcium acetate) and are used extensively in patients with chronic and end-stage kidney disease for many indications.

However, earlier studies demonstrated a relationship between higher calcium intake and higher rates of vascular calcification,[33] and subsequent studies called attention to this association, leading to recommendations for using non–calcium-based intestinal phosphate binders to restore normal phosphate levels while limiting calcium intake to maintain normal serum calcium.[34,35]

A number of randomized trials over the last 20 years have attempted to settle the debate on calcium-based vs non–calcium-based phosphate binders and cardiovascular disease, many of them using vascular calcification as a surrogate end point.

The IMPROVE-CKD trial[36] (Impact of Phosphate Reduction on Vascular End-points in Chronic Kidney Disease) tested lanthanum use in patients with advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m^2) and evaluated changes in aortic calcification and arterial stiffness. It did not find statistically significant differences with lanthanum compared with placebo. Of note, the trial was limited by recruitment, including patients with normal phosphate levels and excluding those with end-stage kidney disease.[36]

The Treat-to-Goal study[37] in patients with end-stage kidney disease on hemodialysis found less coronary artery and aortic calcification and a lower incidence of hypercalcemia in those randomized to sevelamer compared with calcium acetate. These results may correlate with improved all-cause survival rates in patients newly started on hemodialysis, despite lower rates of normophosphatemia when sevelamer is used.[15,38] Subsequent studies comparing lanthanum carbonate with calcium carbonate in patients newly starting on hemodialysis did not find statistically significant differences in calcification scores in heart valves.[39]

The LANDMARK trial[40] (Outcome Study of Lanthanum Carbonate Compared With Calcium Carbonate on Cardiovascular Mortality and Morbidity in Patients With Chronic Kidney Disease on Hemodialysis), published in 2021, looked at patients with end-stage kidney disease in Japan who had risk factors for vascular calcification who were randomized to receive lanthanum or calcium carbonate. It did not find any statistically significant differences
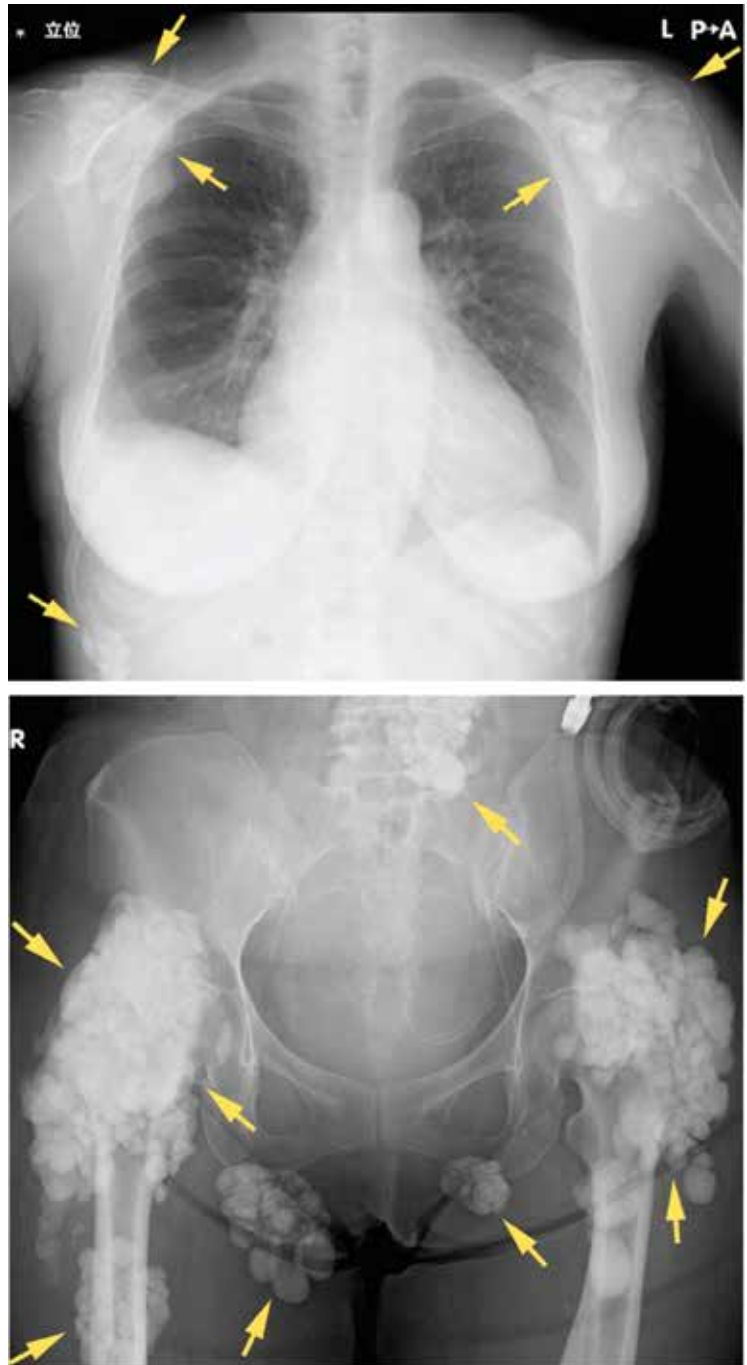
Figure 3. Radiography shows calcified masses (arrows) in a 47-year-old woman with tumoral calcinosis.

From reference 30.

in rates of all-cause mortality or cardiovascular events between the two groups, though the event rates were low. Further, compared with the United States, Japan has lower dietary calcium intake, higher use of arteriovenous fistulas

TABLE 2

Risk factors associated with vascular calcification

Traditional risk factors

Hypertension

Diabetes mellitus

Old age

Smoking

Dyslipidemia

Family history of premature coronary artery disease

Male sex

Increased levels of C-reactive protein or other inflammatory markers

Kidney disease-related risk factors

Longer hemodialysis duration

Persistent hyperphosphatemia

Increased calcium-phosphate product

Calcium-containing phosphate binders

Secondary hyperparathyroidism

Adynamic bone disease

Vitamin D deficiency and excessive vitamin D administration

High dialysate calcium

Hypomagnesemia

Low fetuin-A

Low albumin

Vascular calcification increases cardiovascular risk

for dialysis access, and different cardiovascular screening practices, which could limit wide applicability of the results.[40]

In sum, data conflict regarding whether non–calcium-based intestinal phosphate binders are superior to calcium-based binders in preventing vascular calcification and cardiovascular events.

Bone antiresorptive agents

Pyrophosphates (bisphosphonates), the most commonly used class of drugs for preventing bone resorption, inhibit the activity of osteoclasts, and some of these drugs also induce apoptosis. Bisphosphonates are either retained in the bone or cleared by the kidney.

Robust data exist for using this drug class in bone disorders in patients in the early stages of chronic kidney disease (eGFR > 35 mL/min/1.73 m^2), but data are significantly limited in those with stage 4 or 5 chronic kidney disease or end-stage kidney disease, and there are theoretical safety concerns.[41] Bisphosphonates are less frequently prescribed in these latter populations, possibly due to concerns about toxicity, as these drugs are excreted by the kidney.[42] Reports of worsening kidney disease or kidney injury exist for most drugs in the bisphosphonate class, but larger observational trials have found oral bisphosphonates to be reasonably safe in advanced chronic kidney disease, though bisphosphonate users had a 14% higher risk of progression of chronic kidney disease.[43]

Zoledronic acid, a potent intravenous formulation, should be avoided if the eGFR is less than 30 mL/min/1.73 m^2, in view of stronger associations with direct tubular injury, acute kidney injury, and worsened eGFR.[44,45] Pamidronate is generally the preferred intravenous formulation for patients with advanced chronic kidney disease, usually given at a lower dose or infused over a longer time. Rarely, collapsing focal segmental glomerulosclerosis can occur.[44,45]

Bisphosphonates have been shown to reduce both overall vascular calcification and all-cause mortality in certain groups (eg, patients with osteoporosis or cancer), but not the rate of cardiovascular events.[46] Etidronate, a first-generation bisphosphonate now discontinued due to high rates of osteomalacia, was used to treat soft tissue calcifications.[47–49] Etidronate also reduced vascular calcification in rat models of chronic kidney disease, while human studies showed reduced coronary artery calcification in patients with advanced chronic kidney disease and end-stage kidney disease.[49–51] Newer bisphosphonates have limited data on their effects on vascular calcification in end-stage kidney disease, with one study of alendronate showing no improvement in coronary artery calcification score.[52]

Denosumab, a RANK ligand inhibitor (RANK stands for receptor activator of

nuclear factor kappa B) that prevents osteoclast maturation, has not been studied in soft tissue calcification. Small pilot studies have looked at denosumab's effects on vascular calcification in humans and have suggested it may slow coronary artery calcification, but this has been challenged in other studies.[52,53] More studies are needed to determine the clinical significance of these findings. We are not aware of any studies that have looked at denosumab in soft tissue calcification or calciphylaxis.

Teriparatide is a synthetic formulation of PTH. The only evidence for using it to treat tumoral calcinosis comes from case reports, and no major studies have looked at using it in end-stage kidney disease to prevent vascular calcification.[54]

Calcimimetics

Calcimimetics are drugs that bind allosterically to the calcium-sensing receptor on parathyroid cells to suppress PTH release for a given serum calcium level.

Cinacalcet, the most common drug in this class, has been studied extensively in secondary hyperparathyroidism in 2 trials, the EVOLVE[55] (Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events) and ADVANCE[56] (A Randomized Study to Evaluate the Effects of Cinacalcet plus Low-Dose Vitamin D on Vascular Calcification in Subjects With Chronic Kidney Disease Receiving Heemodialysis). It did not show improvement in aortic calcification or reduction in cardiovascular outcomes or all-cause mortality despite improvements in serum PTH levels.[55,56] In contrast, a more recent meta-analysis of cinacalcet use in end-stage kidney disease did find a benefit in terms of lower rates of all-cause mortality and cardiovascular mortality.[57] Other calcimimetics have been studied only in animal models, and thus their clinical effect in humans is undetermined.

Sodium thiosulfate

Sodium thiosulfate is an older medication with antioxidant properties that has been used off-label for years in calcium disorders including vascular calcification and calciphylaxis. It was recently systematically reviewed in treating calciphylaxis, with conflicting results.[58,59]

More recently, a randomized clinical trial[60] showed reduction of iliac artery calcification and arterial stiffness with sodium thiosulfate compared with placebo in calciphylaxis. Ongoing prospective and randomized trials will hopefully provide clarity of the benefit of sodium thiosulfate in vascular calcification and calciphylaxis. In a small case series, the drug has shown improvement in symptom burden in soft tissue calcification of the shoulder and hip, with partial size regression.[61]

Vitamin K

Vitamin K is an essential cofactor for carboxylation of numerous proteins, including some that inhibit vascular calcification, such as matrix G1a protein.[62] Evidence that lack of vitamin K may be involved in vascular calcification includes a high prevalence of vitamin K deficiency in this population and improvement in carboxylation surrogate markers with supplementation.[63,64]

Warfarin, a vitamin K antagonist, accelerates medial arterial calcification, particularly in end-stage kidney disease.[65] Furthermore, warfarin has been identified observationally as a risk factor for calciphylaxis, and low levels of carboxylation of matrix G1a protein are associated with calciphylaxis in end-stage kidney disease.[66] The suspected mechanism by which warfarin may contribute to calciphylaxis is by inhibiting vitamin K-dependent carboxylation of matrix G1a protein, a mineral-binding extracellular matrix protein that prevents calcium deposition in arteries.

Several phase 3 trials are being conducted to determine the benefit of vitamin K supplementation in vascular calcification and calciphylaxis, though a recent trial in patients with stage 4 chronic kidney disease[67] did not show improvement in vascular stiffness with vitamin K supplementation. There are no current studies looking at tumoral calcinosis and vitamin K supplementation.

Novel therapies, nonmedical management

SNF472, a myoinositol hexaphosphate that inhibits hydroxyapatite growth, has shown promise in early clinical trials in reduction of coronary artery calcium volume, while tissue-nonspecific alkaline phosphatase inhibitors are in earlier stages of development.[68,69]

Data conflict regarding whether non–calcium-based intestinal phosphate binders are superior to calcium-based binders in preventing vascular calcification and cardiovascular events

Magnesium and vitamin D supplementation in chronic and end-stage kidney disease has had varying degrees of success in preventing vascular calcification, though more studies are needed to confirm its clinical utility.[70,71] With particular relevance to soft tissue calcification, surgical debridement and hyperbaric oxygen therapies hold significant promise as adjunctive therapies to the aforementioned medical therapies.[72–74]

■ DISCLOSURES

■ REFERENCES

1. **Murton M, Goff-Leggett D, Bobrowska A, et al**. Burden of chronic kidney disease by KDIGO categories of glomerular filtration rate and albuminuria: a systematic review. Adv Ther 2021; 38(1):180–200. doi:10.1007/s12325-020-01568-8

2. **Moe S, Drüeke T, Cunningham J, et al**. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2006; 69(11):1945–1953. doi:10.1038/sj.ki.5000414

3. **Iseri K, Rashid Qureshi A, Dai L, et al**. Bone mineral density at different sites and 5 years mortality in end-stage renal disease patients: a cohort study. Bone 2020; 130:115075. doi:10.1016/j.bone.2019.115075

4. **Taal MW, Roe S, Masud T Green D, Porter C, Cassidy MJD**. Total hip bone mass predicts survival in chronic hemodialysis patients. Kidney Int 2003; 63(3):1116–1120. doi:10.1046/j.1523-1755.2003.00837.x

5. **Orlic L, Mikolasevic I, Crncevic-Orlic Z, Jakopcic I, Josipovic J, Pavlovic D**. Forearm bone mass predicts mortality in chronic hemodialysis patients. J Bone Miner Metab 2017; 35(4):396–404. doi:10.1007/s00774-016-0766-7.

6. **Disthabanchong S, Jongirasiri S, Adirekkiat S, et al**. Low hip bone mineral density predicts mortality in maintenance hemodialysis patients: a five-year follow-up study. Blood Purif 2014; 37(1):33–38. doi:10.1159/000357639

7. **Hannan FM, Kallay E, Chang W, Brandi ML, Thakkar RV**. The calcium-sensing receptor in physiology and in calcitropic and non-calcitropic diseases. Nat Rev Endocrinol 2018; 15(1):33–51. doi:10.1038/s41574-018-0115-0

8. **Centeno PP, Herberger A, Mun H-C, et al**. Phosphate acts directly on the calcium-sensing receptor to stimulate parathyroid hormone secretion. Nat Commun 2019; 10(1):4693. doi:10.1038/s41467-019-12399-9

9. **Edwards A, Bonny O**. A model of calcium transport and regulation in the proximal tubule. Am J Physiol Renal Physiol 2018; 315(4):F942–F953. doi:10.1152/ajprenal.00129.2018

10. **Bergwitz C, Jüppner H**. Regulation of phosphate homeostasis by PTH, vitamin D, and FGF23. Annu Rev Med 2010; 61:91–104. doi:10.1146/annurev.med.051308.111339

11. **Pereira RC, Salusky IB, Bowen RE, Freymiller EG, Wesseling-Perry K**. Vitamin D sterols increase FGF23 expression by stimulating osteoblast and osteocyte maturation in CKD bone. Bone 2019; 127:626–634. doi:10.1016/j.bone.2019.07.026

12. **Wesseling-Perry K, Pereira RC, Sahney S, et al**. Calcitriol and doxercalciferol are equivalent in controlling bone turnover, suppressing parathyroid hormone, and increasing fibroblast growth factor-23 in secondary hyperparathyroidism. Kidney Int 2011; 79(1):112–119. doi:10.1038/ki.2010.352

13. **Ho BB, Bergwitz C**. FGF23 signalling and physiology. J Mol Endocrinol 2021. 66(2):R23–R32. doi:10.1530/JME-20-0178

14. **Neyra JA, Hu MC, Moe OW**. Klotho in clinical nephrology: diagnostic and therapeutic implications Clin J Am Soc Nephrol 2020; 16(1):162–176. doi:10.2215/CJN.02840320

15. **Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM**. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. Kidney Int 2007; 71(5):438–441. doi:10.1038/sj.ki.5002059

16. **Chudek J, Kocelak P, Owczarek A, et al**. Fibroblast growth factor 23 (FGF23) and early chronic kidney disease in the elderly. Nephrol Dial Transplant 2014; 29(9):1757–1763. doi:10.1093/ndt/gfu063

17. **Muñoz-Castañeda JR, Rodelo-Haad C, de Mier MVP-R, Martin-Malo A, Santamaria R, Rodriguez M**. Klotho/FGF23 and Wnt signaling as important players in the comorbidities associated with chronic kidney disease. Toxins (Basel) 2020; 12(3):185. doi:10.3390/toxins12030185.

18. **Mace ML, Gravesen E, Hofman-Bang J, Olgaard K, Lewin E**. Key role of the kidney in the regulation of fibroblast growth factor 23. Kidney Int 2015; 88(6):1304–1313. doi:10.1038/ki.2015.231

19. **Saki F, Kassaee SR, Salehifar A, Omrani GHR**. Interaction between serum FGF-23 and PTH in renal phosphate excretion, a case-control study in hypoparathyroid patients. BMC Nephrol 2020; 21(1):176. doi:10.1186/s12882-020-01826-5

20. **Pelletier S, Dubourg L, Carlier M-C, Hadj-Aissa A, Fouque D**. The relation between renal function and serum sclerostin in adult patients with CKD. Clin J Am Soc Nephrol 2013; 8(5):819–823. doi:10.2215/CJN.07670712

21. **Wazir, B, Duarte R, Naicker S**. Chronic kidney disease-mineral and bone disorder (CKD-MBD): current perspectives. Int J Nephrol Renovasc Dis 2019: 12:263–276. doi:10.2147/IJNRD.S191156

22. **Schlieper G, Aretz A, Verberckmoes SC, et al**. Ultrastructural analysis of vascular calcifications in uremia. J Am Soc Nephrol 2010; 21(4):689-696. doi:10.1681/ASN.2009080829

23. **Kakani E, Elyamny M, Ayach T, El-Husseini A**. Pathogenesis and management of vascular calcification in CKD and dialysis patients. Semin Dial 2019; 32(6):553–561. doi:10.1111/sdi.12840

24. **Farrow EG, Imel EA, White KE**. Miscellaneous non-inflammatory musculoskeletal conditions. Hyperphosphatemic familial tumoral calcinosis (FGF23, GALNT3 and alph-Klotho). Best Pract Res Clin Rheumatol 2011; 25(5):735–747. doi:10.1016/j.berh.2011.10.020

25. **Slavin RE, Wen J, Barmada A**. Tumoral calcinosis--a pathogenetic overview: a histological and ultrastructural study with a report of two new cases, one in infancy. Int J Surg Pathol 2012; 20(5):462–473. doi:10.1177/1066896912444925

26. **Fathi I, Sakr M**. Review of tumoral calcinosis: a rare clinico-pathological entity. World J Clin Cases 2014; 2(9):409–414. doi:10.12998/wjcc.v2.i9.409

27. **Shetty M, Chowdhury Y, Yegneswaran B**. Calcific uremic arteriolopathy. Cleve Clin J Med 2018; 85(8):584–585. doi:10.3949/ccjm.85a.18009

28. **Ghosh T, Winchester DS, Davis MDP, El-Azhary R, Comfere NI**. Early clinical presentations and progression of calciphylaxis. Int J Dermatol 2017; 56(8):856–861. doi:10.1111/ijd.13622

29. **Colboc H, Moguelet P, Bazin D, et al**. Localization, morphologic features, and chemical composition of calciphylaxis-related skin deposits in patients with calcific uremic arteriolopathy. JAMA Dermatol 2019; 155(7):789–796. doi:10.1001/jamadermatol.2019.0381

30. **Yano H, Kinjo M**. Tumoral calcinosis. Cleve Clin J Med 2021; 88(4):208–209. doi:10.3949/ccjm.88a.20084

31. **Olsen KM, Chew FS**. Tumoral calcinosis: pearls, polemics, and alternative possibilities. Radiographics 2006; 26(3):871–885. doi:10.1148/rg.263055099

32. **Moe SM, Chen NX**. Pathophysiology of vascular calcification in chronic kidney disease. Circ Res 2004; 95(6):560–567. doi:10.1161/01.RES.0000141775.67189.98

33. **Goodman WG, Goldin J, Kuizon BD, et al**. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 2000; 342(20):1478–1483. doi:10.1056/NEJM200005183422003

34. **Jamal SA, Vandermeer B, Raggi P, et al**. Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet 2013; 382(9900):1268–1277. doi:10.1016/S0140-6736(13)60897-1

35. **Ruospo M, Palmer SC, Natale P, et al**. Phosphate binders for preventing and treating chronic kidney disease-mineral and bone disorder (CKD-MBD). Cochrane Database Syst Rev 2018; 8(8):CD006023. doi:10.1002/14651858.CD006023.pub3

36. **Toussaint ND, Pedagogos E, Lioufas NM, et al**. A randomized trial on the effect of phosphate reduction on vascular end points in CKD (IMPROVE-CKD). J Am Soc Nephrol 2020; 31(11):2653–2666. doi:10.1681/ASN.2020040411

37. **Chertow GM, Burke SK, Raggi P**. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int 2002; 62(1):245–252. doi:10.1046/j.1523-1755.2002.00434.x

38. **Qunibi WY, Nolan CR**. Treatment of hyperphosphatemia in patients with chronic kidney disease on maintenance hemodialysis: results of the CARE study. Kidney Int Suppl 2004; (90):S33–S38. doi:10.1111/j.1523-1755.2004.09006.x

39. **Watanabe K, Fujii H, Kono K, Goto S, Nishi S**. Comparison of the effects of lanthanum carbonate and calcium carbonate on the progression of cardiac valvular calcification after initiation of hemodialysis. BMC Cardiovasc Disord 2020; 20(1):39. doi:10.1186/s12872-020-01343-1

40. **Ogata H, Fukagawa M, Hirakata H, et al**. Effect of treating hyperphosphatemia with lanthanum carbonate vs calcium carbonate on cardiovascular events in patients with chronic kidney disease undergoing hemodialysis: the LANDMARK randomized clinical trial. JAMA 2021; 325(19):1946–1954. doi:10.1001/jama.2021.4807

41. **Toussaint ND, Elder GJ, Kerr PG**. Bisphosphonates in chronic kidney disease; balancing potential benefits and adverse effects on bone and soft tissue. Clin J Am Soc Nephrol 2009; 4(1):221–233. doi:10.2215/CJN.02550508

42. **Titan SM, Laureati P, Sang Y, et al**. Bisphosphonate utilization across the spectrum of eGFR. Arch Osteoporos 2020; 15(1):69. doi:10.1007/s11657-020-0702-2

43. **Robinson DE, Ali MS, Pallares N, et al**. Safety of oral bisphosphonates in moderate-to-severe chronic kidney disease: a binational cohort analysis. J Bone Miner Res 2021: 36(5):820–832. doi:10.1002/jbmr.4235

44. **de Roij van Zuijdewijn C, van Dorp W, Florquin S, Roelofs J, Verburgh K**. Bisphosphonate nephropathy: a case series and review of the literature. Br J Clin Pharmacol 2021; 87(9):3485–3491. doi:10.1111/bcp.14780

45. **Perazella MA, Markowitz GS**. Bisphosphonate nephrotoxicity. Kidney Int 2008; 74(11):1385–1393. doi:10.1038/ki.2008.356

46. **Kranenburg G, Bartstra JW, Weijmans M, et al**. Bisphosphonates for cardiovascular risk reduction: a systematic review and meta-analysis. Atherosclerosis 2016; 252:106–115. doi:10.1016/j.atherosclerosis.2016.06.039

47. **Russell RG, Smith R, Bishop MC, Price DA**. Treatment of myositis ossificans progressiva with a diphosphonate. Lancet 1972; 1(7740): 10–11. doi:10.1016/s0140-6736(72)90004-9

48. **Fleisch HA, Russell RG, Bisaz S, Mühlbauer RC, Williams**. The inhibitory effect of phosphonates on the formation of calcium phosphate crystals in vitro and on aortic and kidney calcification in vivo. Eur J Clin Invest 1970; 1(1):12–18. doi:10.1111/j.1365-2362.1970.tb00591.x

49. **Hildebrand S, Cunningham J**. Is there a role for bisphosphonates in vascular calcification in chronic kidney disease? Bone 2021: 142:115751. doi:10.1016/j.bone.2020.115751

50. **Nitta K, Akiba T, Suzuki K, et al**. Effects of cyclic intermittent etidronate therapy on coronary artery calcification in patients receiving long-term hemodialysis. Am J Kid Dis 2004; 44(4):680–688.

pmid:15384019

51. **Hashiba H, Aizawa S, Tamura K, Kogo H**. Inhibition of the progression of aortic calcification by etidronate treatment in hemodialysis patients: long-term effects. Ther Apher Dial 2006; 10(1):59–64. doi:10.1111/j.1744-9987.2006.00345.x

52. **Iseri K, Watanabe M, Yoshikawa H, et al**. Effects of denosumab and alendronate on bone health and vascular function in hemodialysis patients: a randomized, controlled trial. J Bone Miner Res 2019; 34(6):1014–1024. doi:10.1002/jbmr.3676

53. **Chen C-L, Chen N-C, Wu F-Z, Wu M-T**. Impact of denosumab on cardiovascular calcification in patients with secondary hyperparathyroidism undergoing dialysis: a pilot study. Osteoporos Int 2020; 31(8):1507–1516. doi:10.1007/s00198-020-05391-3

54. **Sin H-K, Wong P-N, Lo K-Y, et al**. Treatment of severe tumoral calcinosis with teriparatide in a dialysis patient after total parathyroidectomy. Case Rep Nephrol 2021; 2021:6695906–6695906. doi:10.1155/2021/6695906

55. **EVOLVE Trial Investigators; Chertow GM, Block GA, Correa-Rotter R, et al, Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis**. N Engl J Med 2012; 367(26):2482–2494. doi:10.1056/NEJMoa1205624

56. **Raggi P, Chertow GM, Torres PU, et al**. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. Nephrol Dial Transplant 2011; 26(4):1327–1339. doi:10.1093/ndt/gfq725

57. **Zu Y, Lu X, Song J, Yu L, Wang S**. Cinacalcet treatment significantly improves all-cause and cardiovascular survival in dialysis patients: results from a meta-analysis. Kidney Blood Press Res 2019; 44(6):1327–1338. doi:10.1159/000504139

58. **Peng T, Zhuo L, Wang Y, et al**. Systematic review of sodium thiosulfate in treating calciphylaxis in chronic kidney disease patients. Nephrology (Carlton) 2018; 23(7):669–675. doi:10.1111/nep.13081

59. **Udomkarnjananun S, Kongnatthasate K, Praditpornsilpa K, Eiam-Ong S, Jaber BL, Susantitaphong P**. Treatment of calciphylaxis in CKD: a systematic review and meta-analysis. Kidney Int Rep 2019; 4(2):231–244. doi:10.1016/j.ekir.2018.10.002

60. **Djuric P, Dimkovic N, Schlieper G, et al**. Sodium thiosulphate and progression of vascular calcification in end-stage renal disease patients: a double-blind, randomized, placebo-controlled study. Nephrol Dial Transplant 2020; 35(1):162–169. doi:10.1093/ndt/gfz204

61. **Malbos S, Urena-Torres P, Cohen-Solal M, et al**. Sodium thiosulphate treatment of uraemic tumoral calcinosis. Rheumatology (Oxford) 2014; 53(3):547–551. doi:10.1093/rheumatology/ket388

62. **Shioi A, Morioka T, Shoji T, Emoto M**. The inhibitory roles of vitamin K in progression of vascular calcification. Nutrients 2020; 12(2):583. doi:10.3390/nu12020583

63. **Vlasschaert C, Goss CJ, Pilkey NG, McKeown S, Holden RM**. Vitamin K supplementation for the prevention of cardiovascular disease: where is the evidence? A systematic review of controlled trials. Nutrients 2020; 12(10): 2909. doi:10.3390/nu12102909

64. **Fusaro M, D'Alessandro C, Noale M, et al**. Low vitamin K1 intake in haemodialysis patients. Clin Nutr 2017; 36(2):601–607. doi:10.1016/j.clnu.2016.04.024

65. **Alappan HR, Kaur G, Manzoor S, Navarrete J, O'Neill WC**. Warfarin accelerates medial arterial calcification in humans. Arterioscler Thromb Vasc Biol 2020; 40(5):1413–1419. doi:10.1161/ATVBAHA.119.313879

66. **Nigwekar SU, Bloch DB, Nazarian RM, et al**. Vitamin K-dependent carboxylation of matrix Gla protein influences the risk of calciphylaxis. J Am Soc Nephrol 2017; 28(6):1717–1722. doi:10.1681/ASN.2016060651

67. **Witham MD, Lees JS, White M, et al**. Vitamin K supplementation to improve vascular stiffness in CKD: the K4Kidneys randomized controlled trial. J Am Soc Nephrol 2020; 31(10):2434–2445. doi:10.1681/ASN.2020020225

68. **Savinov AY, Salehi M, Yadav MC, Radichev I, Milán JL, Savinova OVl**. Transgenic overexpression of tissue-nonspecific alkaline phosphatase (TNAP) in vascular endothelium results in generalized arterial

calcification. J Am Heart Assoc 2015; 4(12):e002499. doi:10.1161/JAHA.115.002499.

69. **Raggi P, Bellasi A, Bushinsky D, et al**. Slowing progression of cardiovascular calcification with SNF472 in patients on hemodialysis: results of a randomized phase 2b study. Circulation 2020; 141(9):728–739. doi:10.1161/CIRCULATIONAHA.119.044195

70. **Alshahawey M, Borolossy R, El Wakeel L, Elsaid T, Sabri NA**. The impact of cholecalciferol on markers of vascular calcification in hemodialysis patients: a randomized placebo controlled study. Nutr Metab Cardiovasc Dis 2021; 31(2):626–633. doi:10.1016/j.numecd.2020.09.014

71. **Sakaguchi Y, Hamano T, Obi Y, et al**. A randomized trial of magnesium oxide and oral carbon adsorbent for coronary artery calcification in predialysis CKD. J Am Soc Nephrol 2019 30(6):1073–1085.

doi:10.1681/ASN.2018111150

72. **Charaghvandi DA, Teguh DN, van Hulst RA**. Hyperbaric oxygen therapy in patients suffering from wounds in calciphylaxis: a narrative review. Undersea Hyperb Med 2020; 47(1):111–123. doi:10.22462/01.03.2020.12

73. **Lai L-A, Hsiao M-Y, Wu C-H, Wang T-G, Özçakar L**. Big gain, no pain: tumoral calcinosis. Am J Med 2018. 131(1):45–47. doi:10.1016/j.amjmed.2017.09.003

74. **Gabel CK, Nguyen ED, Chakrala T, et al**. Assessment of outcomes of calciphylaxis. J Am Acad Dermatol 2020; 85(4):1057–1064. doi:10.1016/j.jaad.2020.10.067

Address: Korey Bartolomeo, DO, Department of Kidney Medicine, Q7, Glickman Urological & Kidney Institute, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; krbartolomeo@gmail.com

Sassine Ghanem, MD
Department of Stem Cell Transplantation and Cellular Therapy, UT MD Anderson Cancer Center, Houston, TX

Jason Gonsky, MD, PhD
Acting Director of Hematology and Oncology, Director of Cancer Research, and Chair of the Hematology and Oncology Protocol Committee, NYC Health + Hospitals/Kings County; Assistant Professor of Medicine, SUNY Downstate Medical Center, Brooklyn, NY

Recurrent anemia in a patient with chronic lymphocytic leukemia

A 73-YEAR-OLD MAN PRESENTED with lymphocytosis and retroperitoneal lymphadenopathy and was found to have chronic lymphocytic leukemia (CLL), Rai stage II (possible stages are 0–IV). He was not initially treated for it but was monitored until 5 months later, when he was admitted to the hospital with multilobar pneumonia with acute hypoxic respiratory failure and a white blood cell count of 139×10^9/L (reference range 4.5–10.9×10^9/L). He was treated with a combination of broad-spectrum antibiotics, vasopressor support, and high-dose corticosteroids.

FIRST EPISODE OF ANEMIA

His hospital course was complicated by complement-fixing nonimmunoglobulin G autoimmune hemolytic anemia, as well as tumor lysis syndrome. During this episode, he had the following laboratory values:

- Hemoglobin 5.5 g/dL (14–18 g/dL)
- Mean corpuscular volume 106 fL (80–100 fL)
- Lactate dehydrogenase 903 mg/dL (135–225 mg/dL)
- Reticulocyte count 96×10^9/L, 4.4% (90–130×10^9/L, 1%–2%)
- Haptoglobin undetectable.

Most likely, a factor contributing to tumor lysis syndrome was the use of corticosteroids to treat his respiratory failure, which led to destruction of lymphocytes and spilling of intracellular components. This was manifested by hyperphosphatemia, hyperuricemia, and acute kidney injury, consistent with tumor lysis syndrome.

To control his autoimmune hemolytic anemia, the patient was given a combination of

prednisone 1 mg/kg tapered over 6 weeks and intravenous immune globulin 500 mg/kg daily for 5 days, followed by rituximab 375 mg/m² once a week for 4 doses, and his anemia resolved.

SECOND EPISODE OF ANEMIA

Four months later his anemia recurred, with a hemoglobin level of 6.5 g/dL.

1 What would be your next step in managing this patient's anemia at this time?

- ☐ Restart steroids; this is a recurrence of his autoimmune hemolytic anemia
- ☐ Perform a workup to determine the cause of his anemia, including reticulocyte count, lactate dehydrogenase, haptoglobin, bilirubin counts, direct antiglobulin test, and peripheral smear review
- ☐ Perform bone marrow aspiration and biopsy
- ☐ No need for further evaluation, start treatment of CLL
- ☐ Check flow cytometry

The next step should be to perform a workup to determine the cause of the anemia.

FINDING THE CAUSE OF ANEMIA

Anemia—a hemoglobin below 13 g/dL in men and below 12 g/dL in women[1]—can result from a deficit in red blood cell production, destruction of red blood cells, or blood loss. An evaluation of new anemia following the algorithm outlined in **Figure 1** as an initial step will help define the mechanism and guide its management. The first step is to check the reticulocyte count, a marker of bone marrow production that can help differentiate the underlying mechanism of acquired anemia.

A 73-year-old man with CLL developed autoimmune hemolytic anemia while hospitalized for pneumonia

Anemia
(hemoglobin < 13 g/dL in men,
< 12 g/dL in women)

↓

Check:
Reticulocytes (normal range 1%–2%)
Mean corpuscular volume (MCV; normal range 80–100 fL)
Red cell distribution width (RDW; normal range 11%–15%)

Reticulocytes < 1%   **Reticulocytes > 2%**

Production deficit   **Active bone marrow**

High MCV   **Normal MCV (80–100 fL)**   **Low MCV**   **Blood loss**   **Destruction**
(> 100 fL)   Viral infection   **(< 80 fL)**   (normal MCV followed by   (decreased haptoglobin,
Vitamin B$_{12}$ Drug effect   Iron deficiency   increased MCV and RDW) [a]   elevated lactate dehydrogenase,
  deficiency   Leukemic infiltration   increased indirect bilirubin,
Folate deficiency   Solid tumor infiltration   ↓   increased MCV and RDW on
                      Pure red cell aplasia   peripheral smear)
                        (if isolated anemia)   **Source control**
                      Aplastic anemia   Transfuse as necessary   Immune (Coombs-positive)
                                                                                                            Traumatic
                                                                                                            G6PD deficiency
                                                                                                            Thrombotic microangiopathy

Figure 1. General approach to finding the mechanism of anemia.

[a]Blood loss initially presents with a normal MCV and RDW due to strict whole volume loss. However, with subsequent reticulocytosis, the MCV will increase, thus increasing the RDW. Chronic blood loss leads to iron deficiency, which manifests with anemia that has a low MCV and high RDW.

G6PD = glucose-6-phosphate dehydrogenase

If the reticulocyte count is high

Reticulocytes are immature red blood cells. If there are more of them than usual in the blood of a patient with anemia, it means that the bone marrow is functioning and is responding to the red blood cell destruction or blood loss by increasing the production of red blood cells.

Reticulocytes are larger than mature red blood cells, and an increased proportion of reticulocytes causes an increase in the mean corpuscular volume as well as the red cell distribution width, which represents the variability in size of the red blood cells.

An elevated reticulocyte count associated with low haptoglobin, elevated lactate dehydrogenase, and elevated indirect bilirubin is consistent with a hemolytic process.[2]

A positive direct antiglobulin test (also called the direct Coombs test) and spherocytes on the peripheral smear suggest autoimmune hemolytic anemia. On the other hand, a negative direct antiglobulin test points to traumatic hemolysis, thrombotic microangiopathy, or oxidative hemolysis due to enzyme defects such as glucose-6-phosphate dehydrogenase (G6PD) deficiency as the cause of hemolysis. Traumatic hemolysis and thrombotic microangiopathy present with schistocytes on the peripheral smear, while G6PD deficiency manifests with bite and blister cells.

A negative hemolytic workup with an elevated reticulocyte count suggests hemorrhage. Management of a clinically overt hemorrhage is directed at controlling the source. In cases in which the source of blood loss is not obvi-

ous, imaging and endoscopy to look for internal bleeding can be helpful.

With acute blood loss, the mean corpuscular volume is initially normal until reticulocytes enter circulation. Chronic blood loss leads to iron deficiency, which is associated with a low mean corpuscular volume and elevated red blood cell distribution width, as red blood cells will have different sizes depending on the amount of iron available as they develop.

If the reticulocyte count is normal or low

If the reticulocyte count is not elevated in the setting of anemia, this suggests impaired bone marrow function. Bone marrow dysfunction can be due to a viral illness, drug effect, nutritional deficiency, infiltration of the marrow by malignant cells, infection, fibrosis, pure red cell aplasia, aplastic anemia, or myelodysplasia. The clinical history and review of medications are helpful in identifying a viral or drug effect. Diagnosis of an infiltrative process requires bone marrow aspiration and biopsy.

Vitamin B_{12} and folate are essential for nucleic acid synthesis. Deficiency in either of these nutrients will lead to asynchrony in nucleic acid and cytoplasmic development of red blood cells, leading to megaloblastic anemia with elevated mean corpuscular volume and a low reticulocyte count.

Moreover, because iron, folate, and vitamin B_{12} are required for erythropoiesis, the reticulocyte count could be falsely low in a patient with anemia that is due to red blood cell destruction or blood loss in case of a concomitant nutritional deficiency.

Causes of anemia in chronic lymphocytic leukemia

Anemia is a manifestation of many different diseases, not a disease itself. With each episode of anemia, a new evaluation is needed to determine if it is a recurrence of the previous condition—in our patient, autoimmune hemolysis. Whether or not the patient has CLL, it is important to keep in mind the common causes of anemia in elderly people, such as gastrointestinal angiodysplasia, diverticulosis, and myelodysplasia. However, certain complications and associations are more frequent in patients with CLL, and these include the following:

- Enlarged spleen
- Autoimmune hemolytic anemia (such as in our patient's initial episode)
- Marrow suppression due to extensive disease infiltration
- Marrow suppression secondary to drug or chemotherapy
- Gastrointestinal blood loss that is related to drug adverse effects (glucocorticoids or ibrutinib), thrombocytopenia, or coagulopathy
- Pure red blood cell aplasia.

The prevalence of autoimmune hemolysis in CLL varies among different case series, ranging between 5% and 10%.[3,4] The development of autoimmune hemolysis in CLL is more frequent in men, older patients (over age 65), and patients with a lymphocyte count greater than 60×10^9/L.[4]

Of note, patients with CLL can have a positive direct antiglobulin test without autoimmune hemolysis. In a retrospective series by Ricci et al,[5] the prevalence of direct antiglobulin test positivity in patients with CLL was 14%, but only 8 (40%) of the 20 patients with positive tests had autoimmune hemolysis.

Autoimmune hemolysis in chronic lymphocytic leukemia is treated with steroids

Treatment of autoimmune hemolysis in a patient with CLL follows the same algorithm as for idiopathic autoimmune hemolytic anemia. Glucocorticoids are the initial treatment. However, treatment with steroids should not be started again in our patient before confirming that his second episode of anemia is also of autoimmune origin. Only in cases that are refractory to steroids is treatment of underlying CLL indicated, according to an international working group on CLL.[6] Interestingly, in patients with CLL, autoimmune hemolysis does not have independent prognostic significance.[4]

■ THE PATIENT UNDERWENT BIOPSY

The patient received steroids and intravenous immunoglobulin followed by rituximab, which would affect both the B-cell clone secreting the antibodies causing the hemolytic anemia and the B-cell clone responsible for his CLL.

Laboratory testing during the second episode of anemia revealed a low reticulocyte count,

Anemia is a manifestation of many different diseases, not a disease itself

TABLE 1

The patient's laboratory values in his second episode of anemia

Study	Patient's value	Reference range
Hemoglobin	6.5 g/dL	14–18 g/dL
Reticulocyte count	13.26 x 10⁹/L (0.65%)	90–130 x 10⁹/L (1%–2%)
Mean corpuscular volume	85 fL	78–95 fL
Red cell distribution width	14%	11.5%–15.1%
Lactate dehydrogenase	162 U/L	135–225 U/L
Direct antiglobulin test	Negative	Negative
Haptoglobin	336 mg/dL	30–200 mg/dL
Indirect bilirubin	0.2 mg/dL	1.0–1.0 mg/dL
Peripheral smear		
Red blood cells	Normocytic, decreased in number, no schistocytes, no spherocytes	
White blood cells	Lymphocytes predominant, no immature white blood cells	
Platelets	Normal in size and granulation	

Four months later his anemia recurred– but was it the same?

normal lactate dehydrogenase and indirect bilirubin levels, and a high haptoglobin level, suggesting bone marrow suppression (**Table 1**). The patient did not have any clinical signs to suggest a viral infection, and he was receiving no drugs commonly associated with anemia.

Because the pattern was different than in his first episode and pointed to a problem in the bone marrow, the patient underwent bone marrow aspiration and biopsy, which revealed pure red blood cell aplasia and marrow infiltration by CLL.

Pure red cell aplasia

Pure red cell aplasia is a well-described but uncommon autoimmune complication of CLL, seen in less than 1% of patients.[7] It is characterized by anemia with severe reticulocytopenia, with reticulocyte counts usually less than 10×10^9/L, and by marked reduction or absence of erythroid precursors on bone marrow aspiration and biopsy. Pure red cell aplasia affects only the erythrocyte lineage, leading to a decrease in production of otherwise-normal red blood cells. Therefore, as in our patient, the peripheral smear red blood cells would have a normal morphology.[8]

Viral infections and thymoma should be ruled out in all patients who develop acquired pure red cell aplasia. Thymomas are rare in the general adult population, and although previous reports suggested that up to 50% of patients with pure red cell aplasia had thymomas, the prevalence is now thought to be much lower.[8]

The management of acquired pure red cell aplasia depends on the cause and includes intravenous immune globulin for viral infections and surgical resection for thymomas. In pure red cell aplasia secondary to a lymphoproliferative disorder, the treatment is directed at the underlying disease, which in our patient is CLL.[8]

◾ WHEN SHOULD CLL BE TREATED?

While both autoimmune hemolysis and pure red cell aplasia are associated with CLL, not all cases of anemia that arise in a patient with CLL are due to disease progression. Most patients with CLL are elderly, and therefore the causes of anemia that arise in the elderly population such as gastrointestinal angiodys-

plasia, diverticulosis, or myelodysplasia need to be excluded.

Many people with CLL can forgo therapy for an extended time with close observation. CLL is chronic and currently incurable, and the goal of treatment is to manage its complications. Treatment is indicated when disease is bulky, symptomatic, or rapidly evolving or causes cytopenias.[6]

Indications for treatment, per the CLL working group,[6] include the following:

- Progressive marrow failure evidenced by the development or worsening of anemia or thrombocytopenia
- Splenomegaly that is massive (ie, ≥ 6 cm below the left costal margin), progressive, or symptomatic
- Lymphadenopathy that is massive (ie, ≥ 10 cm in longest diameter), progressive, or symptomatic
- Rapidly progressive lymphocytosis with a doubling of the lymphocyte count over less than 6 months or an increase of more than 50% over a 2-month period
- Autoimmune anemia or thrombocytopenia that is refractory to corticosteroids
- Constitutional "B symptoms."

Constitutional B symptoms include the following:

- Unintentional weight loss of 10% or more within the previous 6 months
- Significant fatigue (ie, Eastern Cooperative Oncology Group performance status ≥ 2 on a scale of 0–5; inability to work or perform usual activities)[9]
- Fever, with a temperature greater than 100.5 °F (38.0 °C) for at least 2 weeks without other evidence of infection
- Night sweats for at least 1 month without evidence of infection.

Is flow cytometry needed?

There is no reason to repeat flow cytometry during an episode of anemia, as it would only reconfirm the diagnosis of CLL and would not have any effect on management.

■ CASE CONTINUED

As noted above, the patient's second episode of anemia was determined to be due to pure red cell aplasia.

A trial of steroids was ineffective, and the

TABLE 2

The patient's complete blood cell count in the emergency department in his third episode of anemia

Study	Patient's value	Reference range
Red blood cell count	1.57×10^{12}/L	4.2–6.1×10^{12}/L
Hemoglobin	4.3 g/dL	14–18 g/dL
Hematocrit	14.2%	42%–52%
White blood cell count	12.15×10^9/L	4.5–10.9×10^9/L
Neutrophils	10.58×10^9/L	1.5–7.30×10^9/L
Lymphocytes	0.84×10^9/L	0.88–5.83×10^9/L
Monocytes	0.61×10^9/L	0.09–1.11×10^9/L
Eosinophils	0.00×10^9/L	0.00–1.04×10^9/L
Basophils	0.02×10^9/L	0.00–1.20×10^9/L
Platelet count	735×10^9/L	130–400×10^9/L

patient was subsequently started on ibrutinib with rituximab to treat his CLL. The anemia resolved, but the patient developed severe neutropenia that resolved after withdrawing the rituximab. The patient remained well for more than 2 years while taking ibrutinib alone, with resolution of anemia and no additional complications of CLL.

A third episode of anemia

At a follow-up telehealth visit, the patient's hemoglobin level was noted to have decreased from 11.6 g/dL to 8.9 g/dL over the course of 6 months. He said he had no signs or symptoms of bleeding and no new palpable lymph nodes. Repeat blood tests and imaging were arranged.

When the patient came in for computed tomography, he appeared pale, his heart rate was rapid, and he reported having dyspnea on exertion. Sent to the emergency department, he said he had had no recent hematochezia, melena, bleeding, or trauma, and he had no palpable lymphadenopathy or hepatosplenomegaly.

He was found to have severe anemia, with a hemoglobin level of 4.3 g/dL (**Table 2**). Results of his basic metabolic panel on presentation are shown in **Table 3**. He was given a transfusion of 3 units of packed red blood cells.

Biopsy revealed pure red cell aplasia as the cause of the second episode

TABLE 3

The patient's basic metabolic panel in the emergency department in his third episode of anemia

Study	Patient's value	Reference range
Sodium	134 mmol/L	136–146 mmol/L
Potassium	5.4 mmol/L	3.5–5.0 mmol/L
Chloride	90 mmol/L	98–106 mmol/L
Carbon dioxide	13 mmol/L	24–31 mmol/L
Creatinine	1.22 mg/dL	0.5–0.9 mg/dL
Urea	25 mg/dL	8–23 mg/dL
Calcium	0.6 mg/dL	9.9–10.2 mg/dL
Glucose	306 mg/dL	70–99 mg/dL

■ WHAT IS THE NEXT STEP?

2 Which of the following is the appropriate next step in evaluating the patient's anemia?

☐ No need for further evaluation, start next-line treatment for CLL
☐ Anemia workup including reticulocyte count, lactate dehydrogenase, haptoglobin, bilirubin, direct antiglobulin test, and peripheral smear review
☐ Bone marrow aspiration and biopsy
☐ Hold ibrutinib
☐ Computed tomography of the chest, abdomen, and pelvis

The patient did well for 2 years on ibrutinib, but then the anemia returned

Anemia workup. As previously mentioned, every episode of anemia requires a new evaluation, following the algorithm outlined in **Figure 1**, and therefore this is again the best next step.

Bone marrow aspiration and biopsy. Findings of a decreased reticulocyte count with normal iron, vitamin B_{12}, and folate would indicate an impaired bone marrow necessitating biopsy and aspiration. While bone marrow biopsy carries minimal risk, it is still an invasive procedure that is uncomfortable for the patient, and therefore it would be unjustified before excluding other causes through a repeat anemia workup.

Holding the ibrutinib would also be reasonable in managing this patient's anemia.

Ibrutinib is an irreversible inhibitor of Bruton tyrosine kinase, an integral component of the B-cell receptor signaling and cytokine receptor pathways that allow malignant B cells to survive. It can contribute to anemia through 2 mechanisms, ie, by inducing cytopenia and by inhibiting platelet activation, leading to bleeding. Drug-induced anemia improves when the inciting factor is removed. Treatment of bleeding in a patient receiving ibrutinib includes discontinuing the ibrutinib and transfusing platelets. The incidence of bleeding with ibrutinib is highest in the first 2 years of treatment, then decreases with time.[10]

Treating the CLL. Clinical examination is helpful in evaluating anemia in CLL. Disease progression can cause splenomegaly that can lead to anemia. Bulky adenopathy can be a manifestation of progression of CLL and is an indication for treatment. However, not all adenopathy is clinically palpable.

Computed tomography. Further investigation with computed tomography is controversial but can be considered to look for lymphadenopathy in nonpalpable sites such as the mediastinum and retroperitoneum.

■ CASE CONTINUED: UNEXPECTED BIOPSY FINDINGS

The results of further laboratory evaluation of the patient's third episode of anemia are included in **Table 4**.

After the patient received a transfusion of packed red blood cells his hemoglobin level increased to 7.2 g/dL. Laboratory testing revealed that he again had decreased reticulocytes and no indications of hemolysis.

The patient again underwent bone marrow aspiration and biopsy, which this time revealed focal clusters of epithelial cell proliferation, mostly in solid nests with focal glandular formation (**Figure 2**). In addition, there was a trace population of kappa light-chain restricted monoclonal B cells (0.08%) with a flow cytometry phenotype consistent with CLL. Staining of the epithelial clusters was positive for AE1 and AE3 (which are cytokeratins positive in carcinomas) and NKX3.1 (which is 98.6% sensitive and 99.7% specific for prostate adenocarcinoma).[11,12]

The biopsy results suggested that the cause

TABLE 4

Further laboratory findings in the patient's third episode of anemia

Study	Patient's value	Reference range
Reticulocyte count	9.9 x 10⁹/L (0.6%)	90–130 x 10⁹/L (1%–2%)
Mean corpuscular volume	90.5 fL	78–95 fL
Red cell distribution width	15.9%	11.5%–15.1%
Lactate dehydrogenase	231 U/L	135–225 U/L
Direct antiglobulin test	Negative	Negative
Haptoglobin	362 mg/dL	30–200 mg/dL
Indirect bilirubin	0.7 mg/dL	0.0–1.0 mg/dL
Peripheral smear Red blood cells	Normocytic, normochromic, rare schistocytes, no nucleated red blood cells, no teardrop cells	
White blood cells	No immature white blood cells noted, neutrophil predominance, small mature lymphocytes	
Platelets	Increased in number, few giant platelets noted	

of the anemia was metastatic prostate adenocarcinoma, and treating the prostate cancer would treat the anemia. In metastatic hormone-sensitive prostate adenocarcinoma, the first step in treatment includes androgen deprivation therapy through either surgical castration or medical castration with the use of gonadotropin-releasing hormone agonists and antagonists.[13]

■ EFFECT OF PROSTATE CANCER ON THE PERIPHERAL BLOOD SMEAR

Myelophthisis refers to displacement of hematopoietic cells from the bone marrow by an infiltrative process, most commonly malignancy, fibrosis, or a granulomatous process. In some cases, hematopoietic stem cells relocate to niches outside of the marrow, a phenomenon known as extramedullary hematopoiesis. Extramedullary hematopoiesis usually develops in the liver, spleen, or both.

Myelophthisis often leads to immature precursors, including nucleated red blood cells, immature granulocytes such as myelocytes or metamyelocytes, as well as teardrop-shaped red blood cells spilling into the circulation. The constellation of these findings on the peripheral blood smear is termed leukoerythroblastosis.[14,15]

Myelophthisis is found in less than 10% of cases of metastatic carcinoma and is most frequent in prostate, breast, and lung cancers.[16] In one review,[17] among patients with carcinoma that was metastatic to the bone marrow, only 44% exhibited signs of leukoerythroblastosis. Our patient's peripheral blood smear did not show any of the typical signs of leukoerythroblastosis, revealing only a normocytic anemia. Treatment of myelophthisis is aimed at managing the underlying infiltrative process, improving bone marrow function, and resolving cytopenias.

This time, biopsy told a different story

■ CASE CONCLUDED

Imaging and blood tests revealed that the patient's previously noted mesenteric lymphadenopathy had decreased in size with no new sites of lymphadenopathy. However, he had new diffuse bony sclerotic lesions and a prostate-specific antigen level of 664 ng/mL (normal < 4 ng/mL). These findings suggested that his CLL was still under control but he also had stage IV prostate cancer with bone metastases.

The patient's CLL continues to be managed with ibrutinib. He was started on anti-androgen therapy with leuprolide, a gonadotropin-releas-
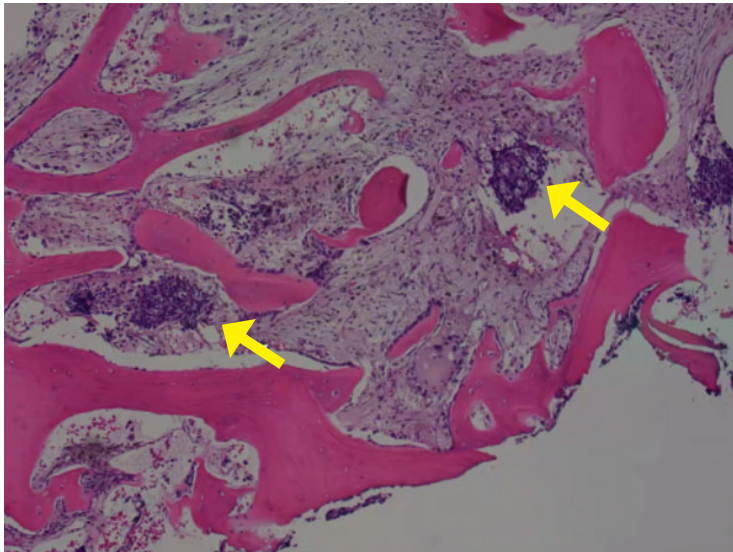
Figure 2. Focal bone marrow infiltration by solid nests of tumor cells (arrows) in the patient's third episode of anemia (hematoxylin and eosin, × 20).

ing hormone agonist, as well as abiraterone acetate, an inhibitor of CYP17, an enzyme required for androgen biosynthesis. His bone metastases have responded to treatment. He feels back to normal and has regained his energy and takes care of all his activities of daily living.

■ TAKE-HOME POINTS

CLL is generally considered an incurable, chronic disease. The current treatment strategy is to manage the complications of the disease, which can include cytopenias. It is therefore essential to understand the multiple mechanisms of anemia in patients with CLL, how to diagnose them, and how to manage them.

Every new episode of anemia does not automatically imply disease progression, and each should be evaluated completely. The initial evaluation should include at least the reticulocyte count to assess bone marrow response, the mean corpuscular volume, the red cell distribution width, and review of the peripheral smear with further testing as needed.

This case also highlights the importance of avoiding anchoring bias, as each new episode of anemia had a different cause that called for different treatment. ■

■ DISCLOSURES

■ REFERENCES

1. **Nutritional anaemias**. Report of a WHO scientific group. World Health Organ Tech Rep Ser 1968; 405:5–37. pmid:4975372
2. **Phillips J, Henderson AC**. Hemolytic anemia: evaluation and differential diagnosis. Am Fam Physician 2018; 98(6):354–361. pmid:30215915
3. **Dührsen U, Augener W, Zwingers T, Brittinger G**. Spectrum and frequency of autoimmune derangements in lymphoproliferative disorders: analysis of 637 cases and comparison with myeloproliferative diseases. Br J Haematol 1987; 67(2):235–239. doi:10.1111/j.1365-2141.1987.tb02333.x
4. **Mauro FR, Foa R, Cerretti R, et al**. Autoimmune hemolytic anemia in chronic lymphocytic leukemia: clinical, therapeutic, and prognostic features. Blood 2000; 95(9):2786–2792. pmid:10779422
5. **Ricci F, Tedeschi A, Vismara E, et al**. Should a positive direct antiglobulin test be considered a prognostic predictor in chronic lymphocytic leukemia? Clin Lymphoma Myeloma Leuk 2013; 13(4):441–446. doi:10.1016/j.clml.2013.02.024
6. **Hallek M, Cheson BD, Catovsky D, et al**. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. Blood 2018; 131(25):2745–2760. doi:10.1182/blood-2017-09-806398
7. **Visco C, Barcellini W, Maura F, Neri A, Cortelezzi A, Rodeghiero F**. Autoimmune cytopenias in chronic lymphocytic leukemia. Am J Hematol 2014; 89(11):1055–1062. doi:10.1002/ajh.23785
8. **Means RT Jr**. Pure red cell aplasia. Hematology Am Soc Hematol Educ Program 2016; 2016(1):51–56. doi:10.1182/asheducation-2016.1.51
9. **ECOG-ACRIN Cancer Research Group**. ECOG performance status. https://ecog-acrin.org/resources/ecog-performance-status. Accessed January 20 2022.
10. **Burger JA, Barr PM, Robak T, et al**. Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia 2020; 34(3):787–798. doi:10.1038/s41375-019-0602-x
11. **Berg A, Berner A, Lilleby W, et al**. Impact of disseminated tumor cells in bone marrow at diagnosis in patients with nonmetastatic prostate cancer treated by definitive radiotherapy. Int J Cancer 2007; 120(8): 1603–1609. doi:10.1002/ijc.22488
12. **Gurel B, Ali TZ, Montgomery EA, et al**. NKX3.1 as a marker of prostatic origin in metastatic tumors. Am J Surg Pathol 2010; 34(8):1097–1105. doi:10.1097/PAS.0b013e3181e6cbf3
13. **Loblaw DA, Mendelson DS, Talcott JA, et al**. American Society of Clinical Oncology recommendations for the initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer. J Clin Oncol 2004; 22(14):2927–2941. doi:10.1200/JCO.2004.04.579
14. **Clifford GO**. The clinical significance of leukoerythroblastic anemia. Med Clin North Am 1966; 50(3):779–790. doi:10.1016/s0025-7125(16)33177-7
15. **O'Keane JC, Wolf BC, Neiman RS**. The pathogenesis of splenic extramedullary hematopoiesis in metastatic carcinoma. Cancer 1989; 63(8): 1539–1543. doi:10.1002/1097-0142(19890415)63:8<1539::aid-cncr2820630814>3.0.co;2-5
16. **Makoni SN, Laber DA**. Clinical spectrum of myelophthisis in cancer patients. Am J Hematol 2004; 76(1):92–93. doi:10.1002/ajh.20046
17. **Delsol G, Guiu-Godfrin B, Guiu M, Pris J, Corberand J, Fabre J**. Leuko-erythroblastosis and cancer frequency, prognosis, and physiopathologic significance. Cancer 1979; 44(3):1009–1013. doi:10.1002/1097-0142(197909)44:3<1009::aid-cncr2820440331>3.0.co;2-j

Address: Sassine Ghanem, MD, Department of Stem Cell Transplantation and Cellular Therapy, UT MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, TX 77030; sghanem@mdanderson.org; sassinegh@gmail.com

Saif Munther Borgan, MD
Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic, Cleveland, OH

Leila Zeinab Khan, MD
Medical Director, Calcium and Parathyroid Center, Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic; Clinical Assistant Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Vinni Makin, MD, FACE
Director, East Region, Department of Endocrinology, Diabetes, and Metabolism, Cleveland Clinic; Assistant Professor of Medicine, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Hypercalcemia and vitamin A: A vitamin to keep in mind

ABSTRACT

Vitamin A, like many things in life, should be consumed in appropriate amounts. Excessive intake of preformed vitamin A, such as that found in supplements and animal sources (animal liver, fish liver oil, dairy, and eggs), is associated with multisystem effects that can include bone resorption and hypercalcemia. Hence, vitamin A toxicity should be explored in unexplained cases of parathyroid hormone-independent hypercalcemia. Serum retinol levels can be helpful in the diagnosis, but the results must be interpreted with caution since they do not always reflect total body levels. Treatment involves supportive care and withdrawal of vitamin A sources, especially preformed ones. Given the long half-life of retinol, normalization of serum levels can take several months.

KEY POINTS

Vitamin A is present in two forms, ie, preformed (retinoids) or as a precursor (carotenoids).

Vitamin A toxicity occurs only from over-ingestion of preformed vitamin A, found in animal sources, supplements, and medications, because absorption of preformed vitamin A is under minimal regulation at the level of the small intestine.

Acute vitamin A toxicity can present with multisystem manifestations including hepatic, neurologic, skin, mucous membrane, and musculoskeletal damage.

Chronic ingestion of vitamin A beyond the recommended daily amount can be associated with increased bone resorption, reduced bone formation, hypercalcemia, and increased risk of fractures.

VITAMIN A TOXICITY IS OFTEN overlooked in the diagnostic evaluation of hypercalcemia, which itself is often detected incidentally during unrelated laboratory testing.[1,2] The diagnostic evaluation of hypercalcemia starts with establishing the role of parathyroid hormone (PTH) in its pathogenesis. An elevated PTH level may indicate primary hyperparathyroidism, tertiary hyperparathyroidism, or familial hypocalciuric hypercalcemia. A low PTH should trigger an evaluation for hypercalcemia induced by PTH-related peptide (PTHrP). Vitamin A toxicity should be considered in the diagnostic workup along with malignancy, bone metastasis, vitamin D or calcium toxicity, increased 1,25-hydroxyvitamin D production (eg, from granulomatous disorders and lymphomas), hyperthyroidism, monoclonal gammopathy, and immobility.[3]

In this article, we explore vitamin A toxicity in the differential diagnosis of hypercalcemia.

■ A CASE SCENARIO: AN ELDERLY WOMAN WITH HYPERCALCEMIA

An elderly woman presented to our outpatient endocrinology practice with mild asymptomatic hypercalcemia. She reported taking 2 different multivitamin tablets for many years. On laboratory testing, her PTH level was suppressed, PTHrP was normal, 1,25-hydroxyvitamin D and thyroid function tests were normal, and serum and urine electrophoresis did not reveal monoclonal gammopathy (**Table 1**). She was not taking any prescription medications that could cause hypercalcemia.

After an extensive workup, her serum vitamin A (retinol) levels were found to be elevated to almost twice the upper limit of normal, indicating vitamin A toxicity. Her multivita-

TABLE 1

Results of initial laboratory tests

Comprehensive metabolic panel	Value[a]	Reference range
Protein	7.2 g/dL	6.3–8.0
Albumin	4.6 g/dL	3.9–4.9
Calcium	**10.6 mg/dL**	8.5–10.2
Bilirubin	0.7 mg/dL	0.2–1.3
Alkaline phosphatase	77 U/L	34–123
Aspartate aminotransferase	26 U/L	13–35
Alanine aminotransferase	24 U/L	7–38
Glucose	155 mg/dL	74–99
Blood urea nitrogen	23 mg/dL	7–21
Creatinine	1.08 mg/dL	0.58–0.96
Sodium	138 mmol/L	136–144
Potassium	4.0 mmol/L	3.7–5.1
Chloride	104 mmol/L	97–105
Bicarbonate	21 mmol/L	22–30
Parathyroid hormone (PTH), intact	**14 pg/mL**	15–65
Calcium, ionized	1.42 mmol/L	1.08–1.30
Vitamin D (25 hydroxy)	38.2 ng/mL	31–80
Vitamin D (1,25 dihydroxy)	29.7 pg/mL	15–60
PTH-related peptide	< 2.0 pmol/L	0.0–3.4
Thyroid stimulating hormone	1.1 µU/mL	0.27–4.2
Vitamin A/retinol	**1.99 mg/L**	0.3–1.2
Protein electrophoresis urine	No definitive M protein identified	
Protein electrophoresis serum	No definitive M protein identified	

[a] Significant values are in boldface.

> **Preformed vitamin A retinoids are derived from animal products; carotenoids occur in plant-based foods**

mins were discontinued, resulting in improved retinol and calcium levels several months later.

■ PREFORMED VS PRECURSOR VITAMIN A

Vitamin A supports the integrity of epithelial cells and structural proteins across the human body. It also has a role in normal cellular immunity, supporting the functions of natural killer cells and macrophages. It is vital for vi-sion and is especially important in pregnancy, as it contributes to organogenesis during early fetal development.[4–8]

Vitamin A is the term applied to a group of fat-soluble retinoids—retinol, retinal, and reti-nyl esters. Vitamin A can be ingested as pre-formed molecules (activated vitamin A), or as vitamin A precursors ("provitamin A") called carotenoids, which the body converts to reti-

TABLE 2

Vitamin A in various food products and over-the-counter supplements, ranked by % RDI

Food product or supplement	Form of vitamin A	Vitamin A content (µg RAE)	Percentage of RDI for adult men
Beef liver, 3 ounces	Activated (preformed)	6,582	731
Cod-liver oil, 1 tablespoon	Activated	4,080	453
Sunmark One Daily Women's Multivitamin, 1 tablet[a]	Mixed (80% activated, 20% provitamin A)	2,500	277
Sweet potato, 1 whole	Provitamin A	1,403	156
Centrum Silver Adults, 1 tablet	Mixed (60% activated, 40% provitamin A)	750	83
One A Day, Women's Complete Multivitamin[a]	Mixed (90% activated, 10% provitamin A)	700	78
Spinach, ½ cup	Provitamin A	573	64
Ricotta cheese, part skim, 1 cup	Activated	263	31
Egg, boiled, 1 large	Activated	75	8
Broccoli, ½ cup	Provitamin A	60	7
Yogurt, 1 cup	Activated	32	4
Chicken meat, ½ breast piece	Activated	5	1

[a] Product used by our patient at the time of presentation.

RAE = retinol activity equivalents; RDI = recommended daily intake

Based on information in references 5, 17, 18, 19, and 20.

Vitamin A toxicity results from excessive intake of preformed vitamin A

noids.[4,5] Preformed vitamin A is derived naturally from animal products such as dairy, fish oils, eggs, liver, and meat, whereas carotenoids occur naturally in plant-based foods such as carrots, sweet potatoes, and pumpkins.[4–6] Preformed vitamin A and carotenoids can be found in the same over-the-counter (OTC) products and in prescription medications such as isotretinoin and tretinoin. If a supplement contains both preformed vitamin A and carotenoids, the ratio is usually reported on the ingredient label on the back of the bottle.

■ THE ROLE OF ABSORPTION IN VITAMIN A TOXICITY

Vitamin A toxicity results from excessive intake of preformed vitamin A, not from exposure to vitamin A precursors because of the way absorption of these substances is regulated at the level of the gut. [4,5,9,10]

Absorption of vitamin A occurs in the lumen of the small intestine. It is picked up in the duodenum by micelles formed with the aid of bile acids released from the gallbladder.[4–6,9,10] Retinoids are hydrolyzed further and converted to retinol, and retinol uptake is facilitated through the brush border of the small intestine via transport proteins.

The efficiency of absorption of preformed vitamin A through gut transport proteins is high—in the range of 70% to 90%—and does not vary based on the ingested amount. Carotenoids, on the other hand, are not transported by carriers but by passive diffusion across the

TABLE 3

Recommended daily intake of vitamin A

Age	Sex, subpopulations	Recommended daily intake of vitamin A (μg RAE)
0–6 months	Male and female	400[a]
7–12 months	Male and female	500[a]
1–3 years	Male and female	300
4–8 years	Male and female	400
9–13 years	Male and female	600
14 years or older	Male	900
14 years or older	Female	700
14–18 years	Female – pregnant	750
14–18 years	Female – lactating	1,200
19–50 years	Male	900
19–50 years	Female	700
19–50 years	Female – pregnant	770
19–50 years	Female – lactating	1,300

[a]Value extrapolated from vitamin A content of consumed breast milk by healthy infants.

RAE = retinol activity equivalents

Based on information in references 4 and 5.

always indicate normal total body levels of vitamin A, and low or high retinol levels can indicate a significant abnormality of the body's vitamin A stores.[12,13] The half-life of vitamin A is estimated to be 128 days, so it can take many months for retinol levels to normalize after vitamin A toxicity.[4]

■ CHALLENGES TO APPROPRIATE VITAMIN A INTAKE

OTC supplements are the most common source of clinically significant preformed vitamin A ingestion. In a national survey, approximately half of the US population reported using an OTC supplement, with 28% to 37% reporting using a multivitamin that contains vitamin A and with a higher proportion in the elderly.[14] This high percentage of use is concerning, given that multivitamin products are not under US Food and Drug Administration regulation, and reported vitamin ingredients are often inaccurate and underestimated.[15] Manufacturers can sell vitamins OTC, often with quantities above the recommended daily intake, and packaging, flavoring, and chewable formulations make the products more desirable, increasing the risk of vitamin A toxicity in children.[16]

The proposed standardized measure for vitamin A is retinol activity equivalents (RAE) in micrograms. The RDI of vitamin A is 900 μg RAE for men and 700 μg RAE for women.[4–6] The RDI for children varies with age but can range from 300 μg RAE to 700 μg RAE.[4,5] **Table 2** shows vitamin A content in different food products and supplements and compares them with the RDI.[5,17–20] **Table 3** shows the RDI of vitamin A based on sex and age groups.[4,5]

luminal border, and this results in poor absorption efficiency, in the range of 9% to 22%. In addition, upon ingestion of excessive amounts of carotenoids, the efficiency of luminal diffusion decreases, which further protects against toxicity from over-ingestion. Based on this, OTC vitamins containing carotenoids may be safer for patients than those containing preformed vitamin A.[11] The patient described in our case scenario was taking a supplement with vitamin A content that was above the recommended daily intake (RDI).

Once absorbed, most vitamin A is stored in the liver and released into the bloodstream, where retinol-binding protein transports it to its target tissues.[12] If the body's supply of vitamin A changes, the liver modifies the release of retinol into the serum to maintain normal plasma retinol levels. However, a normal plasma retinol level does not

■ CONSEQUENCES OF EXCESSIVE VITAMIN A INTAKE

The tolerable upper daily intake level of vitamin A is approximately 3,000 μg RAE.[4] Higher levels increase the risk of vitamin A-induced chronic liver damage and fetal teratogenicity.[21–24] Importantly, chronic daily ingestion of preformed vitamin A above the recommended intake (700 to 900 μg RAE) but below the tolerable upper intake (3,000 μg RAE) may still be harmful, especially to the musculoskeletal system.[5,25,26]

Acute ingestion (ie, a single dose) of more than 200,000 µg RAE of preformed vitamin A is required to cause acute hypervitaminosis A syndrome in adults.[6] This condition is uncommon and was seen historically in Atlantic explorers who inadvertently ate large amounts of animal livers containing preformed vitamin A.[5,10]

Acute over-ingestion of vitamin A can affect multiple systems:

- Neurologic—increased intracranial pressure, headaches, dizziness, vomiting, delirium, and confusion
- Hepatobiliary—nausea, vomiting, and jaundice resulting from hepatitis progressing to cirrhosis
- Musculoskeletal—periosteal bone resorption, osteopenia, elevated alkaline phosphatase, and hypercalcemia
- Skin and mucous membranes—dry, fragile skin, brittle nails, loss of hair.[10,27]

In clinical practice, however, chronic over-ingestion of vitamin A is a much more likely cause of vitamin A toxicity.

■ VITAMIN A AND THE SKELETON: BONE RESORPTION AND HYPERCALCEMIA

The mechanism of vitamin A-induced bone resorption and hypercalcemia is poorly understood. It is hypothesized to be secondary to increased osteoclastic activity, reduced osteoid, suppression of osteoblastic activity, and hormonal dysregulation of calcium homeostasis of parathyroid hormone and vitamin D.[28–31] Vitamin A and vitamin D exhibit a complex relationship that occurs at the molecular transcription level, where they can have stimulatory or inhibitory effects on each other.[32–35] However, the effects of vitamin A toxicity on bone resorption have been observed independent of serum calcium, phosphate, and vitamin D levels.[36]

Results of studies in humans are consistent with those of animals. In a study of 39 pediatric patients treated for neuroblastoma with a high-dose vitamin A derivative, hypercalcemia developed in twelve (31%) patients.[37] In a study of adult patients treated for multiple myeloma with all-trans retinoic acid, hypercalcemia was observed in 3 of 6 patients treated.[38] Myalgia, arthralgia, and skeletal pain were consistently seen in a case series of patients di-

agnosed with hypervitaminosis A syndrome.[39]

Animal studies have shown an increased incidence of bone fractures with exposure to large amounts of vitamin A.[40] In humans, even if the ingestion of preformed vitamin A is increased moderately and incrementally over a long period, skeletal manifestations may occur. In cross-sectional and nested-control studies conducted in 2 counties in Sweden, each 1,000-µg RAE increment intake of daily vitamin A above the 1,500-µg RAE threshold was associated with a 68% increase in the risk of hip fracture.[25]

In a US study,[26] a prospective cohort of 72,337 nurses was followed for 18 years. Those who ingested more than 2,000 µg RAE of vitamin A daily had almost double the risk of hip fracture compared with those who ingested less than 500 µg RAE.[26] In another prospective cohort of postmenopausal women followed for a mean duration of 9.5 years in the United States,[41] the risk of hip fracture was 1.18 times greater in those who used a vitamin A-containing supplement, although the difference did not reach statistical significance (95% confidence interval 0.99–1.41). In a longitudinal cohort of 2,322 men followed for a median of 30 years,[42] a baseline serum retinol level in the upper quartiles was associated with a significantly higher risk of hip fracture and all fractures.

■ TREATMENT RELIES ON ANECDOTAL EXPERIENCE

Treatment of vitamin A toxicity is based on anecdotal data from case reports.[6,36–38] The recommendation is to withdraw sources of vitamin A, especially of preformed vitamin A, and provide standard supportive treatment for multisystem manifestations. Limited data are available regarding the role of antiresorptive agents in treating vitamin A-related skeletal adverse effects and hypercalcemia. With discontinuation of vitamin A ingestion, retinol and calcium levels are expected to improve within weeks to months, although longitudinal prognostic data are limited.

■ TAKE-HOME MESSAGE: CONSIDER VITAMIN A IN HYPERCALCEMIA

Consumption of plant-derived precursor vitamin A (carotenoids) is harmless, but excessive

Absorption of preformed vitamin A through gut transport proteins is highly efficient

consumption of preformed vitamin A commonly found in OTC supplements and some animal products can have negative multisystem manifestations. Vitamin A is an often overlooked cause of hypercalcemia, thought to stem from its adverse effect on the skeletal system through stimulation of bone resorption and inhibition of bone formation. In the setting of unexplained PTH-independent hypercalcemia, serum retinol levels should be checked but interpreted with caution, as they do not always reflect total body levels. Treatment involves withdrawal of vitamin A sources and supportive care. Given the long half-life of retinol, normalization can take several months. ■

■ 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. **Kuchay MS, Farooqui KJ, Jevalikar G, Mithal A**. The changing profile of hypercalcemia in hospital populations. Clin Rev Bone Miner Metab 2017; 15(2):82–89. doi:10.1007/s12018-017-9231-y

2. **Catalano A, Chilà D, Bellone F, et al**. Incidence of hypocalcemia and hypercalcemia in hospitalized patients: is it changing? J Clin Transl Endocrinol 2018; 13:9–13. doi:10.1016/j.jcte.2018.05.004

3. **Carroll MF, Schade DS**. A practical approach to hypercalcemia. Am Fam Physician 2003; 67(9):1959–1966. pmid:12751658

4. **Institute of Medicine (US) Panel on Micronutrients**. Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington, DC: National Academies Press (US); 2001.

5. **National Institutes of Health: Office of Dietary supplements**. Vitamin A: fact sheet for health professionals. https://ods.od.nih.gov/factsheets/VitaminA-HealthProfessional/. Accessed January 20, 2022.

6. **Pazirandeh S, Burns DL**. Overview of vitamin A. UpToDate. https://www-uptodate-com.ccmain.ohionet.org/contents/overview-of-vitamin-a?search=Overview%20of%20vitamin%20A&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed January 20, 2022.

7. **Saari JC**. Vitamin A metabolism in rod and cone visual cycles. Annu Rev Nutr 2012; 32:125–145. doi:10.1146/annurev-nutr-071811-150748

8. **Morriss-Kay GM, Sokolova N**. Embryonic development and pattern formation. FASEB J 1996; 10(9):961–968. doi:10.1096/fasebj.10.9.8801178

9. **Harrison EH**. Enzymes catalyzing the hydrolysis of retinyl esters. Biochim Biophys Acta 1993; 1170(2):99–108. doi:10.1016/0005-2760(93)90058-h

10. **Biesalski HK**. Comparative assessment of the toxicology of vitamin A and retinoids in man. Toxicology 1989; 57(2):117–161. doi:10.1016/0300-483x(89)90161-3

11. **Grune T, Lietz G, Palou A, et al**. Beta-carotene is an important vitamin A source for humans. J Nutr 2010; 140(12):2268S–2285S. doi:10.3945/jn.109.119024

12. **Greaves RF, Woollard GA, Hoad KE, et al**. Laboratory medicine best practice guideline: vitamins A, E and the carotenoids in blood. Clin Biochem Rev 2014; 35(2):81–113. pmid:25210208

13. **de Pee S, Dary O**. Biochemical indicators of vitamin A deficiency: serum retinol and serum retinol binding protein. J Nutr 2002; 132 (9 suppl):2895S–2901S. doi:10.1093/jn/132.9.2895S

14. **Bailey RL, Gahche JJ, Lentino CV, et al**. Dietary supplement use in the United States, 2003–2006. J Nutr 2011; 141(2):261–266. doi:10.3945/jn.110.133025

15. **Andrews KW, Roseland JM, Gusev PA, et al**. Analytical ingredient content and variability of adult multivitamin/mineral products: national estimates for the Dietary Supplement Ingredient Database. Am J Clin Nutr 2017; 105(2):526–539. doi:10.3945/ajcn.116.134544

16. **Lam HS, Chow CM, Poon WT, et al**. Risk of vitamin A toxicity from candy-like chewable vitamin supplements for children. Pediatrics 2006; 118(2):820–824. doi:10.1542/peds.2006-0167

17. **US Department of Agriculture**. FoodData Central. https://fdc.nal.usda.gov/. Accessed January 20, 2022.

18. **GlaxoSmithKline**. Centrum silver adults. https://www.centrum.com/products/multivitamins/centrum-silver-adults-50-plus/. Accessed January 20, 2022.

19. **One A Day**. Women's complete multivitamin supplement. https://www.oneaday.com/vitamins/vitamins-for-women/multivitamin-for-women. Accessed January 20, 2022.

20. **Sunmark**. Sunmark one daily women's multivitamin/multimineral. https://commonfinds.com/products/sunmark-one-daily-womens-multivitamin-multimineral-100-tablets-1-pack-each-by-sunmark?variant=32498280693857. Accessed January 20, 2022.

21. **Institute of Medicine (US) Panel on Dietary Antioxidants and Related Compounds**. Dietary reference intakes for vitamin C, vitamin E, selenium, and carotenoids. Washington, DC: National Academies Press (US); 2000.

22. **Soprano DR, Soprano KJ**. Retinoids as teratogens. Annu Rev Nutr 1995; 15:111–132. doi:10.1146/annurev.nu.15.070195.000551

23. **Penniston KL, Tanumihardjo SA**. The acute and chronic toxic effects of vitamin A. Am J Clin Nutr 2006; 83(2):191–201. doi:10.1093/ajcn/83.2.191

24. **Hathcock JN, Hattan DG, Jenkins MY, McDonald JT, Sundaresan PR, Wilkening VL**. Evaluation of vitamin A toxicity. Am J Clin Nutr 1990; 52(2):183–202. doi:10.1093/ajcn/52.2.183

25. **Melhus H, Michaëlsson K, Kindmark A, et al**. Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. Ann Intern Med 1998; 129(10):770–778. doi:10.7326/0003-4819-129-10-199811150-00003

26. **Feskanich D, Singh V, Willett WC, Colditz GA**. Vitamin A intake and hip fractures among postmenopausal women. JAMA 2002; 287(1):47–54. doi:10.1001/jama.287.1.47

27. **Geubel AP, De Galocsy C, Alves N, Rahier J, Dive C**. Liver damage caused by therapeutic vitamin A administration: estimate of dose-related toxicity in 41 cases. Gastroenterology 1991; 100(6):1701–1709. doi:10.1016/0016-5085(91)90672-8

28. **Frankel TL, Seshadri MS, McDowall DB, Cornish CJ**. Hypervitaminosis A and calcium-regulating hormones in the rat. J Nutr 1986; 116(4):578–587. doi:10.1093/jn/116.4.578

29. **Hough S, Avioli LV, Muir H, et al**. Effects of hypervitaminosis A on the bone and mineral metabolism of the rat. Endocrinology 1988; 122(6):2933–2939. doi:10.1210/endo-122-6-2933

30. **Olson JA**. Serum levels of vitamin A and carotenoids as reflectors of nutritional status. J Natl Cancer Inst 1984; 73(6):1439–1444. pmid:6439934

31. **Scheven BA, Hamilton NJ**. Retinoic acid and 1,25-dihydroxyvitamin D3 stimulate osteoclast formation by different mechanisms. Bone 1990; 11(1):53–59. doi:10.1016/8756-3282(90)90072-7

32. **Metz AL, Walser MM, Olson WG**. The interaction of dietary vitamin A and vitamin D related to skeletal development in the turkey poult. J Nutr 1985; 115(7):929–935. doi:10.1093/jn/115.7.929

33. **Carlberg C, Saurat JH**. Vitamin D-retinoid association: molecular basis and clinical applications. J Investig Dermatol Symp Proc 1996; 1(1):82–86. pmid:9627699

34. **Joo NS, Yang SW, Song BC, Yeum KJ**. Vitamin A intake, serum

vitamin D and bone mineral density: analysis of the Korea National Health and Nutrition Examination Survey (KNHANES, 2008–2011). Nutrients 2015; 7(3):1716–1727. doi:10.3390/nu7031716

35. **Jimenez-Lara AM, Aranda A**. Interaction of vitamin D and retinoid receptors on regulation of gene expression. Horm Res 2000; 54(5-6):301–305. doi:10.1159/000053276

36. **Kindmark A, Rollman O, Mallmin H, Petrén-Mallmin M, Ljunghall S, Melhus H**. Oral isotretinoin therapy in severe acne induces transient suppression of biochemical markers of bone turnover and calcium homeostasis. Acta Derm Venereol 1998; 78(4):266–269. doi:10.1080/000155598441837

37. **Villablanca JG, Khan AA, Avramis VI, Reynolds CP**. Hypercalcemia: a dose-limiting toxicity associated with 13-cis-retinoic acid. Am J Pediatr Hematol Oncol 1993; 15(4):410–415. pmid:8214363

38. **Niesvizky R, Siegel DS, Busquets X, et al**. Hypercalcaemia and increased serum interleukin-6 levels induced by all-trans retinoic acid in patients with multiple myeloma. Br J Haematol 1995; 89(1): 217–218. doi:10.1111/j.1365-2141.1995.tb08936.x

39. **Frame B, Jackson CE, Reynolds WA, Umphrey JE**. Hypercalcemia and skeletal effects in chronic hypervitaminosis A. Ann Intern Med 1974; 80(1):44–48. doi:10.7326/0003-4819-80-1-44

40. **Wolbach SB, Hegsted DM**. Hypervitaminosis A and the skeleton of growing chicks. AMA Arch Pathol 1952; 54(1):30–38. pmid:14932587

41. **Lim LS, Harnack LJ, Lazovich D, Folsom AR**. Vitamin A intake and the risk of hip fracture in postmenopausal women: the Iowa Women's Health Study. Osteoporos Int 2004; 15(7):552–559. doi:10.1007/s00198-003-1577-y

42. **Michaëlsson K, Lithell H, Vessby B, Melhus H**. Serum retinol levels and the risk of fracture. N Engl J Med 2003; 348(4):287–294. doi:10.1056/NEJMoa021171

Address: Vinni Makin, MD, FACE, Department of Endocrinology, Diabetes, and Metabolism, F20, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; makinv@ccf.org

Katherine N. Weller, MD
Department of Allergy and Clinical Immunology,
Respiratory Institute, Cleveland Clinic,
Cleveland, OH

Fred H. Hsieh, MD
Department of Allergy and Clinical Immunology,
Respiratory Institute, Cleveland Clinic,
Cleveland, OH

Anaphylaxis: Highlights from the practice parameter update

ABSTRACT

The practice parameter update on anaphylaxis from the Joint Task Force on Practice Parameters, with the collaboration of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology, addresses key issues in the management and prevention of anaphylaxis. The updated guidelines define diagnostic criteria for anaphylaxis; therapeutic use of epinephrine, antihistamines, and glucocorticoids; prevention of recurrent anaphylaxis; and follow-up care that includes education on trigger avoidance and use of self-injectable epinephrine.

KEY POINTS

Epinephrine is first-line pharmacotherapy for anaphylaxis.

Epinephrine should be administered at the onset of anaphylaxis as delays often increase risks for morbidity and mortality.

Patients with severe anaphylaxis should be observed for biphasic anaphylaxis, even after signs and symptoms resolve.

The updated guidelines are expected to improve outcomes by emphasizing early treatment with epinephrine and identifying risk factors for severe and biphasic anaphylaxis.

THE UPDATED GUIDELINES on the prevention and treatment of anaphylaxis[1] from the Joint Task Force on Practice Parameters address key issues in the prevention and management of anaphylaxis, including diagnostic criteria for anaphylaxis; therapeutic use of epinephrine, antihistamines, and glucocorticoids; prevention of recurrent anaphylaxis; and follow-up care including patient education on trigger avoidance and use of self-injectable epinephrine. This update to the 2015 guidelines[2] was a collaborative effort of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology.

■ GENERAL CONSIDERATIONS OF THE UPDATE

Anaphylaxis is an acute, potentially life-threatening allergic emergency that can present with diverse symptoms that often but not always involve hemodynamic compromise. The updated guidelines note that anaphylaxis is highly likely in a patient experiencing at least 1 of the following 3 clinical scenarios (**Table 1**)[1]:

- Acute onset of symptoms involving the skin or the mucous membrane, or both, including hives, itching, flushing, or swelling; plus the acute onset of respiratory symptoms, with or without hypotension or other symptoms of target-organ dysfunction
- Involvement of 2 or more organ systems that occurs rapidly after exposure to a likely allergen, including skin or mucosal membrane symptoms, respiratory symptoms, hypotension or other symptoms of target-organ dysfunction, and sudden gastrointestinal symptoms

- Hypotension occurring acutely after exposure to a known or established allergen for that patient.

In patients who meet the anaphylaxis criteria, epinephrine is recommended. However, the updated guidelines recognize that epinephrine treatment may still be appropriate in some patients who do not meet anaphylaxis criteria, such as a patient exposed to a likely allergen who develops symptoms in a single organ system. Anaphylaxis is considered to be severe if respiratory failure or cardiovascular collapse occurs.

Risk factors for severe anaphylaxis include cardiovascular disease, asthma, older age, and additional coexisting or comorbid conditions such as atopy, concomitant beta-blocker or angiotensin-converting enzyme (ACE) inhibitor use, or an established mast cell disorder such as bone-marrow biopsy-proven systemic mastocytosis.[1]

In adults, the most common causes of anaphylaxis are medications and stinging insects. In children, foods and stinging insects are the most common triggers. Food allergy is present in 8% to 11% of the US population, and adverse drug reactions occur in up to 10% of the population and in up to 20% of hospitalized patients.[1]

■ ANAPHYLAXIS TREATMENT

Epinephrine is the first-line therapy for anaphylaxis, and its administration should not be delayed, as delays are associated with higher rates of morbidity and mortality. There are no absolute contraindications to epinephrine use, even in pregnant patients or those with coronary artery disease or tachyarrhythmia.

Epinephrine should be administered at the onset of anaphylaxis, intramuscularly in the mid-outer thigh at a dose of 0.01 mg/kg of a 1:1000 (1-mg/mL) solution, up to a maximum dose of 0.5 mg in adults and 0.3 mg in children.[1]

The most commonly used epinephrine autoinjectors are the following:
- EpiPen 0.3 mg/0.3 mL for adult patients
- EpiPen Jr 0.15 mg/0.15 mL for pediatric patients weighing 15 to 30 kg
- Auvi-Q 0.3 mg/0.3 mL for adults
- Auvi-Q 0.15 mg/0.15 mL for pediatric patients weighing 15 to 30 kg
- Auvi-Q (0.1 mg/0.1 mL) for pediatric patients weighing 7.5 to 15 kg.

If possible, the inciting allergen should be re-

TABLE 1

Diagnostic criteria for anaphylaxis

Anaphylaxis is highly likely when any 1 of the following 3 criteria is met:

1	Sudden onset of symptoms (minutes to several hours) with involvement of skin and/or mucosa (eg, generalized hives, itching or flushing, swollen lips/tongue/uvula), AND at least one of the following:
	Respiratory symptoms or signs (eg, shortness of breath, wheezing, cough, hypoxemia)
	Hypotension or other symptoms of target-organ dysfunction (eg, collapse, incontinence)
2	Sudden onset of 2 or more of the following after exposure to a likely allergen or other trigger for that patient (minutes to several hours):
	Skin or mucosal membrane symptoms
	Respiratory symptoms
	Hypotension or other symptoms of target-organ dysfunction
	Gastrointestinal symptoms such as abdominal pain or vomiting
3	Hypotension occurring acutely (minutes to several hours) after exposure to a known or established allergen for that patient. Hypotension is defined as the following:
	Adults: Systolic blood pressure < 90 mm Hg, or a decrease > 30% from patient's baseline
	Infants and children: Low systolic blood pressure (age-specific) or a decrease > 30% in systolic pressure

Based on information from reference 1.

---

moved. Airway, breathing, and circulation should then be assessed, appropriate assistance summoned, and cardiopulmonary resuscitation begun, if needed.[2] Additional interventions include placing the patient in a supine position (left side for pregnant patients), providing supplemental oxygen, and administering intravenous fluid resuscitation to patients with hypotension.

Second-line therapy with beta-2 agonists such as albuterol, antihistamines (histamine-1 and histamine-2 receptor antagonists), and corticosteroids may be considered. Glucagon may be helpful for patients who are receiving beta-adrenergic blocking agents.[2] Unlike epinephrine, these second-line medications will

not effectively treat cardiovascular symptoms such as hypotension and should not be administered in place of epinephrine.[1]

After treatment of anaphylaxis, monitor the patient until signs and symptoms have fully resolved. Extended observation is suggested for patients with severe anaphylaxis and those who require more than 1 dose of epinephrine. This is indicated to monitor for a potential biphasic reaction.[1]

Any patient who has experienced anaphylaxis should be evaluated by an allergy and immunology specialist to determine the causative agent, if any. It is not possible to predict the severity of any future event based on the severity of past events. Therefore, consider prescribing an epinephrine autoinjector to patients who have experienced anaphylaxis. Instruct patients on the use of the device, and educate them on the risk of anaphylaxis recurrence and trigger avoidance.

■ BIPHASIC ANAPHYLAXIS

Biphasic anaphylaxis—a clinical condition in which the symptoms of anaphylaxis recur after medical resuscitation, recovery of vital signs, and resolution of all signs and symptoms—is estimated to occur in 1% to 20% of patients and may occur up to 72 hours after resolution of anaphylaxis.[1] Intramuscular epinephrine is the first-line treatment for both the initial and the delayed reaction.

The most significant risk factor for experiencing a biphasic anaphylactic reaction is a severe initial anaphylactic reaction or the need for more than 1 dose of epinephrine. Other risk factors include a wide pulse pressure at initial presentation, unknown anaphylaxis trigger, cutaneous signs and symptoms (including and urticaria and angioedema), delayed time of administration of the first epinephrine dose (> 60 minutes), and presence of a drug trigger in pediatric patients.[1]

Thus, patients presenting with severe anaphylaxis, especially those requiring more than 1 dose of epinephrine, should be considered for longer direct observation given the potential for biphasic anaphylaxis, even after complete resolution of signs and symptoms of anaphylaxis. From a clinical practice standpoint, for patients with no severe risk factors, a 1-hour asymptomatic observation period may be reasonable. For patients at higher risk, 6 hours or longer should be strongly considered.

Preventing biphasic anaphylaxis

There are no reliable interventions to prevent biphasic anaphylaxis. Antihistamines and glucocorticoids are commonly used for emergency treatment of urticaria, itching, and swelling. However, if anaphylaxis is not recognized and those medications are administered instead of epinephrine therapy, it could delay the start of first-line anaphylaxis treatment with epinephrine.

In addition, the 2020 Joint Task Force did not identify any benefit of antihistamines or glucocorticoids in preventing biphasic anaphylaxis. Rather, it found that glucocorticoid use may actually be associated with increased risk for biphasic anaphylaxis in children, though confounding with severity could not be excluded.[1]

■ ADDRESSING THE POTENTIAL CAUSES OF ANAPHYLAXIS

Chemotherapy

The incidence of anaphylaxis has increased during some chemotherapy protocols that include agents such as pegaspargase, docetaxel, carboplatin, oxaliplatin, and paclitaxel.[1] Premedication with glucocorticoids or antihistamines has been shown to significantly decrease the rate of hypersensitivity reactions to chemotherapy.[1] Therefore, premedication is recommended to decrease the risk of hypersensitivity reactions during these protocols, including prevention of infusion-related reactions in patients who have not previously experienced a reaction to the drug. Premedication may also be considered for some biologics, such as rituximab used to treat autoimmune disorders and B-cell malignancies (eg, diffuse large B-cell non-Hodgkin lymphoma, follicular B-cell non-Hodgkin lymphoma). Of note, this is a conditional recommendation with a very-low-certainty rating of evidence, as studies have not included patients who have experienced anaphylaxis to those drugs.[1]

Radiocontrast media

The current standard approach to reducing hypersensitivity reactions to radiocontrast me-

In adults, the most common causes of anaphylaxis are medications and stinging insects; in children, foods and stinging insects are the most common triggers

dia in patients with a history of radiocontrast reactions involves premedication with antihistamines and glucocorticoids. The updated guidelines highlight recent studies that suggest the evidence supporting premedication to prevent hypersensitivity reactions is not definitive in patients with a history of contrast reactions who are scheduled to receive low- or iso-osmolar, nonionic radiocontrast media.[1] This is based on analyses that suggest the greatest risk reduction in patients with anaphylaxis from ionic, hyperosmolar radiocontrast media may be derived from using low-osmolar, nonionic contrast agents rather than hypo-osmolar, nonionic media plus pretreatment with high-dose glucocorticoids. A meta-analysis described in the guidelines did not find a clear benefit from premedication with a histamine-1 receptor antagonist plus a glucocorticoid in these patients. However, this is a conditional recommendation with a very-low-certainty rating of evidence.

The guidelines continue to suggest consideration of a premedication regimen for patients with a high level of perceived risk of anaphylaxis or comorbidities associated with greater anaphylaxis fatality risk, such as underlying cardiovascular disease, use of beta-blockers, or history of severe anaphylaxis.[1] The use of other strategies (such as rapid desensitization) to treat or prevent delayed reactions to radiocontrast media is not addressed in the current guidelines. In addition, management strategies involving use of non-cross-reactive radiocontrast media without glucocorticoid premedication are proposed, but substantive prospective trials are lacking.

Subcutaneous allergen immunotherapy

In patients receiving venom immunotherapy, ACE inhibitors have been associated with an increased frequency of reactions and should be discontinued whenever possible. Beta-adrenergic blocking agents have also been associated with a higher severity of events and are thought to interfere with the efficacy of epinephrine, and their discontinuation should be considered.[2] A very-low-certainty rating of evidence suggests that premedication with glucocorticoids or antihistamines does not significantly reduce the risk of a hypersensitivity reaction in patients receiving allergen immunotherapy; however, there may be some benefit to premedication in patients undergoing immunotherapy procedures with a high baseline rate of systemic reactions.

■ WHAT'S DIFFERENT FROM THE 2015 GUIDELINES?

The Joint Task Force used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) analysis to rigorously evaluate the certainty of the literature to answer key questions,[1] whereas the 2015 guidelines task force classified recommendations by the strength of the recommendations and the quality of the evidence.[2]

The updated guidelines state that anaphylaxis can present with a variety of clinical manifestations and recommend treatment with epinephrine in patients who experience symptoms after exposure to a likely allergen. They expand and clarify the definition of anaphylaxis and include recommendations for pediatric patients as well.

There was concern that the definition of anaphylaxis in previous guidelines would exclude patients who did not meet certain criteria, such as a patient exposed to a likely allergen who develops symptoms in a single organ system. The updated guidelines address this to promote early treatment of anaphylaxis for more patients.

Compared with previous guidelines, the update more directly addresses the evidence and rationale underlying the recommended approach to treatment and monitoring of patients with biphasic anaphylaxis in the rigorous GRADE format. The guidelines also address the identification and mitigation of risk factors for biphasic anaphylaxis, which was not fully elucidated in prior guidelines.[1]

The guidelines also update recommendations regarding premedication with antihistamines or glucocorticoids based on recent evidence that supports their role for patients undergoing specific chemotherapy protocols and rush aeroallergen immunotherapy (ie, a technique for rapidly advancing the dose of aeroallergen allergy shots to the maintenance dose over a short period of time). However, the task force did not find a convincing benefit in their use to prevent recurrent radiocontrast media anaphylaxis in patients who require low-osmolar or iso-osmolar contrast.[1]

Any patient who has experienced anaphylaxis should be evaluated by an allergy and immunology specialist to determine the causative agent, if any

TABLE 2

Key clinical practice recommendations from the 2020 anaphylaxis guidelines

Treatment of anaphylaxis

Administer epinephrine as first-line pharmacotherapy for uniphasic or biphasic anaphylaxis.

Do not delay the administration of epinephrine for anaphylaxis.

All patients with anaphylaxis should receive education about anaphylaxis, risk of recurrence, trigger avoidance, self-injectable epinephrine, and thresholds for further care. Patients should also be referred to an allergist for follow-up evaluation.

Biphasic anaphylaxis

Risk factors for biphasic reactions include severe anaphylaxis or the need for more than 1 dose of epinephrine to treat anaphylaxis, wide pulse pressure, unknown anaphylaxis trigger, cutaneous signs and symptoms, and drug triggers in children.

Antihistamines and glucocorticoids are not reliable interventions to prevent biphasic anaphylaxis but may be considered as second-line treatment.

After treatment, all patients with anaphylaxis should be kept under observation until symptoms have fully resolved.

Extended observation beyond resolution of symptoms is suggested for patients who had severe anaphylaxis or required more than 1 dose of epinephrine.

Use of histamine-1 antihistamines and glucocorticoids to prevent anaphylactic reactions

Premedication with antihistamine or glucocorticoid or both in specific chemotherapy protocols and specific aeroallergen immunotherapy procedures may decrease the risk of systemic reactions.

Patients with a history of reactions to radiocontrast media should receive low- or iso-osmolar radiocontrast media with future procedures to reduce the risk of future reactions. Routine glucocorticoid or antihistamine premedication may not reduce the risk of hypersensitivity reactions, though they should be considered in patients perceived to be at high risk of anaphylaxis or with comorbidities that increase the anaphylaxis fatality risk.

Based on information from reference 1.

■ WHAT'S THE EXPECTED CLINICAL IMPACT?

The updated guidelines will likely improve outcomes in patients with anaphylaxis by emphasizing early treatment with epinephrine and identifying risk factors for severe and biphasic anaphylaxis. Premedication with antihistamines and glucocorticoids may be utilized less to prevent recurrent radiocontrast media anaphylaxis, especially in patients with comorbidities that increase their risk of adverse effects from these premedication agents. These patients would include those with diabetes mellitus who are at high risk for hyperglycemia from high-dose glucocorticoids. On the other hand, premedication may become more standard practice for certain chemotherapy protocols.

■ DO OTHER SOCIETIES AGREE OR DISAGREE?

The international anaphylaxis guidelines of the World Allergy Organization provide recommendations similar to those of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology, but also address global issues such as the challenge of patient access to epinephrine autoinjectors in some countries.[3]

■ HOW WILL THE GUIDELINES CHANGE DAILY PRACTICE?

The expanded diagnostic criteria for anaphylaxis will likely lead to earlier recognition of the condition and earlier use of epinephrine. Educating patients about unusual symptoms should enable them to identify anaphylaxis earlier and get rapid treatment.

Identifying risk factors for biphasic anaphylaxis will help clinicians target the appropriate patient population for education and consideration of antihistamines or glucocorticoids as secondary treatment. See **Table 2** for a summary of key clinical guideline recommendations.

■ WHEN DO THE GUIDELINES NOT APPLY?

The updated guidelines were published prior to the US Food and Drug Administration approval of Palforzia, a food-desensitization product for peanut anaphylaxis.[4] Therefore, the guidelines do not provide up-to-date recommendations regarding food desensitization as a therapeutic option for patients at risk for food anaphylaxis to peanuts. ■

■ DISCLOSURES

■ REFERENCES

1. **Shaker MS, Wallace DV, Golden DBK, et al**. Anaphylaxis—a 2020 practice parameter update, systematic review, and grading of recommendations, assessment, development and evaluation (GRADE) analysis. J Allergy Clin Immunol 2020; 145(4):1082–1123. doi:10.1016/j.jaci.2020.01.017
2. **Lieberman P, Nicklas RA, Randolph C, et al**. Anaphylaxis—a practice parameter update 2015. Ann Allergy Asthma Immunol 2015; 115(5):341–384.
doi:10.1016/j.anai.2015.07.019
3. **Cardona V, Ansotegui IJ, Ebisawa M, et al**. World allergy organization anaphylaxis guidance 2020. World Allergy Organ J 2020; 13(10):100472.
doi:10.1016/j.waojou.2020.100472
4. **Peanut allergen powder (Palforzia)**. JAMA 2020; 324(2):192–193. doi:10.1001/jama.2020.3599

Address: *Fred H. Hsieh, MD, Department of Allergy and Clinical Immunology, Respiratory Institute, A90, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; hsiehf@ccf.org*

How to earn *AMA PRA Category 1 Credit*™ and ABA, ABIM, ABP, ABPath, ABS 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 now eligible for 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.

February 2022 CME/MOC activities

Estimated time to complete each activity: up to 1 hour

Extraosseous calcification in kidney disease

Hypercalcemia and vitamin A: A vitamin to keep in mind

Release date: February 1, 2022
Expiration date: January 31, 2023

FINANCIAL DISCLOSURES: In accordance with the Standards for Commercial Support issued by the Accreditation Council for Continuing Medical Education (ACCME), the Cleveland Clinic Foundation Center for Continuing Education requires resolution of all faculty conflicts of interest to ensure CME 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.

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.

CREDIT DESIGNATION

American Medical Association (AMA) Cleveland Clinic Foundation Center for Continuing Education designates this journal-based activity for a maximum of 1.0 *AMA PRA Category 1 Credits*™. 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.

MOC/CC PART II ACCREDITATION:

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to:

- **ABA MOC:** 1.0 Lifelong Learning MOC points in the ABA MOCA 2.0® Maintenance of Certification in Anesthesiology Program®.
- **ABIM MOC:** 1.0 Medical Knowledge MOC points in the ABIM MOC Assessment Recognition Program.
- **ABPath CC:** 1.0 Lifelong Learning credits in the ABPath Continuing Certification Program.
- **ABP MOC:** 1.0 Lifelong Learning & Self-Assessment MOC points in the ABP Maintenance of Certification Program.

- **ABS MOC:** 1.0 Accredited CME & Self-Assessment credits toward ABS Continuous Certification Program.

Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABA, ABIM, ABPath, ABP, and ABS credit. Credit will be reported within 30 days of claiming credit.

**Please Note: To receive MOC you must select the MOC option during the online credit claiming process and complete the required steps.