

CLEVELAND CLINIC JOURNAL OF MEDICINE

New *CCJM* faces and features

Gingival overgrowth in acute monocytic leukemia

Caring for patients who wish to die in their home country

Perspectives on travel and healthcare

Parathyroidectomy for patients with primary hyperparathyroidism

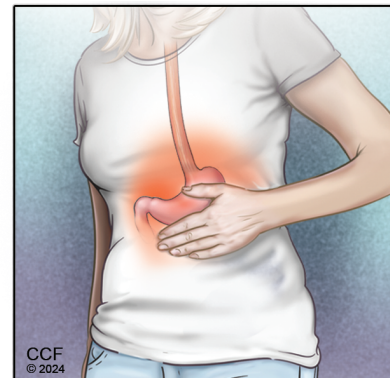
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Is a central venous catheter always needed to administer vasopressors?

Reducing the risks when using benzodiazepines to treat insomnia

Simultaneous hemorrhage and thrombosis in a patient with systemic lupus erythematosus

Functional dyspepsia



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Cleveland Clinic Journal of Medicine [ISSN 0891-1150 (print), ISSN
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STATE OF THE ART TOPICS in the Prevention and Management of Cardiovascular Disease

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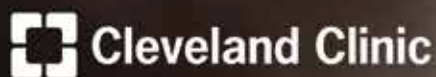
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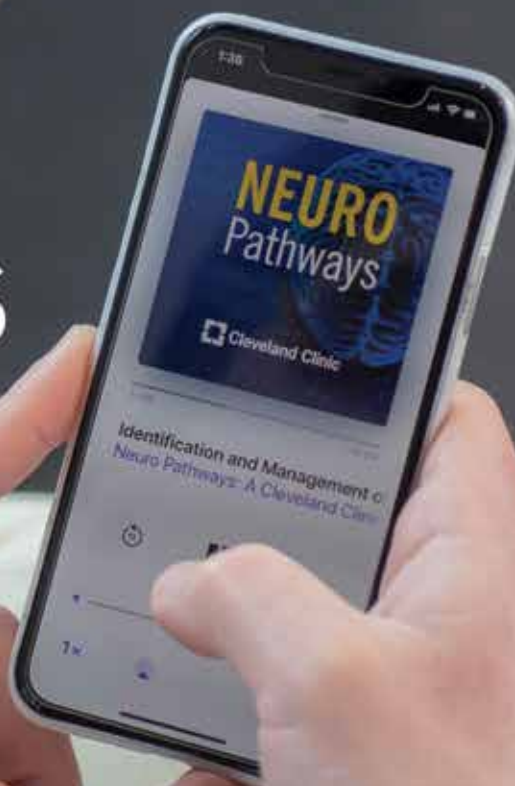
Cardiovascular disease medicine is a rapidly evolving discipline. The depth and complexity of the data from research studies and clinical trials currently being generated make it difficult for practitioners to remain up to date on the advances and their clinical implications. Furthermore, evidence-based recommendations for the appropriate use of diagnostic and therapeutic procedures are frequently updated as research is published, providing additional challenges to busy practitioners to maintain knowledge and competencies. This educational activity will provide a contemporary update on the latest knowledge and advances in cardiovascular medicine.

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New CCJM faces and features

Spring is the poetic time for rejuvenation, and we at the *Journal*, going with the poetic flow, welcome 2 new deputy editors: James Pile, MD, and George Thomas, MD, MPH. They join our current deputy editor, Craig Nielsen, MD. All 3 are master clinical teachers and superb practicing clinicians.

Jim Pile is a hospitalist on our medicine teaching services. He is board certified in internal medicine and infectious disease, and is a former associate program director of the Internal Medicine Residency Program at Cleveland Clinic as well as a former program director of the Internal Medicine Residency Program at MetroHealth in Cleveland, Ohio. He served as editor in chief of the Society of Hospital Medicine's publication *The Hospitalist*, was a founding deputy editor of the *Journal of Hospital Medicine*, and is a former deputy editor of CCJM.

George Thomas is a nephrologist with a long-standing interest and expertise in managing patients with hypertension. He is the director of the Center for Blood Pressure Disorders in the Department of Kidney Medicine at Cleveland Clinic. In addition to caring for patients in his outpatient clinics, he is a well-published clinical trialist and frequent consultant on our inpatient nephrology services.

We also will be freshening up our list of associate editors (highlighted on the *Journal's* masthead) in the coming months, and some of our associate editors will be dedicating time to specific features and series. We will be continuing our The Clinical Picture, Symptoms to Diagnosis, and Guidelines to Practice series. Last year we started a podcast, *Beyond the Pages*, which is structured as an interview with an author(s) of an article published in the *Journal*. As an example, in one episode I had a conversation with Dr. Steve Gordon, chairman of the Department of Infectious Disease at Cleveland Clinic, about bacterial endocarditis and the article he coauthored on antibiotic prophylaxis. Each podcast episode is eligible for continuing medical education credit. We will be continuing the *Beyond the Pages* podcast, which you can easily access on the *Journal's* home page: www.ccjm.org. Some of our associate editors will be involved with this project, as well as with some anticipated new recurring features.



Craig Nielsen, MD



James Pile, MD



George Thomas, MD, MPH

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Editor in Chief

doi:10.3949/ccjm.91b.05024

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2024

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May 2
Cleveland, OH

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

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

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

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

MEDICAL DERMATOLOGY THERAPY UPDATE
May 29–31
Cleveland, OH

JUNE

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

INTENSIVE REVIEW OF INTERNAL MEDICINE
June 10–14
Live stream

ADVANCED DIAGNOSTIC BRONCHOSCOPY
WORKSHOP
June 14–15
Cleveland, OH

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

INNOVATIONS IN CEREBROVASCULAR CARE
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Cleveland, OH

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

AUGUST

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

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

SEPTEMBER

HOSPITAL MEDICINE 2024
September 5–6
Cleveland, OH

GLOBAL EP 2024
September 20–21
Cleveland, OH

OCTOBER

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

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

CONTEMPORARY ISSUES
IN PITUITARY DISEASE
October 17
Cleveland, OH

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

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

CARDIOVASCULAR UPDATE 2024
October 31–November 1
Cleveland, OH

NOVEMBER

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

ADVANCING CARDIOVASCULAR CARE
November 8
Columbus, OH

FUTURE OF STROKE CARE:
STROKE AND CEREBROVASCULAR
DISEASE CONFERENCE
November 9–10
Hollywood, FL, and
Hybrid (Encore)

DIMENSIONS IN CARDIAC CARE
November 10–12
Cleveland, OH

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

DECEMBER

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

CASE-BASED MANAGEMENT OF TRICUSPID
AND MITRAL VALVE DISEASE
December 6–7
New York, NY

2025

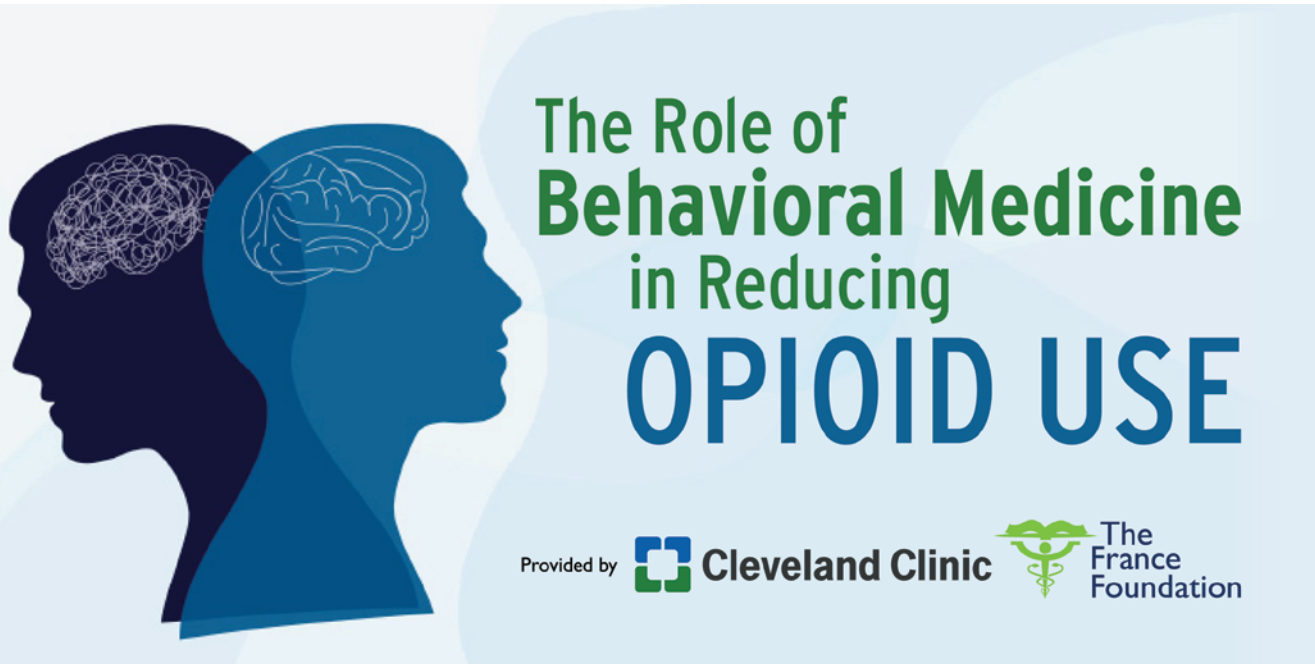
JANUARY

PULMONARY HYPERTENSION SUMMIT
January 16–17
Hollywood, FL

FEBRUARY

INTERNATIONAL COLORECTAL DISEASE
SYMPOSIUM
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THE CLINICAL PICTURE

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Department of Hematology Oncology Fellowship,
Kettering Medical Center, Kettering, OH

Alejandro Calvo, MD, FACP

Program Director, Department of Hematology Oncology
Fellowship, Kettering Medical Center, Kettering, OH

Gingival overgrowth in acute monocytic leukemia



Figure 1. Gingival overgrowth.



Figure 2. Gingiva after completion of induction chemotherapy.

A 55-YEAR-OLD MAN PRESENTED to the emergency department with a 2-month history of progressive gingival swelling and oral pain. Physical examination revealed marked diffuse gingival overgrowth with necrotic lesions throughout the upper and lower gingivae (**Figure 1**). Complete blood cell count showed a marked leukocytosis of $100.2 \times 10^9/L$ (reference range 4.0–10.5) with 11% blasts and few Auer rods. Bone marrow biopsy revealed 80% myeloblasts and promonocytes, cell profiling consistent with acute monocytic leukemia, subtype M5 based on the French-American-British (FAB) classification system. Cytogenetic and molecular studies were consistent with intermediate-risk acute monocytic leukemia.

The patient received induction treatment with idarubicin and cytarabine (7+3 chemotherapy). On repeat bone marrow aspiration and biopsy on day 28 after completing induction therapy, 2% myeloblasts were present, warranting 4 additional cycles of con-

solidation chemotherapy with high-dose cytarabine combined with oral midostaurin due to the presence of the *FLT3* mutation at diagnosis. His course was complicated by septic shock due to streptococcal bacteremia, requiring a prolonged intensive care unit stay. After recovery, he continued maintenance midostaurin and underwent evaluation for allogeneic stem cell transplant.

The patient's gingival overgrowth resolved with the completion of induction chemotherapy (**Figure 2**).

DISCUSSION

Gingival overgrowth is seen as an initial extramedullary manifestation of acute leukemia in about 5% of cases.¹ It occurs most commonly in acute monocytic leukemia (FAB M5) and acute myelomonocytic leukemia (FAB M4), with an estimated occurrence rate of 66% in the M5 subtype.²

When considering the etiology of gingival overgrowth, clinicians must be aware of gingival changes

doi:10.3949/cjcm.91a.23087

that can occur with certain medication classes. These include immunosuppressants (eg, cyclosporine, tacrolimus, sirolimus), anticonvulsants (eg, phenytoin, sodium valproate, phenobarbitone), and calcium channel blockers (eg, nifedipine, amlodipine, felodipine).³ Other causes of gingival overgrowth include deficient periodontal health, sarcoidosis, Crohn disease, tuberculosis, and rare hereditary conditions.⁴

The mechanism of acute leukemia–related gingival overgrowth is believed to be related to massive leukemic infiltration in the gingival connective tissue.^{1,2,4}

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2. **Yacoub A, Mahalwar G.** Dentist to oncologist: gingival hyperplasia in AML accompanied by periodontal infection—case report. *Blood* 2016; 128(22):5187. doi:10.1182/blood.V128.22.5187.5187

Although hematologic causes of gingival overgrowth are rare, clinicians must be aware of the association between gingival hyperplasia and acute leukemia, and obtain screening hematologic profiles (complete blood cell count with differential, coagulation studies) in patients presenting with symptoms of gingival overgrowth or other periodontal abnormalities. ■

DISCLOSURES

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

3. **Tungare S, Paranjpe AG.** Drug-induced gingival overgrowth. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2022. PMID:30860753
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Providing comfort: Caring for patients who wish to die in their home country

IN AN INCREASINGLY GLOBAL WORLD, medical teams must be adept at caring for patients who have immigrated. This includes responding to requests to ensure comfort for patients who, after maximizing disease-directed treatments, wish to return to their country of origin to die.^{1,2} This article offers a framework for responding to these requests with equitable patient care.

See related editorial, page 275

■ TIMING CONSIDERATIONS

Disease trajectories vary. For example, patients with advancing cardiac or pulmonary disease may experience increasing exacerbations punctuated by partial recoveries. Patients with cancer often maintain high physical function until weeks before death, when their functional status declines sharply. It is important to start discussions early enough that, if a patient wishes to return to their country of origin, they are physically able to travel. Families, recognizing that the patient wants to be buried in their country of origin, may have practical concerns about the possibility of travel, and these should be addressed. We evaluate each patient's functional status and likelihood of death during planned travel.

There are realistic options for travel in the setting of terminal illness. Travel can be considered between treatment cycles, when symptoms are relatively controlled, or after all disease-directed treatments have been maximized. A patient may be frail but also clinically stable. For a journey of many hours or even a few days, we generally recommend that the patient be cognitively interactive, able to take medications by mouth, and mobile with single-person support. At this minimum level of function, there is a life expectancy

of many days to several weeks and a high likelihood that the patient will successfully travel home. When a patient's functional status declines beyond this point, we initiate a conversation to recommend that goals be shifted away from travel.

■ TRAVEL OPTIONS

The planning process must include discussion of mode of travel, the anticipated time frame, assistance that will be required, and types of help available along the way.^{3,4} Patients most commonly intend to drive or to fly via a commercial airline to return to their country of origin. Preparing the family to manage eventualities can avoid unnecessary distress during travel.

Questions to ask and resolve during planning include the following:

- Can the patient tolerate the trip physiologically? For example, can their oxygenation be safely maintained in a plane?
- What are the logistics of the journey? Will they stay somewhere overnight, or is the family taking shifts to drive straight through?
- What are the patient's physical requirements? Can they remain upright in an airline or automobile seat for the duration of the trip? Will they need a wheelchair or other assistive device to help with transfers?
- Is there a system in place to manage possible incontinence, the need to physically help the patient toilet, and the control of other symptoms?

■ MEDICATION MANAGEMENT AND ADMINISTRATION

Patients may require medication for comfort or disease modification or both, and their families will need information and training for medication management while traveling.

doi:10.3949/cjcm.91a.23095

TABLE 1
Examples of medications to consider for travel comfort care

Indication	Medications	Considerations
Long-acting pain control	Fentanyl patch Methadone Morphine extended-release	Current and predicted pain Prior pain medication use, familiarity, and tolerance Future ability to take oral medications
Breakthrough pain or dyspnea	Morphine sulfate oral solution	Can be used when patient loses ability to purposefully swallow
Terminal fever or pain	Acetaminophen	Pills can be used orally or rectally Low risk of diversion
Nausea and vomiting	Ondansetron Promethazine	Consider if single medications can be used for multiple symptoms
Pain, nausea, cancer-related swelling, or obstruction	Dexamethasone	Multimodal effect Benefits usually maximized over 2 weeks Use cautiously if hyperglycemia is a concern
Terminal agitation, anxiety, seizures, and nausea	Lorazepam Olanzapine Haloperidol	Useful for spectrum of symptoms in terminal phase
Constipation	Bisacodyl Polyethylene glycol	Bisacodyl oral pill can be used rectally when patient loses ability to swallow
Secretions, death rattle	Atropine 1% drops	Coach family on repositioning

Therapy for comfort

Standard hospice practice in the United States includes creation of medication packs for patients that achieve comfort quickly in a home setting.⁵ Home hospice medication packs may vary because of availability, pharmacy formulary, cost, insurance coverage, and specific patient needs.⁶ The preparation of comfort care packs for terminally ill patients with cancer returning to their country of origin is similar to that used in US hospice practice, but has unique challenges. As a component of equitable and culturally sensitive care, we provide medications and coaching for patients and their families to use during and after travel to their home country.

Table 1 offers examples of medications to consider including in a comfort pack. We create regimens that are simple to administer, favoring pills or liquids that are administered orally or rectally and prioritizing medications that can be used for multiple symptoms, such as opioids for pain or dyspnea, to ensure success. Interdisciplinary teamwork is critical to ensure both the availability and practicality of medications for each patient after discharge. Depending on the patient's prognosis, we recommend prescribing a 1-week to 1-month supply of medication to balance patient care and safety.

Therapy for disease modification

A review of all medications with consideration of whether they still provide comfort can help alleviate polypharmacy as the patient's goals change. For example, some patients may desire to continue oral anticancer therapy as long as possible. Because oral anticancer medications may be unavailable in patients' home countries, our oncology team sometimes prescribes up to a 1-month supply if these medications are thought to be of benefit. Medications such as diuretics and antiarrhythmics provide patients comfort while they are alert and should be continued, but statins may have decreased benefit in the last months of life. Shared decision-making between the patient and their medical team can help to determine which medications to continue.

Medication safety

Comfort medication packs provided to home hospice patients are designed to be used with clinical oversight. Terminally ill patients returning to their country of origin will not have this ongoing oversight from the prescribing team, who must feel confident that they are doing no harm. To ensure excellence in patient care, it is critical to train families in the use of medications,

provide clear instructions, and evaluate who may be able to guide the family after their arrival—for instance, local medical staff or medically trained family members.

Before travel, we recommend that families receive bedside training from experienced nursing staff in medication administration and physical care of the patient. The intent is to create a safe environment for the patient when they are no longer actively under the care of the medical team. This preparation allows family members to assess their ability to care for the patient and gain confidence with tasks such as medication preparation, rectal administration of pills, dressing changes, and physical transfers.

We advise patients and caregivers or travel companions to carry medications in their labeled prescription bottles and with the original prescriptions intact. We recommend keeping them in carry-on bags to prevent loss or theft. As laws vary by country, we counsel patients and families to be aware of laws that may regulate entry with certain medications.

DOCUMENTATION OF END-OF-LIFE DECISIONS

Patients, families, and clinicians all share concerns about death in transit. We recommend travel only when we believe that the patient will successfully complete the journey, but we also recognize the frailty of these patients. We recommend that patients and their travel companions carry these documents:

- A letter that summarizes the patient's medical conditions, clinical status, and medications
- Copies of advance directives, including medical power of attorney and orders for life-sustaining treatment (eg, Medical Orders for Scope of Treatment or Physician Orders for Life-Sustaining Treatment forms).

We provide statements regarding the patient's current medical illnesses but do not make any guarantees

of safety during flights. Airlines make their own determinations regarding safety of travel as patients board the plane.

In-flight death is rare, comprising 0.3% of nearly 11,000 in-flight emergencies reported to a physician-directed communications center from January 2008 through October 2010.⁷ International guidelines purposefully permit airlines and their crews a wide range of responses to in-flight passenger illness and death.⁸ Patients and families should be advised that no worldwide guidelines exist for airlines regarding completion of flight or diversion to the nearest airport should a passenger die on board.^{3,4} To minimize or avoid distress, we recommend a proactive discussion of this scenario that involves all parties—travel companions, the medical team, and the patient. The flight crew's response to an in-flight emergency may be influenced by several factors, including the patient's or accompanying family member's ability to relay their medical information and goals of care, the resources and training of those on board, and cultural comfort with the possibility that the patient may die on the plane.

A STARTING POINT

Providing counsel to terminally ill patients wishing to return to their country of origin is an academically challenging endeavor that many medical teams face. It is also one of the most professionally gratifying scenarios we encounter as we meet the patient's goal of returning home. We hope that this discussion can guide other medical teams with end-of-life care and serve as a starting point for further discussion and guidelines.

DISCLOSURES

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

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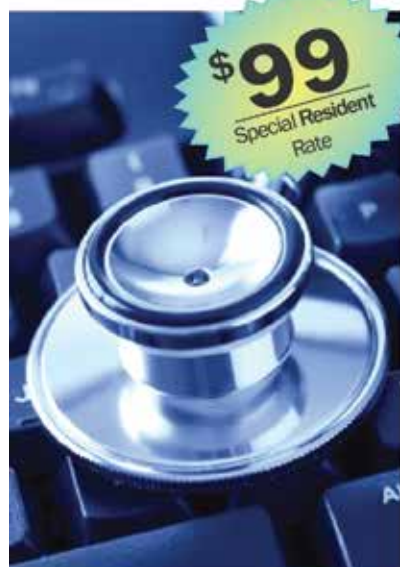
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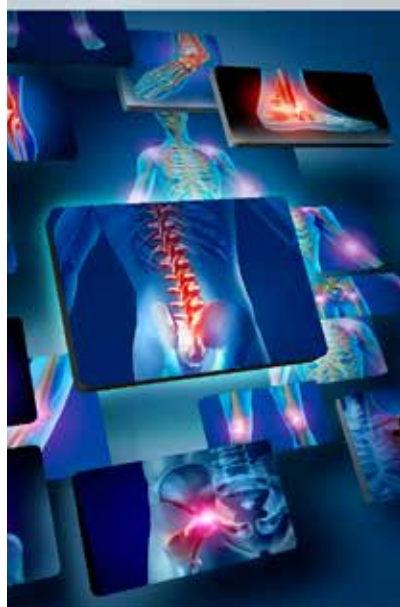
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Perspectives on travel and healthcare

TRAVEL FOR HEALTHCARE has been fueled in recent years by a range of factors. These include innovations in treatment as well as geopolitical drivers of migration that have led more patients to seek medical care away from their country of origin. Indeed, travel for healthcare has seen unprecedented double-digit growth in recent years.¹ In the United States, it is estimated that 0.5% of all airline travelers are arriving for advanced medical care that is unavailable in their country of origin.¹ Consequently, clinicians in the world's advanced economies are increasingly likely to encounter patients who have migrated internationally and become part of the local community, as well as patients who have traveled temporarily to receive more advanced or more affordable care.²

See related article, page 270

These 2 groups share many basic needs, but also present separate challenges.^{3,4} They are part of a trend that is bringing more patients of diverse backgrounds and with challenging needs to clinicians. In some cases, healthcare teams are accidental participants without dedicated training or infrastructure to care for this unique patient population.^{3,5} In our experience, a dedicated global patient services team is necessary to achieve desired outcomes and patient satisfaction. This team is trained to bridge the many invisible gaps between patients and their families on one side and clinicians on the other.

In this issue of the *Journal*, Ferraro et al⁶ address a specific challenge: patients who are receiving healthcare far from their native home and now seek the comfort of dying at home. The authors accurately point to the challenges encountered when arranging the return of dying patients to their home country.

doi:10.3949/ccjm.91a.24018

■ COVERING ALL BASES

The journey home starts when the final diagnosis and prognosis are established. Timing is a crucial part of planning the journey. One must anticipate the various complications likely to occur during travel and upon arrival at the destination. To mitigate these potential complications, the healthcare team should ensure that the patient has adequate medications and nourishment during travel, manage all minor details of transportation, and communicate with the receiving healthcare team.

Pharmaceutical supplies need proper handling, with clear instructions for the caregiver to follow during the journey. For example, intravenous access requires a basic level of training for the traveling companion. One must also attend to the legal aspects of carrying narcotics and painkillers across international borders. It is prudent to equip the family with documents that facilitate their interaction with various authorities.

In all situations, the patient's safety and comfort should be the top priority. In regard to the mode of transportation, this may include prioritizing air travel and, in some cases, consideration of evacuation by a dedicated air ambulance team. It is imperative to review pretravel documents required by international air carriers, as they spell out most details related to transporting a patient across borders. Such details include consideration of mobility, use of oxygen, special dietary needs, and ground transportation on arrival.

■ GOAL: A SEAMLESS TRANSITION

In contrast to terminally ill patients who wish to travel to their home country to die are those who travel internationally in search of lifesaving care. For patients who seek medical care abroad (the term "medical tourism" trivializes the seriousness of this endeavor),⁴ a satisfactory healthcare journey starts with adequate preparation

before the patient's arrival. Every effort should be made to eliminate differences between international and local patients. To achieve this, an international patient center registers international patients before arrival and translates medical records made available to the clinical team in a seamless way that conforms with institutional norms. Once that is achieved, ideally international patients are left with minimal unique cultural and language barriers that could impact their care. The support of a special team of interpreters, as mandated by law, is necessary to achieve good outcomes and improve patient experience.

For international patients to have an overall positive experience throughout their care, their clinicians must also have a positive experience caring for them. The needs of the medical team must be acknowledged so that the international patient is not perceived as

someone who will require a greater share of their time and already limited resources. In our setting, we find that special cultural training is extremely helpful during the onboarding of new healthcare employees; this training should be renewed periodically.

GUIDELINES NEEDED

Further guidelines are needed to reduce the hardship faced by patients and clinicians in the setting of international travel for patient care. This is a unique area in patient care that has become more relevant in today's world. Its significance will only increase.

DISCLOSURES

Dr. Fares reports no relevant financial relationships that could be perceived as a potential conflict of interest in the context of the material presented.

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Q: Should I refer my patient for a parathyroidectomy?

A 60-year-old woman who is otherwise healthy is found to have an elevated serum calcium level of 10.5 mg/dL (reference range 8.5–10.2) during her yearly checkup. Her main complaints are memory loss and fatigue, but she denies prior fractures or kidney stones. Review of her medical record shows that her calcium levels have been persistently elevated for at least the past 5 years. Additional workup demonstrates a parathyroid hormone level (PTH) of 55 pg/mL (15–65), 25-hydroxyvitamin D level of 40 ng/mL (31–80), and 24-hour urine calcium excretion of 240 mg (100–300). She has known osteopenia, with a T-score of –2.4 at the femoral neck. Her serum creatinine level is normal. Should this patient be referred for parathyroidectomy?

A: In patients with primary hyperparathyroidism, the decision to refer for surgery should be individualized and not based solely on whether the patient meets guideline criteria. The first question that must be addressed then is whether our patient has primary hyperparathyroidism.

She has hypercalcemia (serum level of 10.5 mg/dL) with a replete 25-vitamin D level, and although her PTH level at greater than 30 pg/mL is within the normal range, it is still inappropriately high, confirming the diagnosis of primary hyperparathyroidism. Traditionally, the diagnosis of primary hyperparathyroidism was made based on concomitant calcium and PTH levels above the normal limits, but we now recognize that what matters is the relationship of the levels rather than the absolute values.¹

Also, although the diagnosis is clear in this patient with hypercalcemia and an inappropriately high PTH, familial hypocalciuric hypercalcemia should be considered in the differential. Familial hypocalciuric hypercalcemia, though far less common than primary hyperparathyroidism, presents with similar biochemical

patterns, except for hypocalciuria (< 100 mg/24 hours). The urine calcium:creatinine clearance ratio may help distinguish between the 2 conditions.²

The next question—should our patient be referred for parathyroidectomy?—is more complex. According to current international consensus guidelines, she does not meet the criteria for surgery because her serum calcium is not 1.0 mg/dL above the upper limit of normal, she is older than 50, and she does not have osteoporosis, nephrolithiasis, fractures, decreased creatinine clearance, or hypercalciuria (Table 1).² The decision to treat, however, should not rely solely on whether the patient meets guideline criteria. Surgery can improve bone health, reduce the likelihood of nephrolithiasis or even chronic kidney disease, and improve serum calcium values. Also, several neuropsychiatric symptoms are likely to improve with surgery, such as fatigue and brain fog.¹

INDIVIDUALIZING THE DECISION TO TREAT

Research indicates that the level of hypercalcemia does not correlate with the presence of symptoms.³ Thus, our patient may still be prone to symptoms attributable to primary hyperparathyroidism with her calcium level of 10.5 mg/dL. Her age also may not be relevant and should be seen as being part of a continuum rather than a specific cutoff point. Given current life-expectancy estimates, patients older than age 50 can still be at risk for additional long-term manifestations of the disease. In fact, parathyroidectomy is the most cost-effective strategy for patients with at least 3 years of life expectancy based on fracture risk reduction.⁴

Related to bone health, while our patient does not meet the bone mineral density criterion (T-score ≤ –2.5) for surgery, the T-score also should be seen as a continuum. She likely will progress and eventually meet the criterion, as untreated primary hyperparathyroidism can cause

doi:10.3949/cjcm.91a.23076

TABLE 1

International criteria for parathyroid surgery in patients with primary hyperparathyroidism

Surgery is recommended in all patients with at least 1 of the following:

- Serum calcium > 1.0 mg/dL (0.25 mmol/L) above the upper limit of normal
- Bone mineral density by dual-energy x-ray absorptiometry: T-score ≤ -2.5 at lumbar spine, total hip, femoral neck, or distal one-third radius
- Vertebral fracture by radiography, computed tomography, or magnetic resonance imaging
- Estimated glomerular filtration rate or creatinine clearance < 60 mL/minute
- 24-hour urine calcium level > 250 mg in women and > 300 mg in men
- Presence of nephrolithiasis or nephrocalcinosis by radiography, ultrasonography, or computed tomography
- Age < 50

Based on information in reference 2.

significant bone loss.⁵ Parathyroidectomy can improve bone mineral density and reduce the risk of fractures.^{5,6}

Finally, our patient presented with neurocognitive symptoms that included memory loss and fatigue. Though still a matter of debate, there is growing evidence that these symptoms and quality of life can improve after parathyroidectomy.^{1,7,8}

Careful evaluation of this patient indicates she would benefit from consultation with a high-volume parathyroid surgeon.

THE BOTTOM LINE

Primary hyperparathyroidism is frequently underrecognized and underdiagnosed. It is the most common cause

of hypercalcemia in the outpatient setting.⁹ While consensus guidelines may be useful in large population studies, individualizing care is most important. Surgical correction can result in improvements in health and quality of life. It is essential to recognize hypercalcemia with nonsuppressed PTH values and to individualize treatment for each patient even when the exact surgical criteria are not met. In patients presenting at a young age or with strong family history, hereditary endocrinopathies must be considered.

DISCLOSURES

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

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Q: Does every patient with lactational mastitis require antibiotic treatment?

My 4-week-postpartum lactating patient calls into clinic with a complaint of 12 hours of a tender, hot, swollen breast. Because of these symptoms, she is less motivated to continue breastfeeding. Does this patient require antibiotic treatment?

A: Not all patients with lactational mastitis require antibiotics. Depending on the duration and severity of symptoms, some patients can be managed conservatively, while others should receive empiric antibiotics.

DEFINITION

Lactational mastitis is inflammation of the mammary gland ducts, alveoli, and surrounding tissue that occurs during breastfeeding or feeding with breast milk expressed via pumping.¹ Lactational mastitis affects approximately 1 in 4 breastfeeding patients.²

The spectrum of mastitis encompasses a progression of conditions including hyperlactation (production of breast milk beyond the infant's current needs), dysbiosis, ductal narrowing, inflammatory mastitis, bacterial mastitis, phlegmon, infected galactoceles, and abscess.¹ Timely treatment with appropriate conservative measures or empiric antibiotics when indicated is crucial to prevent progression along the aforementioned mastitis spectrum. Management should also include counseling for continued breastfeeding, if desired by the patient.^{1,3}

CAUSES OF LACTATIONAL MASTITIS

Though the exact pathophysiology of lactational mastitis remains unclear, several factors are associated with its occurrence, including hyperlactation, nipple

injury, improper fitting of breast pump flanges, high pump suction, dysbiosis, and abrupt or semi-abrupt breastfeed weaning.^{3,4} Hyperlactation causes prolonged breast engorgement that, when coupled with insufficient drainage of milk, can cause the breast to become inflamed (eg, inflammatory mastitis) or, in some patients, can result in bacterial growth within the lactiferous ducts (eg, bacterial mastitis).¹⁻³

CLINICAL FEATURES AND DIAGNOSIS

Patients with lactational mastitis, whether inflammatory or bacterial, may present with symptoms of breast pain and tenderness, redness, swelling, decreased breast milk production, and constitutional symptoms such as fever, chills, and body aches. When diagnosing lactational mastitis, a physical examination should be conducted with an in-person office visit or, at minimum, a virtual visit, keeping in mind that erythema may present less conspicuously on darker skin. Examination findings concerning for inflammatory or bacterial mastitis include diffuse breast tenderness, induration, erythema, and warmth. A check of vital signs may reveal tachycardia, fever, or hypotension in a patient who is septic or dehydrated, though this is rare.¹

If symptoms are ongoing or progressing for more than 24 to 48 hours and are coupled with a focal, discrete area of swelling and erythema, the clinician should consider a phlegmon, abscess, or infected galactocoele. A phlegmon is a localized inflammatory mass of the soft tissue. An abscess is an enclosed collection of pus within tissue. A galactocoele, which can become infected, is a soft cystic collection that forms in the breast after obstruction of a milk duct. Ultrasonography is useful for diagnosing these conditions. Breast milk

doi:10.3949/cjcm.91a.23080

culture can be helpful in cases of mastitis not responding to first-line antibiotics.¹

■ MANAGEMENT OF INITIAL AND MILD SYMPTOMS

Patients with mild systemic symptoms and focal breast findings that resolve in 24 to 48 hours can be managed with a number of conservative measures and without the need for antibiotics. The clinician should reassure the patient that stopping breastfeeding is unnecessary. Continued breastfeeding with ongoing mastitis does not endanger the infant's health.¹

The patient may apply light sweeping motions in the direction of the lymph nodes that drain the breast (axillary and supraclavicular) to assist with lymphatic drainage, with the same amount of pressure used to pet a cat. Deep breast tissue massage, vibrating devices, or other aggressive massage techniques should be avoided to prevent capillary and tissue injury.^{1,3}

If the breast is very swollen, the patient may find that hand expression is more effective than pumping. The clinician should reiterate proper breast-pump technique if pumping is necessary and offer the following recommendations:

- If pumping exclusively, aim to pump the equivalent volume of fluid consumed by the infant (28–30 ounces of milk/day/infant from 1–6 months of age) to reduce hyperlactation; if the infant is directly breastfeeding and gaining weight appropriately, pumping should be minimized or avoided to prevent hyperlactation³
- Aim for a moderate suction pressure to avoid traumatizing breast parenchyma¹
- Consult a lactation specialist to ensure the pump flanges are the appropriate size¹
- Clean equipment by hand with soap and water or in the dishwasher with hot water⁵

The patient should wear an adequately sized and fully supportive bra to minimize worsening edema from gravity.^{1,6} Also, the patient may promote pain relief and decrease inflammation by using cold compresses while lying on her back after breastfeeding and by taking nonsteroidal anti-inflammatory medications around the clock to help reduce inflammation.^{1,3} There is no evidence for the use of cabbage leaves, which can be contaminated with *Listeria*.^{7,8}

The patient should avoid excess breastfeeding or pumping beyond the infant's needs. Also to be avoided are breast soaks (which can cause skin ulceration and irritation), aggressive massage, and prophylactic antibiotics.^{1,3,8}

■ MANAGEMENT OF SEVERE OR PERSISTENT SYMPTOMS

Patients with severe local symptoms or with systemic symptoms such as fever, myalgias, and rigors who do not improve within 24 to 48 hours of initiating proper conservative measures should be managed promptly with the following measures.³

Empiric antibiotic treatment for bacterial mastitis

First-line treatments include dicloxacillin 500 mg 4 times daily and cephalexin 500 mg 4 times daily, each for 10 to 14 days.³ Second-line treatment is clindamycin 300 mg 4 times daily or trimethoprim-sulfamethoxazole 160 mg/800 mg twice daily, each for 10 to 14 days.³ Avoid trimethoprim-sulfamethoxazole in patients with pregnancies complicated by prematurity, neonatal hyperbilirubinemia, or glucose-6-phosphate dehydrogenase deficiency.

Breast milk culture

If symptoms persist after 48 hours of antibiotic treatment, obtain a breast milk culture from the affected breast to rule out methicillin-resistant *Staphylococcus aureus* and other resistant pathogens.¹ To do this, clean the nipple with a topical antiseptic (eg, an alcohol pad), and avoid contact between the nipple and the sterile container when collecting the sample for culture. The clinician or the patient can put on sterile gloves and hand-express breast milk into a sterile container. The clinician should submit 5 to 10 mL of breast milk to the laboratory as a “body fluid culture.” Patients can continue to breastfeed or pump while awaiting culture results, as breastfeeding with mastitis is considered safe.

Ultrasonography

When an abscess, phlegmon, or infected galactocele is suspected, ultrasonography and prompt (same-day) consult with radiology and breast surgery are recommended. Fluid collections may be surgically drained under ultrasonographic guidance.¹ Referral to a breast specialist is advisable to rule out inflammatory breast cancer in patients whose symptoms do not respond to antibiotics.

Avoid deroofing nipple blebs

Avoid popping or deroofing nipple blebs (papules that can occur in association with ductal inflammation from mastitis), and prescribe triamcinolone 0.1% topical steroid cream twice daily for a week.¹ Advise the patient to wipe off the cream with a towel before feeding.

■ PREVENTION AND MANAGEMENT OF RECURRENT MASTITIS

Clinicians should provide anticipatory counseling regarding proper breastfeeding techniques and recommend that the patient feed their infant “on demand” with direct breastfeeding, as this encourages more physiologic breast milk removal.

Consider referral to a lactation consultant or breastfeeding medicine specialist who can help downregulate supply safely if the patient has an oversupply or hyperlactation. Also, consider a psychology or psychiatry consult for mental health management, as mastitis, especially if recurrent, is associated with a history of anxiety and depression.¹

Although evidence is mixed, prophylactic probiotics can be considered for the breastfeeding parent (*Limosilactobacillus fermentum* or, preferably, *Ligilactobacillus salivarius*).¹ Clinicians may also recommend oral sunflower or soy lecithin 5 to 10 g daily to help emulsify the

milk to prevent clogging of ducts.¹ When appropriate, clinicians can promote healthy mammary microbiota by avoiding prophylactic antibiotics.⁸

If pumping is necessary, ask the patient to pump only in place of feeds to produce what the infant needs and to avoid creation of a “stash” of milk that exceeds the infant’s needs. Patients should avoid nipple shields (silicone devices worn over the nipples) when latching the infant because the shields can lead to inadequate milk transfer.

The healthcare team should support the patient when breastfeeding challenges are encountered, as doing so helps ensure that the patient will continue to provide human milk to the infant, which has health benefits for both parent and child. ■

■ DISCLOSURES

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

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Q: Do I always need a central venous catheter to administer vasopressors?

A: Vasopressors are the cornerstone of treatment for shock, and a central venous (CV) catheter is generally preferred for their administration. The CV catheter carries risks, however, including procedural complications, infection, thrombosis, and hazards associated with its invasiveness. A growing number of studies are assessing the safety and feasibility of the peripheral intravenous (PIV) catheter for vasopressor administration, which may have a better risk profile than the CV catheter. Clinicians are obliged to assess, case by case, whether the PIV catheter can be used for vasopressor administration.

■ BACKGROUND

Vasopressors are used to restore blood pressure and tissue perfusion in 27% of patients admitted to intensive care units, and their use has been increasing over the past decade.¹ The CV catheter is the preferred mode for vasopressor administration because peripheral administration is associated with complications such as local extravasation and potential tissue damage.²⁻⁴ CV catheter insertion and maintenance also carry risks, however, which vary by the site of insertion. Complications include pneumothorax (1.5%–3.1% of patients), arterial puncture (6.3%–15%), hematoma (3.8%–4.4%), deep vein thrombosis (15%), and bloodstream infections.^{5,6} Further, the time required for CV catheter placement could delay delivery of vasopressors and, therefore, hemodynamic stabilization, leading to higher mortality.⁷

■ PERIPHERAL VASOPRESSOR ADMINISTRATION

Safety and risk

Studies assessing the safety and efficacy of peripheral administration have found relatively few instances of complications. For example:

- Among 202 patients with PIV catheters located in the forearm and antecubital fossa, 4% experienced extravasation events, all of which were managed conservatively⁸
- In a systematic review and meta-analysis of studies that included 1,835 patients, the total rate of complications with peripheral administration was 7%, of which 96% were minor⁹
- In a group of 310 patients, of whom more than 55% received peripheral administration, an adverse event of skin necrosis was reported in 1 patient (0.6%)¹⁰
- More recent studies have reported extravasation rates ranging from 0.6% to 3.4%¹¹⁻¹³; most adverse events, occurring in local and distal sites, were deemed nonfatal.

Only 1 randomized controlled trial has compared the complication rates of CV and PIV catheters regardless of the need for vasopressors.¹⁴ In this study, approximately 48% of patients in the PIV catheter group experienced major or minor complications vs 36% in the CV catheter group.¹⁴ The most frequent complication in the PIV catheter group was difficulty of insertion. The risks of infection and thrombus were similar in both groups. In addition, given that less than half of the PIV catheter group received vasopressors, all the reported complications might not have been related to peripheral vasopressor administration.¹⁴

More recently, Yerke et al¹⁵ reported that extravasation occurred in 5.5% of 635 patients who received peripheral

TABLE 1
Adverse events with peripheral vasopressor administration

Study type	Number of patients	Vasopressors	Dose ^a	Duration	PIVC site	Events
Retrospective cohort ⁸	202	Norepinephrine (72%), phenylephrine (36%)	Median initial to maximum: norepinephrine 0.04–0.13, phenylephrine 25–95 µg/minute	Median 11.5 hours, maximum 19 hours	Forearm, antecubital fossa, hand	8 events (4%), all local extravasation
Randomized controlled trial ¹⁰	310 (155 early vasopressor, 155 standard treatment)	Norepinephrine (67.7%) and epinephrine (17.4%) in early vasopressor group	Median (IQR) maximum in early vasopressor group: norepinephrine 0.1 (0.05–0.18), epinephrine 0.41 (0.28–1.2)	NR	NR	6 events in early vasopressor group (3.8%): 1 skin necrosis, 5 acute limb or intestinal ischemia
Unblinded superiority trial ¹¹	1,563 (782 restrictive fluid, 781 liberal fluid)	NR	NR	9.6 hours in restrictive fluid group	NR	3 events in PIVC vasopressor group (n = 500), all 3 were site extravasation
Prospective cohort ¹³	64	Epinephrine (66%), norepinephrine (41%)	Median (IQR): norepinephrine 0.1 (0.01–0.48), epinephrine 0.12 (0.6–0.38)	Median (IQR) 19 hours (8.5–37)	Antecubital fossa, forearm, hand	2 events (2.9%), extravasation with local tissue swelling
Randomized controlled trial ¹⁴	263 (128 PIVC, 135 CVC)	Epinephrine, norepinephrine	< 2 mg/hour, if more, crossover to CVC	NR	NR	133 total events: 56 insertion difficulty, 20 erythema, 19 extravasation, 9 catheter infection
Prospective cohort ¹⁵	635	Norepinephrine	Median (IQR) maximum: 10 µg/minute (6–15)	Median (IQR) 5.8 hours (2–20)	Antecubital fossa	35 extravasation ^b events (5.5%)
Retrospective cohort ¹⁶	212 patients (39 PIVC, 155 PIVC followed by CVC, 18 CVC only)	Phenylephrine (41%), norepinephrine (38%)	Median (IQR) maximum in PIVC-only group: phenylephrine 0.17 (0.09–0.27), norepinephrine 0.99 (0.6–1.64)	Median (IQR) 10.5 hours (4.7–15.9) in PIVC-only group	NR	75 events (35%): 28 leakage, 25 tissue cannula, 19 extravasation, 2 erythema

^aDosing is given as µg/kg/minute except where noted.

^bOther complications were not reported in this study.

CVC = central venous catheter; IQR = interquartile range; NR = not reported; PIVC = peripheral intravenous catheter

vasopressor administration. Most extravasation events were reported to be infiltration grade 0 to 2, with the worst resulting in edema at the infiltration site with mild pain.¹⁵

Table 1 summarizes adverse events associated with peripheral vasopressor administration.^{8,10,11,13–16} Given case reports of catastrophic events such as compartment

syndrome and amputation,^{17,18} these complications should not be underestimated. Although such complications are rare, their consequences are significant.

Type and duration

Although most studies report the safety of peripheral norepinephrine administration, some also note the safety of peripheral phenylephrine administration.^{19–21} At least 1 study of peripheral epinephrine and dopamine administration suggests that peripheral strategies for these agents are safe.¹³ A comparative study of these different vasopressors is warranted to assess which vasopressors or inotropes can be administered peripherally.

Despite reports that support peripheral vascular administration of vasopressors, the safe duration for its use is unknown. A systematic review reported the time to onset of adverse events to be 55.9 hours.²² In a more recent report, extravasation occurred primarily in the first 24 hours.¹⁵ There is evidence to support a protocol allowing peripheral vasopressor administration for up to 24 to 48 hours.^{15,23,24} Given the mixed data, however, the safe duration of peripheral administration requires further investigation.

■ PROTOCOLS TO PREVENT COMPLICATIONS

Despite the reported safety and feasibility of peripheral administration of vasopressors, variations in setting and management across institutions are a consideration. Various protocols that emphasize certain practices have been implemented and reported:

- Guidance on size and location along with assessment of PIV catheters every 2 hours²⁵
- Preset sizes and locations of catheters, confirmation of catheter placement with ultrasonography, assessment of the catheter every 2 hours, and maximum norepinephrine dosage limited to 15 µg/min with a maximum duration up to 48 hours¹⁵
- In the event of extravasation, stopping the vasopressor infusion, aspiration of the residual vasopressor, and application of phentolamine to the site (in this protocol, none of the 2% of patients with extravasation had tissue injury).^{24,26}

While these protocols sound clinically reasonable, 1 study reported no associations between peripheral catheter diameters, dosage of vasopressors, patient age, and risk of extravasation.¹³ A wide range of norepinephrine concentrations, from 4 to 64 µg/mL, administered via PIV catheter has been described in the literature.²⁷ In a study supporting the safety of peripheral administration, most patients received 16 or 32 µg/mL of norepinephrine.⁸ In the absence of comparisons of different concentrations of norepinephrine,

a concentration in the range of 16 to 32 µg/mL may be a safer option than higher doses.

A protocol that defines the duration of peripheral administration, norepinephrine concentration, assessment frequency, and catheter type and size will minimize complications, delays in their identification, and confusion among staff.

■ BENEFITS OF PERIPHERAL ADMINISTRATION

The potential benefits of peripheral administration include earlier hemodynamic stabilization and avoidance of CV catheter placement.

In a post hoc analysis of a clinical trial on early septic shock, when compared with patients who received CV catheter administration, those in the peripheral administration group had a shorter median time to commencement of vasopressors (2.4 vs 4.9 hours) and antimicrobials (55 vs 71.5 minutes).²⁸ In a randomized controlled trial assessing early use of norepinephrine in septic shock resuscitation, the median time to CV catheter insertion from the diagnosis of septic shock was approximately 4 hours, whereas vasopressors were initiated via PIV or CV catheter within approximately 70 minutes.¹⁰ Early norepinephrine led to a significantly increased rate of shock control by 6 hours, implying that we should not delay starting norepinephrine until a CV catheter is placed. The authors suggested that rapid hemodynamic stabilization potentially benefits clinical outcomes.¹⁰

In addition to its potential clinical benefits, peripheral administration can help avoid unnecessary CV catheter insertion. In a study of 734 patients who received peripheral administration of vasoactive medication, only 13% needed CV catheter insertion.²⁵ Even when peripheral administration was limited to up to 24 hours in another study, approximately one-third of patients who received vasopressors did not require CV catheter placement.²³ A successful peripheral administration protocol could offer a significant patient-centric benefit of comfort by avoiding CV catheter-related complications.

The impact of safe vasopressor administration via PIV catheter can be significant in a resource-limited setting, although few studies have assessed its effect in such settings.^{13,29}

■ CURRENT PERCEPTIONS AND CONCERNS

The Surviving Sepsis Campaign guidelines suggest starting peripheral vasopressor administration to restore adequate mean arterial pressure until a CV catheter can be placed.³⁰ General acceptance of peripheral vasopressor administration is limited, however. A survey of

62 hospitals in Michigan reported that 36.5% supported PIV catheter use for vasopressors, 25% preferred CV catheter use only, and the remaining 36.5% preferred CV catheter use over peripheral administration.²⁴ Compared with rural institutions, urban hospitals tended to favor peripheral administration of vasopressors.²⁴ Low acceptance of peripheral vasopressor administration might reflect concerns about adverse events and lack of familiarity with the process.

We suggest a protocol-based approach to address these concerns. A recent before-and-after study using a nursing protocol for peripheral vasopressor administration showed a significant reduction in extravasation events, from 2.4% to 1.1%.³¹ The investigators protocolized the use of ultrasonography for peripheral placement, peripheral location, line assessment every 2 hours, and vasopressor infusion rates. A similar protocol that also included peripheral vasopressor administration for up to 48 hours was used in another study.¹⁵ Most studies of peripheral administration are conducted in the intensive care unit, where it is reasonable to implement peripheral vasopressor administration because the need for frequent assessment can be accommodated and clinicians are familiar with the medication.

Protocol-based approaches that include guidance on patient selection and location of placement of the PIV catheter, training on use of ultrasonography for placement of the PIV catheter, standardized assessment of

the peripheral site, and ready availability of antidotes can increase the safety of peripheral vasopressor administration.^{24,26} A large prospective study to confirm the duration of safe peripheral vasopressor administration is warranted, but the requirement for a vasopressor does not automatically translate to the need for a CV catheter.

TAKE-HOME POINTS

- Peripheral administration shortens the time to start vasopressors.
- PIV catheter use is associated with local adverse events such as tissue infiltration, which infrequently requires intervention but rarely leads to catastrophic adverse events such as compartment syndrome or amputation.
- Peripheral vasopressor administration requires close attention, especially during the first 24 hours.
- Most studies used protocols that allow peripheral administration of vasopressors for up to 24 to 48 hours.
- PIV catheter use can lessen the need for CV catheter placement, decreasing the risk of complications associated with the procedure and catheter maintenance.

DISCLOSURES

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

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Reducing the risks when using benzodiazepines to treat insomnia: A public health approach

ABSTRACT

Benzodiazepines are widely used but can cause considerable harm, including sedation, addiction, falls, fractures, and cognitive impairment, especially with long-term use and in elderly patients. The authors propose a public health approach to reduce the potential for harm when using benzodiazepines to treat insomnia. Primary prevention involves judicious patient selection and patient education. Secondary prevention requires keeping the duration of use as short as possible according to guidelines. Tertiary prevention, for patients who have been taking a benzodiazepine for a long time, uses shared decision-making to introduce a gradual and carefully monitored taper.

KEY POINTS

Be judicious about starting benzodiazepines, and avoid prescribing them to treat insomnia for longer than 4 weeks.

Provide ongoing education to patients currently on benzodiazepines about the risks and benefits and offer alternative treatment options.

Discuss deprescribing with patients on long-term therapy, and use shared decision-making to come to an agreement about when and how to initiate a gradual taper.

BENZODIAZEPINES are not inherently bad medications and can be safe and effective when used judiciously. With their anxiolytic, hypnotic, muscle-relaxant, and anticonvulsant properties, they are widely used, and primary care doctors often use them for rapid, short-term relief of insomnia, for which their efficacy is well established.¹⁻⁵

But these medications carry serious risks, including falls, fractures, overdose, misuse, and dependence, all of which increase with patient age and length of use.⁵ Neutel et al⁶ estimated the population risk of serious falls attributable to long-term benzodiazepine use at 3%. A South Korean study found a twofold higher risk of falls in patients taking benzodiazepines.⁷ Additional data suggest that the risk of fracture is increased by 50% to 110% in patients taking benzodiazepines.⁸ In the United States, benzodiazepine-related emergency room visits have been increasing substantially, as have cases of fatal opioid overdose in people also taking benzodiazepines.⁹ More than a few people are taking both types of drugs concurrently: Gerlach et al¹⁰ reported that 56.8% of long-term benzodiazepine users had also been prescribed an opioid.

Tolerance to the hypnotic effects of benzodiazepines (loss of efficacy) can develop in days.^{7,9} Likewise, physiologic dependence on benzodiazepines develops after 3 to 6 weeks at therapeutic doses,^{5,9} meaning that stopping abruptly will lead to rebound (worsening of original symptoms) or withdrawal.¹¹

Consequently, in most instances, the use of a benzodiazepine should be temporary.^{5,6} Cross-national guidelines recommend limiting their use for anxiety or insomnia to 2 to 4 weeks in adults.^{5,12,13} This recommendation is based on data that suggest that these drugs start to lose their efficacy for insomnia after 4 weeks, while the risk of side effects and addiction remains.^{4,5,8} In the elderly, clinical guidelines are stricter: benzodiazepine use for anxiety is restricted to low doses and for less than a month, and using them as hypnotics is discouraged altogether.^{5,11–14}

However, for many patients and their doctors, the short-term benefits of benzodiazepines overshadow their long-term risks, and these drugs continue to be widely used.¹¹ Moreover, clinicians may unintentionally discount the risks and fail to adhere to prescribing guidelines.^{3,6}

■ A PUBLIC HEALTH APPROACH

Below, we outline a “public health” approach to decreasing long-term complications of benzodiazepines prescribed for insomnia. We frame the discussion in terms of the following:

- **Primary prevention**, ie, measures aimed at preventing harm before benzodiazepines are prescribed¹⁵
- **Secondary prevention**, ie, efforts to decrease any harm of benzodiazepines within 4 weeks after the initial prescription^{3,16}
- **Tertiary prevention**, ie, attempts to limit the harmful effects of long-term prescribing.^{5,10,11}

■ PRIMARY PREVENTION: PRESCRIBE BENZODIAZEPINES JUDICIOUSLY

Of concern, one of the most salient correlates of benzodiazepine misuse is the receipt of a prescription for one.⁹ Primary prevention efforts can include educational public campaigns as well as judicious prescribing.^{8,12–14} Benzodiazepines should be used to treat insomnia only when it is severe, disabling, or causing extreme distress.⁸ Patients should be screened for risk of misuse and informed of the risks of long-term use.^{5,8}

Cognitive behavioral therapy is the first-line treatment

Clinical guidelines for insomnia recommend cognitive behavioral therapy as the first-line treatment and pharmacotherapy as the second line.^{10,12–14} This treatment aims to identify and target modifiable variables that influence sleep such as hyperarousal, as well as maladaptive thoughts and behaviors.^{10,12–14}

Unfortunately, despite empirical validation, cognitive behavioral therapy is not readily available, does not offer immediate results, and is time-consuming, making this a difficult mandate to follow in practice.¹⁷ Up to half of primary care patients say they have trouble sleeping, and they often present with a sense of urgency,² whereas the benefits of cognitive behavioral therapy are not seen for several weeks. Furthermore, cognitive behavioral therapy is time-consuming for the busy primary care physician to administer, and experts are scarce. While some primary care–friendly versions of this therapy look promising,¹⁷ they remain underutilized. For these reasons, both patients and practitioners prefer the simpler and more immediate effects of a sleeping pill.

Alternatives to formal cognitive behavioral therapy include online resources and apps based on its principles.¹⁸ For example, Dalhousie University’s initiative Sleepwell has a website (<https://mysleepwell.ca/insomnia/>) with links to self-help options for patients, such as books, other websites, and apps.⁵ Several commercially available apps have been studied and found to be effective in delivering self-guided cognitive behavioral therapy.¹⁸ These incorporate modules on sleep hygiene, challenging negative thoughts, sleep diaries, and sleep restriction. While these apps can be helpful, a drawback is that users must be familiar with technology and be self-motivated to use the app daily. Other alternatives to formal cognitive behavioral therapy are presented in **Table 1**.^{5,12,18}

Other drugs are approved

If cognitive behavioral therapy is not available or not acceptable to the patient, benzodiazepines are just 1 of several types of medication that have been approved for short-term treatment of insomnia.¹⁴ The so-called Z drugs—zopiclone, eszopiclone, zaleplon, and zolpidem—have also been approved by the US Food and Drug Administration.^{12,14} Other approved options include dual orexin receptor antagonists such as suvorexant, lemborexant, and daridorexant; melatonin receptor agonists (ramelteon); and the antidepressant doxepin in low doses.^{12,14} Clinicians can also prescribe other drugs such as sedating antidepressants and antipsychotics off-label to treat insomnia.^{12,14}

Persons taking opioids are at higher risk

Benzodiazepine use disorder refers to a strong desire to take the drug (cravings), difficulty in controlling its use, using more than intended, and using it despite adverse consequences in various domains of functioning.⁸ Fortunately, it is uncommon. Data from 102,000 participants in the 2015–2016 National Surveys on

Drug Use and Health¹⁹ revealed that although 12.5% of adults in the United States used benzodiazepines, only 17.1% of users misused them, and less than 2% of users met the criteria for benzodiazepine use disorder.¹⁹

People who have an opioid use disorder are at higher risk of developing benzodiazepine use disorder.¹⁹ Many states require that physicians check the state prescription monitoring program before issuing a prescription for a benzodiazepine.²⁰ These programs allow the clinician to see other undisclosed prescriptions for benzodiazepines or opioids. An existing prescription for opioids is a relative contraindication for beginning a benzodiazepine. A frank, individualized discussion of these risks, including any red flags found on the prescription monitoring program search, can lead to alternative approaches, a critical goal of primary prevention.²¹

A shared decision

Shared decision-making involves discussing the pros and cons of these options and noting patient characteristics that may influence medication choice.^{12,14} As discussed, risks of benzodiazepines include falls, fractures, overdose, and misuse and are greater for the elderly, frail individuals, and people with a history of personal or familial addiction.^{11,13}

If, after carefully considering all options, a benzodiazepine is selected, it is essential to set realistic expectations.^{8,11} Clinicians must convey the message that this is a crisis-oriented, short-term strategy and set the stage for deprescribing. Patients need to know that benzodiazepines are reinforcing and have long-term risks. They should be informed that tolerance may develop and that increasing the dose at that point will only lead to further tolerance and dependence. Setting the stage in this way will help avoid long-term use, a critical goal of secondary prevention.³

■ SECONDARY PREVENTION: KEEP THE DURATION OF USE SHORT

Secondary prevention refers to efforts to decrease any harm of benzodiazepines after appropriate short-term use.^{3,16} The American College of Physicians guideline suggests slowly tapering the dose in adults who have been regularly using the drugs for more than 4 weeks, particularly the elderly.¹⁴ Similarly, Canadian guidelines recommend tapering benzodiazepines used for insomnia, irrespective of age.⁵

Arguably, it is easier to write guidelines than to implement them,⁶ and preventing short-term use from turning into long-term use may be difficult.^{7,11,22–24} In a British study,⁴ 35% of patients taking benzodiazepines

TABLE 1

Alternatives to formal cognitive behavioral therapy for insomnia

Online apps and self-help books

Online resources include books patients can read on their own and apps that guide patients through cognitive behavioral therapy for insomnia

Brief therapies for insomnia

Abridged versions of cognitive behavioral therapy that emphasize behavioral aspects of sleep regulation

Education is given on sleep hygiene, factors that affect sleep, and principles of sleep restriction (described below)

After examining a sleep diary, primary care clinicians can inquire about the patient's sleep habits and provide education on patient-specific factors that may be affecting sleep (eg, excess alcohol, using screens in bed, attempting to go to bed too early)

Sleep-restriction therapy

Aims to limit a patient's time in bed to when asleep

Patients are asked to limit their time in bed to their average sleep time, go to bed only when sleepy, get up if they cannot fall asleep, and return to bed only once sleepy: the idea is that most of the time spent in bed is sleeping

Gradually the time spent in bed is increased as sleep duration and quality improve

Stimulus control

The idea is to extinguish the association between the bed and wakefulness

Patients should be instructed to use the bed only for sleep and sex, establish a consistent bedtime and waking time, go to bed only when sleepy, get out of bed if unable to sleep, and refrain from daytime naps

Relaxation therapies

Includes exercises designed to decrease tension, eg, deep breathing, abdominal breathing, progressive muscle relaxation, and meditation

A variety of applications can be used for guided meditation and relaxation

Based on information in references 5, 12, and 18.

had been on them for more than 1 year, far longer than the recommended 2 to 4 weeks.⁵

Some physicians may not think that stopping is necessary, or know how to conduct the taper, or how to communicate the rationale to patients. Patients may not always accept that the effectiveness of benzodiazepines decreases with time, even when that has been explained to them. In fact, the advice to restrict benzodiazepine prescriptions to severely anxious and sleepless individuals may contribute to these

challenges, as patients with more severe symptoms may feel more attached to benzodiazepines because previous treatments have failed. Further, it is challenging to convince patients of decreased effectiveness if they have rebound symptoms on discontinuation.¹¹

Efforts to decrease the gap between theory and practice include strategic interventions targeting prescribers. An example is the Reducing Use of Sedatives program in Australia,¹⁶ in which interdisciplinary case reviews at 3 and 6 months led to reduced use of benzodiazepines in nursing homes.

Brief interventions

Additional examples of secondary prevention include patient education delivered in brief interventions.¹¹ In essence, a brief intervention consists of discussing risks of benzodiazepines with the patient and then advising the patient to decrease or discontinue use. Brief interventions can be done via letters, brochures, or face-to-face discussions.²³

In the Eliminating Medications Through Patient Ownership of End Results (EMPOWER) study, face-to-face discussions combined with informational pamphlets resulted in 27% of participants quitting benzodiazepines within 6 months, compared with 5% in the control group.²² Subsequently, Lynch et al³ conducted a systematic review of 8 studies assessing the effects of brief interventions in 2,071 patients in primary care. The main outcome was discontinuation of the benzodiazepine or reduction of use by at least 25%. Relative to usual care, individuals who received brief interventions were more likely to be off the drug at 6-month and 12-month follow-up. The authors concluded that brief interventions were more effective than usual care in reducing or discontinuing benzodiazepines.³

The results, while suggestive, do not provide clear evidence about which subset of benzodiazepine users benefits most from brief interventions.³ In practice, long-term users are a clinically heterogeneous population.^{1,7,10} Patients taking benzodiazepines a short time may respond better to brief interventions,³ while those who have been on them for a long time may have higher levels of physiologic and psychological dependence and thus be less responsive.^{4,25} While some users may respond to brief interventions, failure to do so contributes to persistent use.

■ TERTIARY PREVENTION: STOPPING AFTER LONG-TERM USE

Tertiary prevention includes strategies to decrease harm in patients who have been on benzodiazepines for more than 6 months and are likely to have sub-

stantial problems with stopping.^{4,10} In a study of long-term benzodiazepine users, only 13% had stopped after 1 year, and the number was lower in those who also used opioids, despite the serious risks of fatal overdose in this cohort.¹⁰

Such difficulties are further illustrated by a Canadian study examining clinical encounters for deprescribing long-term proton pump inhibitors and benzodiazepines in primary care.²³ Educational brochures were distributed to patients and conversations were recorded to explore to what extent the content reflected dose instructions, medication efficacy, risks, side effects, attitudes, emotions, and follow-up. Of interest, conversations of deprescribing for proton pump inhibitors focused on medication efficacy and the need for follow-up, while conversations about stopping benzodiazepines were more likely to center on the “if” rather than the “how.” The nuts and bolts of how to conduct the taper were not addressed, perhaps reflecting patient concerns about the consequences of stopping benzodiazepines.²³ Complementary data show that patients are more receptive to deprescribing if they understand the rationale (risk for harm), are engaged in the tapering process, and are offered behavioral advice.⁵

Stages of change

Patients who regularly use benzodiazepines focus mainly on the benefits rather than the risks.²⁶ Since many patients overestimate the benefits and don’t want to stop, clinicians must ascertain an individual’s readiness to change to optimally engage them in conversations about deprescribing, ie, the supervised discontinuation or dose reduction of a medication that may cause harm (or no benefit) to improve outcomes.^{5,23,27} According to motivation theory, people go through several stages when changing their behavior, including benzodiazepine use^{8,25}:

Precontemplation. Precontemplators do not see their benzodiazepine use as a problem. They may believe that the medication is utterly necessary to their life, functioning, and well-being.²⁵ Hence, the goal is to help them to develop ambivalence about long-term benzodiazepine use instead of ordering them to stop.^{25,26} Asking patients about balance problems, daytime sedation, or falls may help them recognize benzodiazepine-related problems.⁵ It is also important to appreciate the patient’s perception of benefits of benzodiazepines.²⁵ It is helpful to present a summary of the patient’s responses reflecting both sides of their experience. For example, “While Xanax helped you to fall asleep at first, you may also find that 1 tablet is no longer enough and that you need to take 2 now.”²⁵

TABLE 2
Strategies and tips for tapering benzodiazepines

Strategies

Taper by 25% every 2 weeks

If dosage forms do not allow for a 25% reduction, consider a 50% reduction

Consider slowing to 12.5% for the final 2 weeks of the taper

Consider alternate-day dosing for the final 2 weeks of the taper

Tips

Educate patients on what to expect and reassure them that symptoms will resolve

Consider switching to a medication formulation with lower dose options

Consider using a nonaddictive medication alternative

Some patients may require an extremely slow taper—over months, not weeks

Based on information in reference 5.

Contemplation. Contemplators recognize the harm of long-term benzodiazepine use, but they are ambivalent about change.²⁵ Getting a commitment from the patient to reduce benzodiazepine use is the appropriate goal for contemplators²⁵: “Mrs. A, you told me that clonazepam helps you sleep. But you had several falls that left you bruised and shaken. Have you considered alternatives to help you sleep?”

Preparation. Patients in the preparation stage show curiosity about the process but may have doubts about their ability to manage without benzodiazepines.²⁵ It is important to enhance their confidence in tapering off the drug and to offer strategies to manage stress and insomnia by means other than benzodiazepines.²⁵

Action. Once patients reach the action stage, they show a willingness to discontinue benzodiazepine use.²⁵ This is the appropriate stage at which to begin deprescribing.⁵

Stopping is difficult but possible

While stopping benzodiazepines is often difficult,^{23,24} there is evidence that it is possible.²⁸ In a meta-analysis of 10 randomized controlled trials, Soni et al²⁸ evaluated benzodiazepine deprescribing in 1,431 outpatients. The primary measure was complete medication discontinuation. Studies were classified by the type of intervention, ie, pharmacologic or nonpharmacologic. Despite heterogeneity in these interventions, study design, and effects, a gradual taper supported by nonpharmacologic interventions was more successful than routine care.²⁸

TABLE 3
Preventing harm from benzodiazepines

Primary prevention¹⁵

Educate the public about benzodiazepine harms

Educate prescribers and patients about cognitive behavioral therapy for insomnia

Educate patients about risks of falls, fractures, and addictive potential

Limit use to a carefully selected population

Set the stage for limiting use to less than 4 weeks

Secondary prevention^{13,22}

Taper after 4 weeks

Use behavioral interventions, letters, brochures, or face-to-face interventions to encourage patients resistant to intervention

Educate prescribers about the need to discontinue benzodiazepines

Tertiary prevention^{5,11}

Use motivational interviewing to evaluate the stage of change

Use shared decision-making to discuss risks and benefits to help move the patient to the action level of change

Optimize deprescribing by addressing rebound (through education), withdrawal (through gradual tapering), and relapse (through addition of psychological support)

For the primary care clinician, the first step in deprescribing can be to discuss the risks and benefits of stopping.⁵ Benefits may include improved alertness and prevention of falls and accidents. From a patient’s perspective, addressing relapse and discontinuation syndromes is critical.^{5,8} In particular, patients must know what to expect and be reassured that the clinician will appropriately treat any symptoms that emerge.⁵

Rebound is a reemergence of symptoms with increased intensity after a period of recovery.^{8,11} It is self-limited and can last approximately 3 weeks.²⁹

Also, withdrawal symptoms can develop in people who have regularly been using benzodiazepines if the medication is stopped suddenly. Withdrawal is heralded by new autonomic symptoms such as sweating, increased heart rate, myoclonus, paresthesias, and tremors. In severe cases, seizures or delirium may occur. These symptoms generally begin a week or so after stopping treatment and last 2 to 4 weeks, but they can persist in an attenuated fashion for several months. There are case reports of individuals experiencing residual symptoms such as tinnitus for several years.²⁹

Relapse is the return of symptoms that were initially controlled with a benzodiazepine.²⁹ It can be prevented by initiating alternative treatments, particularly cognitive behavioral therapy.²

Tapering is essential to minimize these difficulties, along with the patient's apprehension and fear.⁸ Canadian guidelines recommend gradual decreases such as 25% every 2 weeks and, if possible, 12.5% reductions near the end of the taper. If symptoms return, the taper is paused for 1 or 2 weeks before proceeding slowly.⁵

Patients with high levels of medical or psychological stress may require an extra-slow taper that may take up to a year. Negotiating a flexible taper responsive to the patient's level of distress may increase its chance of success. If the first attempt is unsuccessful, patients should be encouraged to try again, as even dose reductions may be beneficial to decrease long-term harm. Some approaches to tapering can be found in Table 2.⁵

CONCLUSION

Prolonged benzodiazepine use can cause harm and remains a challenge for healthcare systems worldwide. Public health strategies to decrease benzodiazepine-related harm are a novel approach to this problem

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(Table 3).^{5,11,13,15,22} Primary prevention aims to decrease prescribing levels by employing judicious prescribing. Secondary prevention can be accomplished by improving adherence to existing guidelines. Tertiary prevention efforts recognize that in clinical practice we are likely to encounter patients who have been on benzodiazepines for a long time.

Clinicians must become comfortable with the principles of motivational interviewing and deprescribing guidelines to improve outcomes for these patients. With practice, patience, and support from their mental health colleagues, even busy clinicians can master these techniques and derive professional satisfaction from the knowledge that they have made a significant difference in their patient's health status and quality of life.

Acknowledgment: We would like to acknowledge Daniel Rauch, MD, for his help in editing an earlier draft of this article.

DISCLOSURES

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

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Functional dyspepsia: How to manage the burn and the bloat

ABSTRACT

Functional dyspepsia is defined as persistent symptoms of postprandial bloating, early satiety, or pain in the center of the upper abdomen, without findings on upper endoscopy such as peptic ulcer disease to explain these symptoms. It is common, affecting up to 30% of the global population, but it often goes undiagnosed for years. There are 2 subtypes: epigastric pain syndrome (burning and pain) and postprandial distress syndrome (bloating and satiety). The authors discuss how to diagnose and treat both subtypes.

KEY POINTS

The pathophysiology of functional dyspepsia is poorly understood, but there are clear associations with visceral hypersensitivity and disruptions of normal gastroduodenal motility, and a number of proposed mechanisms.

No treatment carries an approved indication for functional dyspepsia, but agents of several classes are used off-label.

Clinical guidelines recommend starting proton pump inhibitor therapy in patients with functional dyspepsia who test negative for *Helicobacter pylori* or who continue to have dyspeptic symptoms after *H pylori* eradication.

A 41-year-old woman reported having epigastric fullness and bloating with meals for more than 10 years, but denied having heartburn, regurgitation, dysphagia, or weight loss. She underwent upper endoscopy 5 years before, and her esophagus, stomach, and duodenum appeared normal. Biopsies of the gastric antrum and gastric corpus were negative for *Helicobacter pylori*, and biopsies of the duodenum were normal. She had tried 2 different proton pump inhibitors without success.

TWO CATEGORIES

Dyspepsia refers to a group of symptoms in the upper region of the gastrointestinal tract. Functional dyspepsia (ie, not due to an identifiable abnormality) can be divided into 2 categories:

- Postprandial distress syndrome (fullness or early satiety after meals)
- Epigastric pain syndrome (epigastric burning or pain).¹

While many patients and clinicians assume that dyspeptic symptoms indicate peptic ulcer disease, recent studies have found that up to 85% of patients with dyspeptic symptoms have normal findings on upper endoscopy.²

The global prevalence of functional dyspepsia ranges between 10% and 30%.³ Risk factors include female sex, high socioeconomic status, older age, living in a rural location, using nonsteroidal inflammatory drugs, and being married. Smoking is weakly associated with functional dyspepsia, whereas coffee and alcohol consumption have no known association with it.^{1,3}

■ FUNCTIONAL DYSPEPSIA VS IRRITABLE BOWEL SYNDROME

Irritable bowel syndrome is a disorder of recurring abdominal pain combined with bowel movement changes (constipation, diarrhea, or both). It is similar to functional dyspepsia in many ways: symptoms are related to diet, there are often psychiatric comorbidities, and treatments are similar. Hence, irritable bowel syndrome is often misdiagnosed as functional dyspepsia. However, functional dyspepsia refers to symptoms in the upper abdomen, whereas irritable bowel symptoms present in the lower abdomen and are connected to changes in bowel habits.⁴

The 2 conditions can overlap. A 2022 study from Australia found that 45% of patients with functional dyspepsia also met the criteria for irritable bowel syndrome.⁵ A careful discussion with the patient is required to tease out specific symptoms of functional dyspepsia and irritable bowel syndrome so that they are treated optimally.

■ PATHOPHYSIOLOGY

The pathophysiology of functional dyspepsia, like that of all disorders of gut-brain interaction, is poorly understood. However, there are clear associations with visceral hypersensitivity, disruptions of normal gastroduodenal motility, or both. Potential mechanisms include the following:

Delayed gastric emptying can be found in 25% to 35% of patients with functional dyspepsia.^{1,6} However, some patients with functional dyspepsia actually have rapid gastric emptying.⁷

Abnormal gastric accommodation. Normally, gastric accommodation is modulated by food consumption triggering the vagovagal response and nitrergic nerve excitement in the gastric wall. This process is often impaired in patients with functional dyspepsia, who may experience uneven gastric food distribution, antral pooling of chyme, and reduced proximal reservoir content. After eating, up to a third of patients with functional dyspepsia have impaired gastric accommodation.^{1,8}

Hypersensitivity in response to chemical and mechanical stimulation in the upper bowel and stomach is common in cases of functional dyspepsia, and this hypersensitivity is suspected to occur in response to stimuli such as lipids and intraluminal acid.¹

H pylori infection can retrospectively be presumed to be the cause of functional dyspepsia if the symptoms resolve after the organism is eradicated. However, eradicating *H pylori* does not guarantee that dyspepsia will

go away: in various studies, between 7 and 15 patients needed to undergo *H pylori* eradication for 1 case of functional dyspepsia to be resolved.^{9,10}

Gut microbiome dysbiosis. Numerous studies have found a strong link between gut microbiome dysbiosis and functional dyspepsia, as the biological barrier and immune functions of the intestinal mucosa are disrupted. The microbiota in the gastrointestinal tract and mouth have been shown to be imbalanced in patients with functional dyspepsia, and small intestinal bacterial overgrowth has been associated with functional dyspepsia. Damage to the intestinal mucosal barrier increases its permeability and thereby decreases its ability to block noxious substances. Additionally, studies have found microinflammatory cell infiltration in the duodenum of more than 40% of patients with functional dyspepsia.^{11,12}

Environmental factors. Eosinophilia in the duodenum and a correlation with early satiety have been observed in patients with functional dyspepsia. Changes in permeability and inflammation in the duodenal mucosal lining have been associated with stress, food allergies, smoking, infection, and acid exposure.¹

Psychological component. A relationship between psychiatric disease, anxiety, depression, and functional dyspepsia has been confirmed, and a relationship between functional dyspepsia and neuroticism is often acknowledged.¹ Troubles managing life affairs and experiencing emotional and physical abuse as an adult may contribute to functional dyspepsia. Because having a functional gastrointestinal disease makes a patient more susceptible to psychological issues, the relationship is probably bidirectional.

■ CRITERIA FOR DIAGNOSIS

The Rome Foundation is a global initiative that creates guidelines for diagnosing and treating functional gastrointestinal conditions. The Rome criteria were initially developed for research, but more recent iterations have also focused on clinical care. The most recent update, Rome IV,^{1,13} was released in 2016. The Rome IV criteria for functional dyspepsia are as follows:

- Patients must present with symptoms of postprandial fullness, epigastric burning, epigastric pain, or early satiation; for **postprandial distress syndrome**, patients must experience postprandial fullness affecting daily activities or early satiation affecting their ability to consume a normal-size meal at least 3 days each week; for **epigastric pain syndrome**, patients must experience epigastric pain or burning, or both, affecting daily activities at least 1 day each week

- There should be no sign of a structural problem (including at upper endoscopy) that could be correlated with symptoms
- Symptoms must be present for at least 6 months, and diagnostic criteria must be met for 3 months.^{1,13}

Regarding testing, current guidelines suggest upper endoscopy for patients age 60 and older to rule out malignancy. However, routine upper endoscopy to rule out malignancy is not recommended for patients under age 60, as their risk of cancer is less than 1% even if they have alarm features.¹⁰ For patients younger than 60, noninvasive testing for *H pylori* such as stool antigen assay is recommended.^{10,14}

■ SYMPTOMS CAN WAX AND WANE

Although symptoms of functional dyspepsia can be managed, it is a lifelong medical condition that can wax and wane over time. The aim of treatment is to improve quality of life by decreasing or eliminating symptoms. Patients can often reduce the dosage or even stop treatments once their symptoms resolve. It is, however, reasonable to expect symptom exacerbations throughout the life span, especially in response to stress or triggers, which may require patients to restart treatment.¹⁵ Importantly, functional dyspepsia has not been shown to affect long-term survival.¹⁶

■ TREATMENTS ARE ALL OFF-LABEL

Currently, no therapy for functional dyspepsia has US Food and Drug Administration approval. All the agents listed below are used off-label for treating this condition.

Antisecretory agents

Famotidine is a histamine-2 receptor antagonist used to decrease the production of stomach acid in patients with duodenal and gastric ulcers, gastroesophageal reflux disease, and erosive esophagitis. Famotidine twice daily was found to be more effective than the prokinetic medication mosapride and the antianxiety medication tandospirone in a study in patients with functional dyspepsia.¹⁷ No specific subtype of functional dyspepsia was reported to respond better to famotidine.¹⁷

Tachyphylaxis develops rapidly in response to histamine-2 receptor antagonists, which may limit their long-term use in functional dyspepsia.¹⁸

Proton pump inhibitors are often used to treat symptoms of acid reflux and gastroesophageal reflux disease. They work by irreversibly inhibiting the hydrogen-potassium adenosine triphosphatase proton pump in

the parietal cell membrane on the luminal surface of the stomach.¹⁹

Clinical guidelines recommend starting proton pump inhibitor therapy in patients with functional dyspepsia who test negative for *H pylori* or who continue to have dyspeptic symptoms after *H pylori* eradication.¹⁰ Meta-analyses have found proton pump inhibitors to be better than placebo and possibly slightly better than histamine-2 receptor agonists and prokinetics.^{10,20} Subgroup analysis suggested that more patients responded to proton pump inhibitors if their symptoms were related to heartburn.¹⁰ On the other hand, there was no difference in efficacy according to functional dyspepsia subtype, ie, whether patients had epigastric pain syndrome or postprandial distress syndrome, and therefore experts do not recommend using the type of symptom to guide treatment choice.²¹

Possible long-term adverse effects of proton pump inhibitors include hip fracture, electrolyte imbalances, dementia, pneumonia, and *Clostridioides difficile* infection. However, experts have concluded that these associations are probably not causal and that even if they were, the number needed to harm would be more than 1,000 in most cases.¹⁰ A 3-year randomized double-blind trial found pantoprazole was not associated with any adverse event, with the possible exception of an increased risk of enteric infection.²² Patients should stop the drug if there is no response after taking the standard dose for 8 weeks, and should try to withdraw from the drug within 6 to 12 months, regardless of the response.

Neuromodulators

Antidepressant and antianxiety medications are often used to treat irritable bowel syndrome, but their efficacy in treating functional dyspepsia is less well known. These medications may improve central analgesic function, improve sleep, normalize orocecal transit, and augment gastric accommodation, all of which are hypothesized to help alleviate functional dyspepsia symptoms.^{23–26}

Buspirone is a serotonin 5-HT_{1A} receptor agonist. In a study in 17 patients with functional dyspepsia, buspirone 10 mg before meals was found to augment fundic accommodation and improve postprandial fullness, bloating, and early satiety.²³

Buspirone may also have a role in treating functional dyspepsia in patients with rapid gastric emptying. In 1 reported case, early satiety, nausea, vomiting, and diarrhea all improved within 1 week of starting buspirone 10 mg 3 times a day before meals.²⁴

Mirtazapine. The antidepressant mirtazapine is an antagonist to histamine-1 receptor, serotonin receptors

5-HT_{2C} and 5-HT₃, and the A₂ adrenergic receptor. Mirtazapine has been studied in patients with symptoms of functional dyspepsia and associated weight loss, as the drug is associated with weight gain and its antagonist activity on the 5-HT₃ receptor specifically is associated with nausea suppression. One study reported a mean weight gain of nearly 4 kg in patients with functional dyspepsia after 8 weeks of treatment with mirtazapine 15 mg daily, along with improvements in early satiety, nausea, quality of life, meal volume tolerance, and gastrointestinal-specific anxiety.²⁵

Tricyclic antidepressants. Amitriptyline is a tricyclic antidepressant used most commonly to treat major depressive disorder, pain disorders, migraine, headaches, and fibromyalgia.

The Antidepressant Therapy for Functional Dyspepsia trial²⁶ measured the benefits of amitriptyline and the selective serotonin reuptake inhibitor escitalopram in patients with functional dyspepsia who were not on antidepressants and did not present with depression. Patients were given amitriptyline 50 mg, escitalopram 10 mg, or placebo for 10 weeks. The patients on amitriptyline had a higher response rate (53%) than those on escitalopram (38%) or placebo (40%, $P = .05$), leading to the conclusion that amitriptyline has therapeutic benefit in functional dyspepsia while escitalopram does not. In the subset of patients with ulcer-like symptoms, the response rate for those receiving amitriptyline was 67%, compared with 39% with placebo and 27% with escitalopram. In patients who had normal gastric emptying, amitriptyline significantly improved abdominal pain, suggesting that tricyclic antidepressants could be used for patients with pain-leading symptoms. Amitriptyline and citalopram did not improve the symptom of satiety compared with placebo, and patients with delayed gastric emptying were less likely to benefit.²⁶

Gabapentin is a gamma-aminobutyric acid analog anticonvulsant medication used to treat neuropathic pain and seizures.²⁷ There is also evidence that it has therapeutic effects on visceral hypersensitivity. An open-label trial indicated that gabapentin could help in treating functional dyspepsia.²⁷ Patients were started on gabapentin 25 to 100 mg at bedtime, which was increased at 2-week intervals to 300 mg 3 times per day. They reported significant improvement in postprandial fullness, upper and lower abdominal pain, heartburn, nausea, and vomiting, while no change in bloating was noted.²⁷

Although gabapentin significantly reduced functional dyspepsia symptoms, more studies are needed to establish it as a treatment.

Pregabalin is a gabapentinoid neuromodulator currently used to manage partial-onset seizures, postherpetic

neuralgia, pain induced by impairment to the nerves due to spinal cord injury or diabetes, and fibromyalgia. It works within the central nervous system, acting on voltage-gated calcium channels.

Pregabalin has been studied to determine its potential benefit on reducing visceral hypersensitivity in patients with functional dyspepsia who did not respond to proton pump inhibitors.²⁸ Patients reported significant improvement in some symptoms, particularly epigastric burning and pain and the feeling of regurgitating acid. However, postprandial fullness, nausea, bloating, and early satiety did not improve with pregabalin.²⁸

Prokinetic therapy

Prokinetic drugs have shown success in treating functional dyspepsia. The prokinetic drug metoclopramide has antidopaminergic and cholinergic actions. Its antidopaminergic properties are primarily responsible for its antiemetic effect.

In a randomized, double-blind trial, metoclopramide improved symptoms in 83% of patients in the subgroup with regurgitation or heartburn compared with 89% with cisapride, the comparator treatment.²⁹ In patients with epigastric symptoms, the response rates were 72% with metoclopramide vs 86% with cisapride. However, 2 weeks after treatment stopped, the response rates dropped to 39% in the metoclopramide group vs 71% in the cisapride group.²⁹

Use of metoclopramide is limited by adverse effects including tardive dyskinesia, and expert recommendations advise caution when using it for functional dyspepsia.¹⁰

Antibiotics

Rifaximin, an antibiotic commonly used to treat diarrhea associated with irritable bowel syndrome, has been shown to reduce global dyspeptic symptoms, postprandial bloating and satiety, and belching in patients with functional dyspepsia.³⁰

A study by Tan et al³⁰ in 2017 postulated a relationship between gut dysbiosis and functional dyspepsia symptoms. Rifaximin has been shown to improve bloating and pain symptoms in patients with irritable bowel syndrome, 2 symptoms common in patients with functional dyspepsia. It has also been shown to decrease gut inflammation and visceral hyperalgesia (contributors to functional dyspepsia), and to act as an antibiotic. After 8 weeks, 78% of patients who had received rifaximin 400 mg 3 times a day for 2 weeks had global dyspepsia symptom relief, compared with 52% with placebo ($P = .02$), and this trend was more apparent in female patients.³⁰

Complementary and alternative medicine

STW 5 is a preparation consisting of extracts of 9 herbs: chamomile flower, celandine herb, caraway fruit, milk thistle fruit, licorice root, balm leaf, peppermint herb, angelica root, and bitter candytuft. It has demonstrated effects on hypertension and gastric motility and has antioxidative, anti-inflammatory, antacid, and gastroprotective properties. Particularly, the extract from bitter candytuft (*Iberis amara*) has shown promising effects on intestinal motility.³¹ In a randomized, double-blind trial, patients receiving STW 5 (20 drops before meals) improved by 6.9 points on the 40-point Gastrointestinal Symptom Score after 8 weeks, compared with 5.9 points with placebo ($P < .05$).³¹

Caraway oil and L-menthol (COLM-SST) is a preparation of caraway oil 25 mg and L-menthol 20.75 mg. In a randomized trial, 2 capsules of COLM-SST twice daily provided relief of functional dyspepsia symptoms within 24 hours compared with placebo.³² Patients experiencing more extreme symptoms had a stronger response. At 24 hours after the start of treatment, patients who received COLM-SST had a statistically significant decrease in postprandial distress symptoms of heaviness, pressure sensations, and fullness. Epigastric pain symptoms also improved, but the difference was not statistically significant. After 28 days of treatment, however, none of these reductions were statistically significant.³²

Capsaicin, an active component of red peppers, can be a treatment for functional dyspepsia symptoms, as it desensitizes visceral nociceptive C-type fibers. Bortolotti et al³³ found that symptoms decreased by 60% in patients taking red pepper powder daily, compared with 30% with placebo. Symptoms actually increased the first day patients took red pepper powder, but subsequently there were statistically significant reductions in general symptom score, epigastric pain, nausea, and epigastric fullness, and a borderline significant reduction in early satiety. There were no statistically significant differences in bloating, epigastric burning, or burping or belching.³³ The dosage used in the study was 500 mg before breakfast and 1,000 mg before lunch and dinner.³³

Acupuncture. In a study in patients with functional dyspepsia, acupuncture in 4 specific areas (stomach meridian-specific acupoints, stomach meridian-nonspecific acupoints, transport and alarm acupoints, and gallbladder meridian-specific acupoints) 5 times a week for 1 month resulted in significant symptom improvement compared with sham acupuncture.³⁴ Patients with postprandial distress syndrome had a

TABLE 1
Effect of various treatments on functional dyspepsia

Treatment ^a	Effect on postprandial distress ^b	Effect on epigastric pain ^b
Antisecretory agents		
Famotidine ¹⁷	++	++
Proton pump inhibitors ^{10,20}	++	++
Neuromodulators		
Buspirone ^{23,24}	++	0
Mirtazapine ²⁵	++	0
Amitriptyline ²⁶	0	++
Escitalopram ²⁶	0	+
Gabapentin ²⁷	+	NA
Pregabalin ²⁸	++	++
Prokinetic therapy		
Metoclopramide ²⁹	++	++
Antibiotics		
Rifaximin ³⁰	++	++
Complementary and alternative medicine		
STW 5 ³¹	NA	NA
Caraway and L-menthol ³²	++	++
Capsaicin ³³	++	++
Acupuncture ³⁴	+	+
Hypnotherapy ³⁵	NA	+

^aAll treatments are off-label. No treatment for functional dyspepsia has yet been approved by the US Food and Drug Administration.

^bQualitative estimates of effect are based on experience and the studies summarized in the text: 0 = no effect, + = some effect, ++ = moderate effect, +++ = strong effect.

NA = information not available

stronger response to acupuncture, particularly stomach meridian-specific acupoints, than patients with epigastric pain syndrome. There were statistically significant decreases in postprandial fullness, early satiety, and quality of life, but no statistically significant decreases in epigastric burning and epigastric pain.³⁴

Hypnotherapy. Hypnosis induces a conscious state with focused attention, decreased awareness peripherally, and increased susceptibility to external suggestion. Neuroimaging studies show changes in brain activity in networks of the prefrontal cortices, thalamus, anterior cingulate, and basal ganglia associated with hypnosis.³⁵

Popa et al³⁵ performed a systematic review of 4 studies of hypnotherapy for functional dyspepsia. One study found that 1 session of hypnosis was more effective than cisapride in alleviating epigastric pain, abdominal discomfort, epigastric fullness, and gastric emptying. Another study showed hypnotherapy was more effective than ranitidine 300 mg/day. A third study reported that 80% of patients had improvements in pain frequency and severity with hypnotherapy, compared with 23% of control patients.³⁵ Further randomized controlled trials are needed to definitively determine the efficacy of hypnotherapy in treating functional dyspepsia.

■ GENERAL MANAGEMENT PRINCIPLES

In our practice, we follow the recommendations of the Rome Committee and the American College of Gastroenterology guidelines in diagnosis and treatment of functional dyspepsia. In particular, the American College of Gastroenterology guidelines do not recommend upper endoscopy in patients under age 60, as their risk of cancer is less than 1%, even with alarm symptoms.¹⁰ If *H pylori* testing or upper endoscopy is negative, patients can be diagnosed with functional dyspepsia per the Rome IV criteria.

Our general practice is to treat with a proton pump inhibitor for 2 months. If symptoms respond, then we taper off the medication or reduce it to the lowest effective dose. If dyspepsia does not respond to a proton pump inhibitor, we use an individualized approach, discussing the agents listed above and summarized in Table 1.^{10,17,20,23–35}

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■ CASE FOLLOW-UP: IMPROVEMENT WITH BUSPIRONE

The 41-year-old patient in the introductory scenario was diagnosed with functional dyspepsia (postprandial distress subtype) and given information about the disease. She started taking buspirone 10 mg 15 to 30 minutes before meals, and her postprandial bloating improved significantly. The proton pump inhibitor she had been taking was then discontinued without worsening her symptoms. A plan was made to continue therapy for 12 months, then reassess the need for buspirone.

■ EDUCATIONAL SOURCES

A thorough understanding of functional dyspepsia is vital for healthcare professionals and patients. Two patient sources of information about functional dyspepsia are:

- American College of Gastroenterology (<https://gi.org/topics/dyspepsia/>, also available in Spanish)
- Cleveland Clinic (my.clevelandclinic.org/health/diseases/22248-functional-dyspepsia).

Additionally, the American College of Gastroenterology Patient Care Committee, in conjunction with its patient-education partner Gastro Girl (gastrogirl.com), has prepared a free podcast for patients and clinicians about functional dyspepsia (www.youtube.com/watch?v=7ggCB8VJHHA).

■ DISCLOSURES

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

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Simultaneous hemorrhage and venous thrombosis in a patient with systemic lupus erythematosus

A 40-YEAR-OLD WHITE WOMAN with systemic lupus erythematosus (SLE), reported positive lupus anticoagulant, and avascular necrosis of the left hip underwent elective left-hip hemiarthroplasty at an outside facility. No complications were reported in the intraoperative period. The postoperative period was complicated by a left-hip surgical-bed hematoma measuring 6.9 by 4.3 cm, with evidence of soft-tissue-hematoma formation throughout the pelvis. The hematoma was greatest in the left gluteal region, hip, and thigh, causing peroneal nerve palsy. The patient had a significant drop in hemoglobin requiring 5 units of red blood cells and 2 units of fresh frozen plasma. Her activated partial thromboplastin time (aPTT) was 150 seconds, prompting transfer to the intensive care unit.

On physical examination, the patient was tachycardic and pale. Active bleeding from the surgical site was noted. She had a left foot drop and no sensation to light touch over the left foot.

The patient's complete blood cell count and laboratory results from the period after hip surgery through hospital discharge are shown in **Table 1**. Her coagulation profile results after hip surgery through hospital discharge are shown in **Table 2**.

On postoperative day 3, computed tomography of the abdomen and pelvis showed a large area of soft-tissue thickening and inflammation throughout the pelvis that was greatest in the left gluteal region, hip, and thigh. Computed tomography angiography did not show any active arterial bleeding.

1 What is the most likely etiology of bleeding in this patient?

- ☐ Arterial injury during surgery
- ☐ Disseminated intravascular coagulation
- ☐ Lupus anticoagulant
- ☐ Deficiency of intrinsic pathway factors or presence of an acquired inhibitor

When a bleeding disorder is suspected, a thorough bleeding assessment and family history of bleeding diathesis or known bleeding disorders should be obtained.^{1,2} A detailed history on current medications is also warranted, as certain prescription drugs, dietary supplements, and herbal preparations may interfere with platelet function and coagulation proteins. A complete blood cell count, coagulation profile including prothrombin time, aPTT, and fibrinogen, and a peripheral blood smear should be completed.²

The computed tomography angiogram in the patient did not show active arterial bleeding, ruling out an arterial injury. The complete blood cell count and coagulation profile were not consistent with disseminated intravascular coagulation. Disseminated intravascular coagulation can be diagnosed using a simple scoring system proposed by the International Society on Thrombosis and Haemostasis,³ which has a sensitivity of 91% and specificity of 97%.⁴ In patients with disseminated intravascular coagulation, both prothrombin time and aPTT are prolonged. The serum fibrinogen is low, D-dimer is markedly elevated, and platelets are low owing to consumptive coagulopathy. Prothrombin time is most sensitive to disseminated intravascular coagulation. Because factor VII has the shortest half-life of all clotting factors, an isolated prolonged prothrombin time can be the

TABLE 1
Patient's complete blood cell count and laboratory results

Laboratory test (reference range)	After hip surgery	Hospital day 30
White blood cell count ($3.7\text{--}10.4 \times 10^9/\text{L}$)	10.3	4.3
Platelet count ($150\text{--}400 \times 10^9/\text{L}$)	155	215
Hematocrit (35.5%–44.9%)	17.9	34.2
Hemoglobin (12–16 g/dL)	6.3	11.5

TABLE 2
Patient's coagulation test results

Laboratory test (reference range)	After hip surgery	Hospital day 30	Discharge (hospital day 50)
Prothrombin time (10.6–13.6 seconds)	12.9	< 10	11.4
International normalized ratio (0.88–1.16)	0.98		
Fibrinogen (230–510 mg/dL)	319	330	
Activated partial thromboplastin time (27.5–35.5 seconds)		61.5	98.6
Baseline	92.4		
1:1 immediate	43.4		
1:1 after 1 hour	75.9		
Diluted thrombin time (16.0–25.0 seconds)	15.4		
D-dimer (< 0.5 $\mu\text{g/mL}$)	0.65	2.09	
Factor II (79%–135%)	90		
Factor IX (72%–184%)	122		
Factor XI (58%–135%)	70		
Factor XII (46%–196%)	77		
Factor VIII inhibitor assay (0.0–0.5 Bethesda units/mL)	80	21.4	57.6

earliest manifestation of disseminated intravascular coagulation.⁵

The differential diagnosis of a patient with bleeding and an isolated prolonged aPTT includes deficiency of factors VIII, IX, or XI, deficiency of von Willebrand factor, and the presence of an acquired inhibitor. In mild von Willebrand disease, factor VIII activity is usually in the low normal range and the aPTT is normal. In severe von Willebrand disease, however, a marked reduction in von Willebrand factor can lead to a decrease in factor VIII sufficient to prolong aPTT. Also, antibodies that inhibit factors VIII, IX, and XI and von Willebrand factor and anticoagulants like

heparin and direct thrombin inhibitors can prolong aPTT.⁶ Lupus anticoagulant can prolong aPTT, but patients with lupus anticoagulant often present with thrombotic events and only rarely experience bleeding diathesis, a disorder known as lupus anticoagulant-hypoprothrombinemia syndrome.¹

After finding a prolonged aPTT, the presence of heparin and other coagulation inhibitors must be ruled out. The anti-factor Xa assay can exclude the presence of heparin. A mixing study differentiates factor deficiency from the presence of an inhibitor.² Prolonged aPTT that corrects into the normal range on immediate repeat testing after

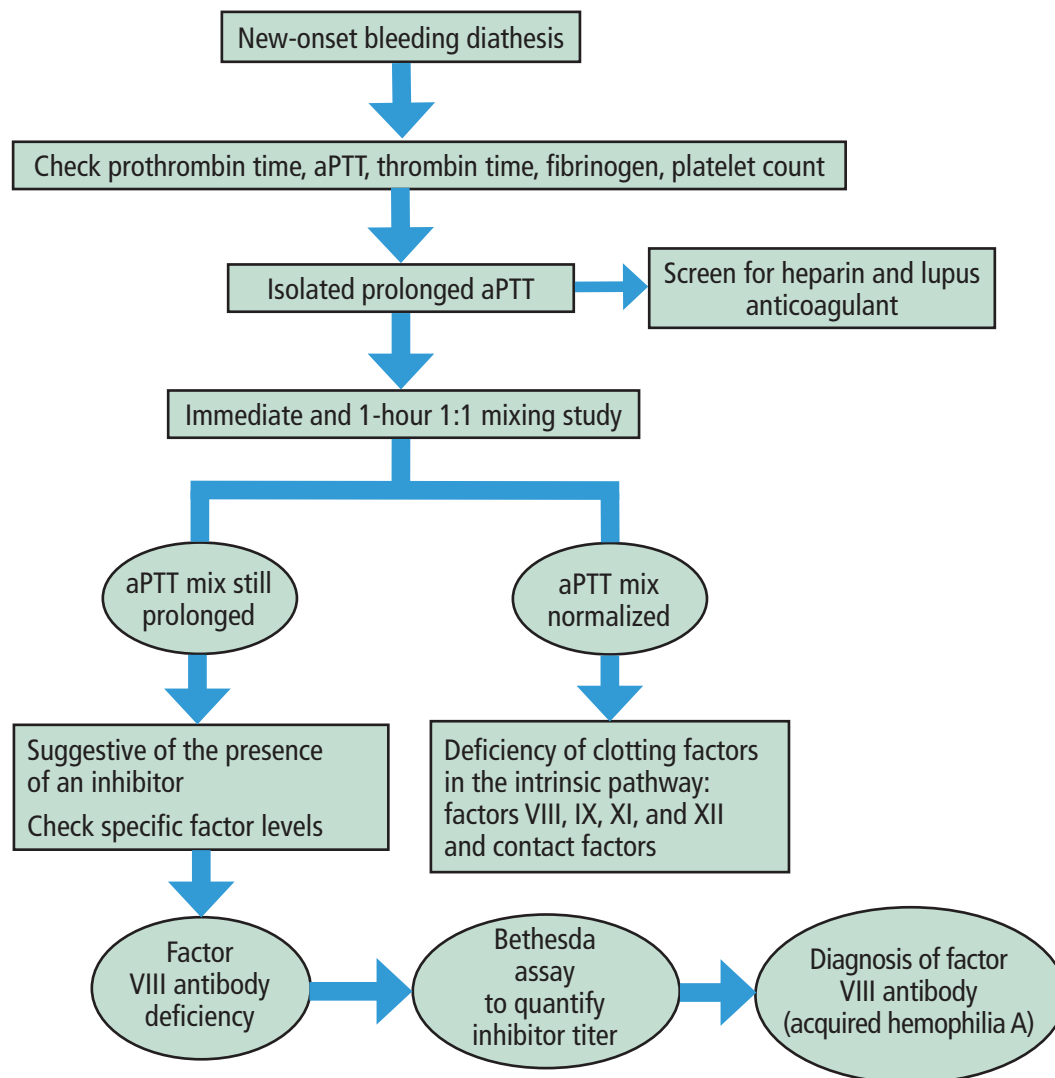


Figure 1. Approach to a patient with bleeding diathesis and prolonged activated partial thromboplastin time (aPTT).

Based on information from reference 2.

patient plasma is mixed with normal plasma in a 1:1 ratio implies factor deficiency in the intrinsic pathway, whereas persistent prolongation of aPTT implies the presence of an inhibitor or antibody.² Factor VIII inhibitors can be time- and temperature-dependent; hence, prolonged aPTT may partially correct on testing done immediately after mixing but not correct on testing done after 1 to 2 hours of incubation at 37°C.² In patients who have prolonged aPTT and lupus anticoagulant, aPTT will not fully correct with normal plasma, but partial correction may be seen after an hour of incubation at 37°C.

Figure 1 summarizes our approach to a patient presenting with bleeding diathesis and prolonged aPTT.²

PATIENT HISTORY AND EVALUATION

The patient had been diagnosed with SLE in her twenties when she presented with fever, malar rash, pleurisy, anemia, synovitis, and photosensitivity. Serologies were positive for antinuclear antibody and double-stranded DNA (titer of 1:160). Her medications for SLE included hydroxychloroquine 300 mg daily, mycophenolate mofetil 500 mg twice daily, and

subcutaneous belimumab 200 mg weekly. She denied taking herbal remedies or over-the-counter medications. Personal and family history were negative for thrombotic events or bleeding diathesis, except for the event after her hip surgery. However, the patient reported first having significant bruising almost 2 years before her surgery. The surgery initially had been canceled during preoperative evaluation owing to a significantly elevated aPTT. Despite that, surgical clearance was provided by an outside hematologist, who attributed the prolonged aPTT to the patient's autoimmune disorder.

Laboratory test results after hip surgery

On testing done in the postoperative period after her hip surgery, peripheral blood smear showed normal platelet morphology. Her coagulation profile at that time showed a markedly elevated aPTT, with a chromogenic factor VIII level less than 1% and a 1-stage factor VIII level less than 0.7% (reference range 50%–242%). Results of the mixing study showed that her prolonged baseline aPTT of 92.4 seconds (27.5–35.5 seconds) partially corrected (43.4 seconds) immediately after mixing and did not correct after 1 hour of incubation at 37°C. Her diluted thrombin time was normal at 5.4 seconds. The factor VIII inhibitor human assay titer was positive at 80 Bethesda units/mL (Table 2).

Results of other laboratory tests done after the patient's hip surgery are shown in Table 3.

2 What is the diagnosis?

- ☐ Hemophilia A
- ☐ Hemophilia B
- ☐ Factor XI deficiency
- ☐ Factor XII deficiency
- ☐ Acquired hemophilia A (AHA)

An isolated prolonged aPTT should always be investigated further even if the patient is asymptomatic. Hemophilia A and B are X-linked disorders characterized by inherited deficiency of factors VIII and IX, respectively. The aPTT fully corrects during the mixing study in patients with hemophilia A and B and inherited deficiencies of factor XI, factor XII, and contact factors.⁷ Hemophilia C, or factor XI deficiency, is an autosomal dominant or recessive trauma-associated bleeding disorder caused by factor XI deficiency and is commonly seen in Ashkenazi and Iraqi Jewish populations.⁸ Although factor XII deficiency and other contact factors (high-molecular-weight kininogen and plasma prekallikrein) cause markedly prolonged aPTT, factor XII deficiency does not cause any bleeding diathesis.⁹

New-onset bleeding diathesis in a patient with no family history of bleeding, as seen in our patient, is highly suggestive of AHA. The constellation of clinical and laboratory features, including a prolonged aPTT, failure of the aPTT to correct during the mixing study, and presence of a high-titer inhibitor, also pointed to a diagnosis of AHA.

The patient reported a history of new-onset easy bruising that began almost 2 years before diagnosis. Her abnormal preoperative aPTT with a history of significant bruising should have been thoroughly investigated, avoiding this life-threatening situation.

3 What is the most likely etiology of AHA in this patient?

- ☐ Surgery
- ☐ SLE
- ☐ Malignancy
- ☐ Drug-induced

AHA is a rare and potentially fatal autoimmune disease characterized by antibodies against factor VIII. It has a reported incidence of 1.3 to 1.5 per million per year.^{10–12} AHA typically manifests with bleeding diathesis, which can occur spontaneously, post partum, or after surgery.¹² Bleeding in AHA may include extensive subcutaneous ecchymoses, large hematomas, and gastrointestinal, genitourinary, or retroperitoneal bleeding. Spontaneous hemarthroses, a hallmark of congenital hemophilia, are rare in AHA. Bleeding associated with AHA is a medical emergency and tends to be more severe than bleeding in congenital hemophilia even with the same factor VIII levels.¹² The mortality rate in AHA ranges from 7.9% to 22%.^{11,12}

The most common predisposing factors for AHA include autoimmune diseases, pregnancy or the postpartum period, and malignancy.^{12–14} The patient had a known history of SLE, and this was the likely trigger for AHA. Among autoimmune disorders, AHA is often seen in patients with SLE and rheumatoid arthritis.¹⁵ Very rarely, drugs such as clopidogrel, alemtuzumab, and omalizumab have been associated with AHA.¹⁶ The patient did not have exposure to these drugs. Extensive imaging did not reveal an underlying malignancy.

■ CASE CONTINUED

Autoimmune serologies revealed a positive antinuclear antibody with a titer of 1:80. Negative results were reported for the following tests: anti-double-stranded DNA, anti-Ro (Sjögren syndrome [SS]-A) and anti-La (SS-B) antibodies, rheumatoid factor, cytoplasmic and perinuclear antineutrophil cytoplasmic antibody, antiribonucleoproteins and liver kidney microsomal

TABLE 3
Results of other laboratory tests done after hip surgery

Laboratory test (reference range)	Result
Prothrombin (G20210A) gene mutation	Negative
Factor V Leiden mutation	Negative
Protein C functional (70%–150%)	101
Protein S functional (70%–160%)	69
Antithrombin (80%–120%)	85
Anticardiolipin antibody, immunoglobulin M (< 12.5 MPL U/mL)	2.0
Anticardiolipin antibody, immunoglobulin G (< 15 GPL U/mL)	4.1
Beta-2 glycoprotein I antibody, immunoglobulin M (≤ 20 SMU U/mL)	1.9
Beta-2 glycoprotein I antibody, immunoglobulin G (≤ 20 SGU U/mL)	4.9
Partial thromboplastin time-lupus anticoagulant screen (33.8–46.1 seconds)	68
Dilute Russell's viper venom time screen ratio (≤ 1:20)	1:30
Hexagonal phase confirmation (≤ 40 seconds)	22.8

antibody, Jo-1 (histidyl-tRNA synthetase) antibody, and antimitochondrial antibody serologies.

The patient was started on oral prednisone 1 mg/kg daily and weekly rituximab 375 mg/m². For AHA, she received 2 doses of activated prothrombin complex concentrate (aPCC), known as FEIBA (factor eight inhibitor bypass activity). Hydroxychloroquine and mycophenolate mofetil for SLE were continued.

Two days later, after the infusion of the third dose of aPCC, she developed severe abdominal pain, nausea, and vomiting. Computed tomography revealed a retroperitoneal bleed, raising concern for ischemic colitis. The patient was taken for exploratory laparotomy and found to have colon necrosis. On day 13 after her hip surgery, she underwent subtotal colectomy with colostomy placement at the outside facility.

Ischemic colitis is a rare and challenging clinical situation in a patient with AHA. The patient likely developed spontaneous retroperitoneal hematoma in the setting of AHA, and the necrotic bowel was probably secondary to ischemia caused by the pressure effect from the hematoma. A vascular event such as superior mesenteric artery or vein thrombosis in the setting of aPCC cannot be completely ruled out. Suzuki et al¹⁷ reported a case of a 66-year-old man with AHA who developed ischemic colitis and was managed conservatively, with a favorable outcome.

Transfer to our facility

The day after undergoing colectomy, the patient was critically ill and transferred to our hospital for a higher

level of care. She had life-threatening hemorrhage requiring massive transfusion support and admission to the intensive care unit. At the time of transfer, she was alert, awake, and oriented to person, place, time, and situation, and did not require vasopressors. Cardiovascular examination showed tachycardia, and abdominal examination revealed active bleeding from the laparotomy wound vacuum device and drains. Peripheral smear examination did not show any schistocytes or evidence of hemolysis.

The patient was started on therapeutic daily plasma exchange to decrease factor VIII antibodies, and recombinant activated factor VII (90 µg/kg) was given every 4 to 6 hours to stop the bleeding. She also received 2 doses of recombinant porcine factor VIII. Immunosuppressive therapy was continued.

Three days after laparotomy, the patient developed extensive bilateral venous thrombosis of the lower extremities.

4 What is the most likely etiology of thrombosis in this patient?

- ☐ AHA
- ☐ Immunosuppressive therapy
- ☐ Plasma exchange
- ☐ Multifactorial from recent surgery, massive transfusion, history of SLE, use of bypassing agents

Venous thrombosis is a rare event in patients with AHA. Cases of patients with AHA and simultaneous thrombosis are summarized in **Table 4** (expanded

TABLE 4
Summary of patients with acquired hemophilia A and thrombosis

Study	Risk factors for thrombosis	At diagnosis			Hematologic treatment	Immunosuppression regimen
		Activated partial thromboplastin time, seconds	Factor VIII, U/dL	Inhibitor, Bethesda units/mL		
1. Poli et al ¹⁸	Pregnancy	57 at deep vein thrombosis diagnosis and on anticoagulation	1.9	NA	Vitamin K	Prednisone 1 g/kg/day (4 weeks)
2. Deitcher et al ¹⁹	Idiopathic	54.3 (24–33)	5.3	57	Factor VIII concentrate and desmopressin	NA
	Lymphoma	61.4 (22–33)	2	47	Factor VIII concentrate and desmopressin	NA
	Postoperative	54.8 (22–33)	2	5	Factor VIII concentrate and desmopressin	NA
3. Spencer et al ²⁰	Pregnancy	3.01	2	35	Recombinant activated factor VII	Prednisolone 1 mg/kg/day (6 weeks) and cyclophosphamide 100 mg/day (6 months)
4. Paudel et al ²¹	Trauma or surgery	> 100	< 1	12	Vitamin K, fresh frozen plasma, recombinant activated factor VII	Methylprednisolone 120 mg/day, then rituximab 375 mg/m ² /weekly for 4 doses
5. Wool et al ²²	Idiopathic	76.9 (24–34)	4	27	Factor VIII concentrate (2 days), then recombinant activated factor VII (30 µg/kg/dose), then therapeutic plasma exchange	Dexamethasone 8 mg/12 hours, therapeutic plasma exchange days 5 and 6, then rituximab 375 mg/m ² /week (2 doses)
6. Maral et al ²³	Malignancy	107 (22–34)	3	350	NA	Prednisolone 1 mg/kg/day and cyclophosphamide 500 mg/week
7. Chhabra et al ²⁴	Idiopathic	78.6	< 1	82	Recombinant activated factor VII	Prednisolone 1 mg/kg/day and cyclophosphamide 100 mg/day
8. Aslam et al ²⁵	Addison disease	81.8	< 6	NA	Activated prothrombin complex concentrate, vitamin K	Intravenous methylprednisolone 30 mg/12 hours

NA = not available

version of table available online).^{18–25} Thrombotic events in the patients in studies 3, 4, 5, 7, and 8 were associated with use of bypassing agents.^{20–22,24,25} Hemorrhage and thrombosis represent opposite ends of the coagulation cascade, but each can be independently fatal. Deep vein thrombosis can be triggered by recent surgery, malignancy, autoimmunity, or inherited or acquired thrombophilia. Massive transfusion protocols in trauma patients can increase the risk of venous thromboembolism, presumably from overcorrection of the coagulation factor deficit.²⁶ Plasma exchange with immunosuppressive therapy alone does not significantly increase the risk of venous thrombosis.²⁷

Although thrombosis associated with aPCC therapy has been described, it is a rare event. Clinical trial data have shown that thrombosis is rare in patients with congenital hemophilia and inhibitors who are treated with bypassing agents.^{28,29} Similarly, a thrombosis risk of 1% was reported in patients with congenital hemophilia and inhibitors treated with aPCC.³⁰ However, risk of thrombosis is higher in patients with AHA treated with bypassing agents. Data from the European AHA (EACH2) registry showed a 2.9% thrombosis risk with recombinant activated factor VII and a 4.8% risk with aPCC.³¹ Aslam et al²⁵ reported on a 64-year-old woman with AHA who developed fatal pulmonary embolism with aPCC therapy.

Administration of recombinant activated factor VII seemed most temporally related to our patient's deep vein thrombosis. However, it is possible that she already had deep vein thrombosis when she was transferred from the outside hospital, as we did not perform Doppler ultrasonography until day 3 of admission. Both bypassing agents may have contributed to the deep vein thrombosis. It is difficult to establish a causal relationship between bypassing agents and thrombotic risk in AHA, but older age, medical comorbidities, and presence of other thrombotic risk factors also play a role. Our patient was an active smoker, and smoking is a well-established risk factor for venous thrombosis. Although debatable, it is believed that the risk of venous thrombosis is significantly higher in patients with SLE than in the general population.³² Our patient's postoperative state and immobility also contributed to her risk for venous thrombosis.

CASE CONCLUSION

Simultaneous thrombosis and life-threatening hemorrhage can be extremely challenging to manage, and the treatment priority should be to control bleeding. Given the patient's contraindication to anticoagula-

tion, an inferior vena cava filter was placed to minimize the risk of pulmonary embolism. Glucocorticoids were weaned over a period of 4 weeks, and a maintenance dose of prednisone 10 mg daily was continued. Mycophenolate mofetil 1 g twice daily was continued, and the patient completed 4 doses of rituximab and 10 sessions of therapeutic plasma exchange. During hospitalization, she required 30 units of packed red blood cells, 17 units of fresh frozen plasma, 8 units of platelets, and 3 units of cryoprecipitate. Her hospital course was complicated by acute kidney and liver injury; both improved with conservative measures. At the time of discharge, she was hemodynamically stable, and there was no evidence of active bleeding.

DISCUSSION

As noted above, AHA is a life-threatening hematologic emergency associated with high mortality. The most important steps in the management of a bleeding patient with AHA are to achieve hemostasis and eradicate the antibody.

Controlling bleeding

There is poor correlation between factor VIII levels, inhibitor titer, and bleeding, and these laboratory results should be interpreted with caution.³³ Three drugs are currently approved to treat bleeding in patients with AHA: recombinant activated factor VII, aPCC (FEIBA), and recombinant porcine factor VIII. High doses of factor VIII concentrate can be used in patients with low-titer inhibitors (eg, < 5 Bethesda units/mL), but high-dose factor VIII is generally not recommended in patients with high-titer inhibitors (≥ 5 Bethesda units/mL) given the superior efficacy of recombinant porcine factor VIII and the factor-bypassing agents aPCC and recombinant activated factor VII.^{31,34,35}

Recombinant porcine factor VIII theoretically is less likely to be inactivated by the factor VIII inhibitor because its protein sequence is different from that of human factor VIII.^{36,37} Autoantibodies to human factor VIII may cross-react with recombinant porcine factor VIII in up to 49% of patients with AHA and high-titer inhibitors.³⁸ In a study of 28 patients with AHA and severe bleeding, recombinant porcine factor VIII controlled the bleeding in 24 patients (86%).³⁹

It is reasonable to use recombinant porcine factor VIII as the initial hemostatic therapy in AHA. The US Food and Drug Administration–approved starting dose of recombinant porcine factor VIII is 200 U/kg.⁴⁰ A potential advantage of recombinant porcine factor VIII is that the standard 1-stage clotting FVIII assay

can be used to monitor factor VIII levels and help guide dosing. Using bypassing agents as first-line therapy is another option in AHA, reserving recombinant porcine factor VIII for patients with life-threatening hemorrhage that is unresponsive to a bypassing agent.

aPCC or recombinant activated factor VII is highly recommended in patients with higher-titer factor VIII inhibitors (ie, ≥ 5 Bethesda units/mL) and life-threatening hemorrhage. These agents are believed to have similar efficacy, with preference typically based on cost and the experience of the treating physician.^{41,42} The aPCC FEIBA contains mainly nonactivated therapeutic levels of factors II, IX, and X and activated factor VII; this agent facilitates thrombin generation.⁴³ For life-threatening hemorrhage, aPCC is dosed at 100 U/kg, with repeat doses every 4 to 12 hours as needed; recombinant activated factor VII is dosed at 90 μ g/kg and repeated every 2 to 3 hours as needed.^{40,44-46} Standard laboratory assays cannot be used to monitor the efficacy of aPCC or recombinant activated factor VII. Accordingly, dosing frequency depends on improvement in bleeding symptoms. In refractory bleeding events, sequential administration of aPCC and recombinant activated factor VII has been used successfully.⁴⁵

An important consideration when using a bypassing agent is the risk of thrombosis, which appears to be similar with aPCC and recombinant activated factor VII. However, there are conflicting reports on thrombosis risk with these agents. In postmarketing surveillance studies of aPCC, thromboembolic events were reported with doses above 200 units/kg/day.⁴⁶ A pharmacovigilance study found a higher thrombotic risk with recombinant activated factor VII compared with aPCC.⁴⁷ A recent French multicenter study of patients with AHA showed that recombinant activated factor VII was safe, with no thromboembolic events reported.⁴⁸

Concomitant use of aPCC and antifibrinolytics is another therapy option, although theoretically this combination might increase the risk of thrombosis. A retrospective study from the FEIBA on Acquired Hemophilia A Italian Registry (FAIR) showed that combination aPCC and antifibrinolytics was highly effective in achieving hemostasis in AHA without increasing thrombosis risk.⁴⁹

Emicizumab is a factor VIII-mimetic therapeutic bispecific antibody that bridges enzyme factor IXa and the substrate factor X. A study with 12 patients showed that emicizumab was safe and highly effective in achieving hemostasis in patients with AHA.⁵⁰ There are reports of patients with

acquired hemophilia developing thromboembolic events after receiving emicizumab. For this reason, our patient was not given emicizumab, especially after she developed an ischemic bowel. Larger studies are currently ongoing (NCT05345197) to investigate the role of emicizumab in AHA.

Suppressing the antibody

Although some coagulation inhibitors may regress spontaneously, immunosuppressive therapy remains an important pillar in the management of AHA. The optimal immunosuppressive therapy paradigm is unclear. The EACH2 study (N = 31) showed that steroids in combination with cyclophosphamide achieved a higher rate of complete remission (70%) compared with glucocorticoids alone (48%) or rituximab-based regimens (59%).⁵¹ The median time to achieve complete remission in the cyclophosphamide group was 5 weeks, and was longer with rituximab-based therapy. The choice of first-line therapy did not determine the clinical outcome, and the likelihood of achieving stable remission was predicted by the factor VIII level and inhibitor titer, not by the underlying etiology of AHA.⁵¹

Prolonged immunosuppressive therapy in AHA is associated with significant illness and infection-related deaths. Green et al⁵² evaluated prednisone, cyclophosphamide, and these agents in combination. The complete remission rate for single-agent prednisone was 32%, and this is a good option for patients with high factor VIII levels (≥ 1 IU/dL) and antibody titers of 20 Bethesda units/mL or less.^{44,52,53} Tiede et al⁵³ analyzed the prognostic factors in AHA and observed that patients with low factor VIII levels (< 1 IU/dL) and inhibitor concentrations greater than 20 Bethesda units/mL had a lower remission rate and decreased survival. Hence, most experts agree on a risk-adapted immunosuppressive therapy regimen involving more intense therapy with glucocorticoids and cyclophosphamide or rituximab in this high-risk population.⁴⁴

Infection risk seems to be lower with rituximab-based regimens (12%) than with the cyclophosphamide-based regimen (27%).⁵¹ Given our patient's postoperative state and higher risk of infection, we opted for a rituximab-based regimen in addition to mycophenolate mofetil. Alternatively, recent studies have shown that upfront triplet immunosuppressive therapy consisting of cyclophosphamide, dexamethasone, and rituximab is highly effective and can achieve a durable complete remission rate of 96.8%.⁵⁴ In patients with inhibitor titers exceeding 100 Bethesda units/mL, it is reasonable to consider triplet immunosuppressive therapy after carefully considering the infection risk.^{55,56}

When first-line therapy fails, approximately 60% of patients can achieve a stable complete remission with second-line therapy. The choice of second-line therapy, rituximab vs cyclophosphamide, is primarily dictated by the initial regimen.

Therapeutic plasma exchange can also be used as an adjuvant to immunosuppressive therapy in patients with AHA.⁵⁷

TAKE-HOME POINTS

- This rare case of a patient with AHA was secondary to SLE, and the diagnosis was missed preoperatively despite a positive clinical history of bruising and prolonged aPTT.
- Venous thromboembolism is a rare but potentially fatal complication associated with AHA.
- Hemostatic therapy with agents such as recombinant

activated factor VII and aPCC is an important pillar in the management of AHA, although these agents can increase thrombotic risk.

- Simultaneous life-threatening hemorrhage and venous thrombosis in AHA is rare and poses major therapeutic challenges.
- A complex clinical case like the one described here should be managed by an expert hematologist and a multidisciplinary team of specialists.

Acknowledgment: The authors thank Virginia Mohlere for editorial assistance.

DISCLOSURES

Dr. Escobar disclosed consulting for Bayer, Biomarin, Genentech/Roche, Hemabiologics, LFB, Magellan, NovoNordisk, Regeneron, Sanofi, Takeda; participating in a clinical trial sponsored by Bayer, Genentech/Roche, Regeneron, Sanofi, Takeda; being principal investigator for LFB research. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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