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Evaluation of Interventions at the Transition of Care from Hospital to Home
Tuesday, March 8, Noon – 1:30 pm | Virtual

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Professor of Medicine
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Vanderbilt University Medical Center

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Anita Misra-Hebert, MD, MPH, FACP
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LEARNING OBJECTIVES

› Discuss how a learning health system structure can advance research on transitions of care from hospital to home

› Discuss results of recent research completed to evaluate readmission risk prediction as well as a post-discharge home visit program in the Cleveland Clinic Health System

› Discuss appropriate methods to capture implementation outcomes for inpatient-based transitional care interventions

This activity has been approved for AMA PRA Category 1 Credit™
Anaphylaxis: Expanding our perspective

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

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

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

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

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

Brian F. Mandell, MD, PhD
Editor in Chief


doi:10.3949/ccjm.89b.02022
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With the exception of the physical examination module, these activities have been approved for AMA PRA Category 1 Credit™.
OUR PEER-REVIEWERS FOR 2021

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

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

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

Not every inpatient awaiting surgery under general anesthesia requires an order for nothing by mouth (NPO) after midnight, and it is important for internists to be aware of recommendations on this matter. Ordering NPO after midnight has been a common practice to lower the risk of aspiration of gastric contents during general anesthesia, which is due in part to suppression of laryngeal reflexes from anesthesia.1,2 Unfortunately, delays, cancellations, and postponements of surgical procedures are common, and disallowing oral intake for prolonged periods in these situations may lead to patient harm and frustration. A recent review by Black et al3 reported that orders for NPO after midnight were low-value patient care, a practice that is not evidence-based practice and causes significant patient dissatisfaction.

Further, the use of midnight as the cutoff for oral intake is arbitrary, chosen more for the convenience of the operating room schedule and the ordering provider rather than the patient. A 2003 Cochrane review4 concluded that there was no support for lengthier fasting periods such as the standard NPO after midnight when compared with shortened fluid fasts. In fact, the American Society of Anesthesiologists (ASA) guidelines for preoperative fasting allow light meals up to 6 hours and clear liquids up to 2 hours before elective procedures utilizing general anesthesia.5 These guidelines are similar to those of the European Society of Anaesthesiology and Intensive Care (ESAIC).6

CONSIDERATIONS BEFORE ORDERING NPO AFTER MIDNIGHT

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

ELECTIVE OR SEMI-URGENT PROCEDURES

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

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

■ PATIENTS AT HIGH RISK OF ASPIRATION

Prolonged fasting became a standard in the mid-1900s, when catastrophic surgical complications were reported in obstetric patients who aspirated during labor.8 Although this practice has incorrectly been extrapolated to nearly all surgical and radiologic procedures, patients in labor, patients with obesity, those with a history of esophageal surgery, and those with gastrointestinal obstruction are at highest risk of aspiration1 and thus may require a prolonged fast. Clinicians should be able to identify these patients early in the hospital course when taking a careful history.

■ THE BOTTOM LINE

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

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

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

■ DISCLOSURES

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

REFERENCES


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

The patient’s medical history revealed that 2 years earlier she had been prescribed the topical steroid betamethasone butyrate propionate for treatment of xerotic dermatitis, which had subsided within a short period. However, she had continued to apply the corticosteroid to her left arm for more than 2 years after the dermatitis had subsided, and she was still using it at the time of presentation.

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

■ DIFFERENTIAL DIAGNOSIS OF HYPERTRICHOsis

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

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

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

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

■ TOPICAL CORTICOSTEROIDS AND HYPERTRICHOsis

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

■ CASE CONCLUSION

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

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

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

■ DISCLOSURES

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

REFERENCES


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Soft tissue sarcoma: Recognizing a rare disease

ABSTRACT

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

KEY POINTS

- The rarity of soft tissue sarcoma, its heterogeneity, and overlap of symptoms with benign conditions are challenges to timely diagnosis.
- A smaller tumor at diagnosis (< 5 cm) is associated with better prognosis.
- Patients suspected of having a soft tissue sarcoma require prompt referral to a sarcoma center for assessment and treatment.

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

THE EPIDEMIOLOGY OF SOFT TISSUE SARCOMA

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

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

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

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

■ CHALLENGES TO CLINICAL RECOGNITION OF SOFT TISSUE SARCOMA

STS is a heterogeneous group of tumors of mesenchymal cell origin that can occur anywhere in the body, affecting the extremities in 50% of cases, the trunk and retroperitoneum in 40%, and the head and neck in 10%.³ Awareness of STS is low among both the general public and healthcare providers. The wide range in presentation sites, lesion size, and patient ages and the overlap of symptoms with those of benign conditions make this diagnosis challenging. Lumps may often be dismissed or misdiagnosed as harmless cysts or fatty tissue. A UK survey found that patients with STS were significantly more likely to be treated for another condition or advised that their symptoms were not serious.⁸ In 2006, Grimer et al⁹ published a sarcoma database review that included a plea for greater recognition of potential malignant lumps and bumps, especially those larger than a golf ball (5 cm). This led to a campaign to raise public awareness of STS in the United Kingdom.¹⁰ But despite attempts to increase recognition of STS, the typical size at presentation (10 cm) has changed very little.

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

TABLE 1
Clinical features of soft tissue masses that require urgent investigation

<table>
<thead>
<tr>
<th>Feature</th>
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<tbody>
<tr>
<td>Increasing size</td>
</tr>
<tr>
<td>Size greater than 5 cm (ie, golf-ball size)</td>
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<tr>
<td>Deeper-lying mass (deep to fascia)</td>
</tr>
<tr>
<td>Firmer than surrounding tissue</td>
</tr>
<tr>
<td>Patient has potential risk factors (previous radiotherapy, chronic lymphedema, inherited syndrome such as Gardner syndrome, Li-Fraumeni syndrome, and von Recklinghausen disease)</td>
</tr>
<tr>
<td>Local symptoms and signs of infiltration</td>
</tr>
<tr>
<td>With or without pain (large painless lumps should raise concern)</td>
</tr>
<tr>
<td>The greater the number of clinical features, the greater the risk of malignancy.</td>
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</table>

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

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

STS tends to present as a large, painless, unexplained mass anywhere in the body that has been increasing in size. The belief that only painful masses are worrisome is wrong. The UK guidelines⁵ suggest that a lump that is larger than 5 cm, exhibits growth, is deep in the body, and is painful should be considered malignant until proven otherwise (Table 1). Increasing size is the best individual indicator of a greater risk of malignancy.⁵ A mass growing slowly over a period of weeks to months, painful or not, should raise more concern than a painful mass growing rapidly over a period of days. No change in the size of a tumor over a longer time period favors a benign diagnosis.

Adding to the diagnostic challenges is a lack of known risk factors for STS. In most cases, there is no identifiable underlying cause. The risk of developing sporadic STS is increased in patients with a history of previous radiotherapy and chronic lymphedema. Certain genetic mutations, particularly chromosomal translocations, and inherited syndromes such as Gardner syndrome, Li-Fraumeni syndrome, and von Recklinghausen disease can also predispose patients to STS.¹¹ Systemic signs such as weight loss, fatigue, fevers, chills, and night sweats are uncommon.¹
Late diagnosis affects the prognosis
Studies have found an almost linear relationship between the increasing lesion size and poorer prognosis that is independent of other factors, even for patients without metastatic disease at diagnosis.9 This is particularly true of tumors larger than 5 cm, emphasizing the point that a smaller tumor at diagnosis and treatment is associated with better prognosis.9 A smaller lump is easier to remove and reduces the surgical and long-term functional impact on the local anatomical area. Other factors associated with worse clinical outcomes are high-grade histology, positive margins after resection, and patient age over 60.

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

 WHICH DIAGNOSTIC TESTS ARE PREFERABLE?

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

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

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

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

The role of biopsy
The standard diagnostic approach must also include biopsy, in most cases multiple percutaneous core needle specimens obtained under ultrasonographic guidance.3 In some cases, incisional or excisional (open) biopsy may be required. Biopsy should be performed by a team composed of a tumor-trained orthopedic surgeon, radiologist, and pathologist to ensure that optimal samples are taken and analyzed without compromising the final surgical treatment and unnecessary contamination of healthy tissue. Poorly performed biopsies can lead to a higher risk of adverse outcomes and expenses.20 A high degree of suspicion for STS based on the biopsy results should trigger prompt referral to a sarcoma center for triple assessment of clinical history, imaging, and biopsy, all of
which should be done on the same day. And if STS is diagnosed, these centers have multidisciplinary teams trained to maximize long-term survival, minimize local recurrence, optimize function, and minimize morbidity, and they also have resources to perform additional staging studies to identify distant spread of proven STS. This additional information helps tailor treatment to the individual patient.

■ AVOIDING A ‘WHOOPS PROCEDURE’

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

Whoops procedures have been shown to cause the following:

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

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

■ LITIGATION AND COST

Medical malpractice claims related to STS care have been increasing in both the United Kingdom and the United States, and common reasons are poor awareness, lack of knowledge, false reassurance, and late referrals. In one review, litigation rates dramatically fell if a patient had been referred to a sarcoma center.26 In the United States, the mean indemnity payment favoring the patient was approximately $2.30 million (£1.7 million) in 2020, with delay in diagnosis being the main reason (86%). These cases were mostly filed against the primary care physicians. Thus, educating practitioners and raising awareness of STS in order to prompt early referral are keys to providing better care and reducing malpractice claims.

■ TAKE-HOME MESSAGE

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

■ DISCLOSURES

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


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Extraosseous calcification in kidney disease

ABSTRACT

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

KEY POINTS

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

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

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

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

CHRONIC KIDNEY DISEASE, DEFINED AS AN ESTIMATED glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m² or structural kidney damage sustained over 3 months, is increasing in prevalence worldwide. It is estimated to affect between 2% and 17% of all adults, and the United States is at the high end of this prevalence range.1

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

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

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

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CALCIFICATION IN KIDNEY DISEASE

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

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

In the kidney, PTH directly increases calcium reabsorption in the distal tubule and loop of Henle and increases phosphate excretion by inhibiting its reabsorption in the proximal tubule.9,10 Also in the kidney, PTH upregulates production of 1-alpha-hydroxylase, leading to increased conversion of active vitamin D (1,25-dihydroxycholecalciferol) from its precursor, 25-hydroxycholecalciferol. In turn, in the intestine, active vitamin D increases the absorption of calcium and to a lesser degree phosphate, and in the bone, it has direct actions on both osteoblasts and osteocytes, promoting maturation, expression of skeletal hormones such as fibroblast growth factor 23 (FGF-23), and proper mineralization.11,12

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

### Vascular calcification

Vascular calcification is an active process involving de-differentiation of vascular smooth muscle cells. It begins with amorphous development of calcium phosphate nanocrystals in con-

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**TABLE 1**

**Common terms used to describe calcification**

<table>
<thead>
<tr>
<th>Soft tissue calcification</th>
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<tbody>
<tr>
<td>Dystrophic calcification: occurring in damaged or degenerated tissue in the setting of normal metabolic factors</td>
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<tr>
<td>Metastatic calcification: occurring in otherwise normal tissue, secondary to deranged metabolic factors, as in hypercalcemia</td>
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Calciphylaxis (calcific uremic arteriopathy): ischemic skin lesions characterized by calcium deposition and thrombosis in the dermis and subcutaneous adipose tissue, most commonly associated with advanced kidney disease

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

Tumoral calcinosi: massive deposition of calcium-phosphorus crystals in perianterial areas

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

**Vascular calcification**

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

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

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

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As chronic kidney disease progresses to its end stage, FGF-23 levels keep getting higher, and the elevation is accompanied by other calcium-phosphate axis derangements such as excess PTH release, increased 1,25-dihydroxycholecalciferol, and increased sclerostin (an inhibitor of bone formation).10,21 Together, these derangements lead to the clinical manifestations described below.

**Vascular calcification**

Vascular calcification is an active process involving de-differentiation of vascular smooth muscle cells. It begins with amorphous development of calcium phosphate nanocrystals in con-
Deposition of these nanocrystals can begin in the intima of the artery near sites of cholesterol buildup, either progressing into the media or beginning in the media itself, the latter of which is most specific to kidney disease. In end-stage kidney disease, progression of vascular calcification occurs earlier than in normal aging and is likely driven by hyperphosphatemia, a positive calcium balance, inflammation, and dysregulation between pro-calcification and anticalcification regulatory factors. An in-depth discussion of the pathogenesis of vascular calcification is beyond the scope of this paper and can be found elsewhere.

**Soft tissue calcification**

Soft tissue calcification is fairly common in chronic and end-stage kidney disease, but only a small number of patients develop tu-
moral calcinosis, characterized by massive calcium phosphate deposition in periarticular locations predisposed to microtrauma.

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

### PRESENTATION AND DIAGNOSIS

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

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

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

### MEDICAL THERAPY

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

Dietary phosphate restriction, phosphate binders

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

The most commonly used phosphate intestinal binders are calcium-based (eg, calcium carbonate, calcium acetate) and are used extensively in patients with chronic and end-stage kidney disease for many indications.
However, earlier studies demonstrated a relationship between higher calcium intake and higher rates of vascular calcification, and subsequent studies called attention to this association, leading to recommendations for using non–calcium-based intestinal phosphate binders to restore normal phosphate levels while limiting calcium intake to maintain normal serum calcium.

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

The IMPROVE-CKD trial (Impact of Phosphate Reduction on Vascular End-points in Chronic Kidney Disease) tested lanthanum use in patients with advanced chronic kidney disease (eGFR < 30 mL/min/1.73 m²) and evaluated changes in aortic calcification and arterial stiffness. It did not find statistically significant differences with lanthanum compared with placebo. Of note, the trial was limited by recruitment, including patients with normal phosphate levels and excluding those with end-stage kidney disease.

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

The LANDMARK trial (Outcome Study of Lanthanum Carbonate Compared With Calcium Carbonate on Cardiovascular Mortality and Morbidity in Patients With Chronic Kidney Disease on Hemodialysis), published in 2021, looked at patients with end-stage kidney disease in Japan who had risk factors for vascular calcification who were randomized to receive lanthanum or calcium carbonate. It did not find any statistically significant differences in rates of all-cause mortality or cardiovascular events between the two groups, though the event rates were low. Further, compared with the United States, Japan has lower dietary calcium intake, higher use of arteriovenous fistulas.
Vascular calcification increases cardiovascular risk

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

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

Bone antiresorptive agents

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

Robust data exist for using this drug class in bone disorders in patients in the early stages of chronic kidney disease (eGFR > 35 mL/min/1.73 m²), but data are significantly limited in those with stage 4 or 5 chronic kidney disease or end-stage kidney disease, and there are theoretical safety concerns.41 Bisphosphonates are less frequently prescribed in these latter populations, possibly due to concerns about toxicity, as these drugs are excreted by the kidney.42 Reports of worsening kidney disease or kidney injury exist for most drugs in the bisphosphonate class, but larger observational trials have found oral bisphosphonates to be reasonably safe in advanced chronic kidney disease, though bisphosphonate users had a 14% higher risk of progression of chronic kidney disease.43

Zoledronic acid, a potent intravenous formulation, should be avoided if the eGFR is less than 30 mL/min/1.73 m², in view of stronger associations with direct tubular injury, acute kidney injury, and worsened eGFR.44,45 Pamidronate is generally the preferred intravenous formulation for patients with advanced chronic kidney disease, usually given at a lower dose or infused over a longer time. Rarely, collapsing focal segmental glomerulosclerosis can occur.44,45

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

Denosumab, a RANK ligand inhibitor (RANK stands for receptor activator of
nuclear factor kappa B) that prevents osteoclast maturation, has not been studied in soft tissue calcification. Small pilot studies have looked at denosumab’s effects on vascular calcification in humans and have suggested it may slow coronary artery calcification, but this has been challenged in other studies.\textsuperscript{52,53} More studies are needed to determine the clinical significance of these findings. We are not aware of any studies that have looked at denosumab in soft tissue calcification or calciphylaxis.

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

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

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

Sodium thiosulfate
Sodium thiosulfate is an older medication with antioxidant properties that has been used off-label for years in calcium disorders including vascular calcification and calciphylaxis. It was recently systematically reviewed in treating calciphylaxis, with conflicting results.\textsuperscript{58,59} More recently, a randomized clinical trial\textsuperscript{60} showed reduction of iliac artery calcification and arterial stiffness with sodium thiosulfate compared with placebo in calciphylaxis. Ongoing prospective and randomized trials will hopefully provide clarity of the benefit of sodium thiosulfate in vascular calcification and calciphylaxis. In a small case series, the drug has shown improvement in symptom burden in soft tissue calcification of the shoulder and hip, with partial size regression.\textsuperscript{61}

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

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

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

Novel therapies, nonmedical management
SNF472, a myo-inositol hexaphosphate that inhibits hydroxyapatite growth, has shown promise in early clinical trials in reduction of coronary artery calcium volume, while tissue-nonspecific alkaline phosphatase inhibitors are in earlier stages of development.\textsuperscript{68,69}
Magnesium and vitamin D supplementation in chronic and end-stage kidney disease has had varying degrees of success in preventing vascular calcification, though more studies are needed to confirm its clinical utility.\textsuperscript{70,71} With particular relevance to soft tissue calcification, surgical debridement and hyperbaric oxygen therapies hold significant promise as adjunctive therapies to the aforementioned medical therapies.\textsuperscript{72–74}

\section*{REFERENCES}


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Recurrent anemia in a patient with chronic lymphocytic leukemia

A 73-year-old man presented with lymphocytosis and retroperitoneal lymphadenopathy and was found to have chronic lymphocytic leukemia (CLL), Rai stage II (possible stages are 0–IV). He was not initially treated for it but was monitored until 5 months later, when he was admitted to the hospital with multilobular pneumonia with acute hypoxic respiratory failure and a white blood cell count of 139 × 10⁹/L (reference range 4.5–10.9 × 10⁹/L). He was treated with a combination of broad-spectrum antibiotics, vasopressor support, and high-dose corticosteroids.

FIRST EPISODE OF ANEMIA

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

- Hemoglobin 5.5 g/dL (14–18 g/dL)
- Mean corpuscular volume 106 fL (80–100 fL)
- Lactate dehydrogenase 903 mg/dL (135–225 mg/dL)
- Reticulocyte count 96 × 10⁹/L, 4.4% (90–130 × 10⁹/L, 1%–2%)
- Haptoglobin undetectable.

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

To control his autoimmune hemolytic anemia, the patient was given a combination of prednisone 1 mg/kg tapered over 6 weeks and intravenous immune globulin 500 mg/kg daily for 5 days, followed by rituximab 375 mg/m² once a week for 4 doses, and his anemia resolved.

SECOND EPISODE OF ANEMIA

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

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

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

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

FINDING THE CAUSE OF ANEMIA

Anemia—a hemoglobin below 13 g/dL in men and below 12 g/dL in women—can result from a deficit in red blood cell production, destruction of red blood cells, or blood loss. An evaluation of new anemia following the algorithm outlined in Figure 1 as an initial step will help define the mechanism and guide its management. The first step is to check the reticulocyte count, a marker of bone marrow production that can help differentiate the underlying mechanism of acquired anemia.
If the reticulocyte count is high
Reticulocytes are immature red blood cells. If there are more of them than usual in the blood of a patient with anemia, it means that the bone marrow is functioning and is responding to the red blood cell destruction or blood loss by increasing the production of red blood cells.

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

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

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

A negative hemolytic workup with an elevated reticulocyte count suggests hemorrhage. Management of a clinically overt hemorrhage is directed at controlling the source. In cases in which the source of blood loss is not obvi-
ous, imaging and endoscopy to look for internal bleeding can be helpful.

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

If the reticulocyte count is normal or low

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

Vitamin B₁₂ and folate are essential for nucleic acid synthesis. Deficiency in either of these nutrients will lead to asynchrony in nucleic acid and cytoplasmic development of red blood cells, leading to megaloblastic anemia with elevated mean corpuscular volume and a low reticulocyte count.

Moreover, because iron, folate, and vitamin B₁₂ are required for erythropoiesis, the reticulocyte count could be falsely low in a patient with anemia that is due to red blood cell destruction or blood loss in case of a concomitant nutritional deficiency.

Causes of anemia in chronic lymphocytic leukemia

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

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

The prevalence of autoimmune hemolysis in CLL varies among different case series, ranging between 5% and 10%. The development of autoimmune hemolysis in CLL is more frequent in men, older patients (over age 65), and patients with a lymphocyte count greater than 60 × 10⁹/L. Of note, patients with CLL can have a positive direct antiglobulin test without autoimmune hemolysis. In a retrospective series by Ricci et al, the prevalence of direct antiglobulin test positivity in patients with CLL was 14%, but only 8 (40%) of the 20 patients with positive tests had autoimmune hemolysis.

Autoimmune hemolysis in chronic lymphocytic leukemia is treated with steroids

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

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

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

Laboratory testing during the second episode of anemia revealed a low reticulocyte count,
normal lactate dehydrogenase and indirect bilirubin levels, and a high haptoglobin level, suggesting bone marrow suppression (Table 1). The patient did not have any clinical signs to suggest a viral infection, and he was receiving no drugs commonly associated with anemia.

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

**Pure red cell aplasia**

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

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

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

### WHEN SHOULD CLL BE TREATED?

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

---

**TABLE 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient’s value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin</td>
<td>6.5 g/dL</td>
<td>14–18 g/dL</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>13.26 x 10^9/L</td>
<td>90–130 x 10^9/L (0.65%)</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>85 fl</td>
<td>78–95 fl</td>
</tr>
<tr>
<td>Red cell distribution width</td>
<td>14%</td>
<td>11.5%–15.1%</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>162 U/L</td>
<td>135–225 U/L</td>
</tr>
<tr>
<td>Direct antiglobulin test</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>336 mg/dL</td>
<td>30–200 mg/dL</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>0.2 mg/dL</td>
<td>1.0–1.0 mg/dL</td>
</tr>
<tr>
<td>Peripheral smear</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red blood cells</td>
<td>Normocytic, decreased in number, no schistocytes, no spherocytes</td>
<td></td>
</tr>
<tr>
<td>White blood cells</td>
<td>Lymphocytes predominant, no immature white blood cells</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>Normal in size and granulation</td>
<td></td>
</tr>
</tbody>
</table>
plasia, diverticulosis, or myelodysplasia need to be excluded.

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

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

- Progressive marrow failure evidenced by the development or worsening of anemia or thrombocytopenia
- Splenomegaly that is massive (ie, ≥ 6 cm below the left costal margin), progressive, or symptomatic
- Lymphadenopathy that is massive (ie, ≥ 10 cm in longest diameter), progressive, or symptomatic
- Rapidly progressive lymphocytosis with a doubling of the lymphocyte count over less than 6 months or an increase of more than 50% over a 2-month period
- Autoimmune anemia or thrombocytopenia that is refractory to corticosteroids
- Constitutional “B symptoms.” Constitutional B symptoms include the following:
  - Unintentional weight loss of 10% or more within the previous 6 months
  - Significant fatigue (ie, Eastern Cooperative Oncology Group performance status ≥ 2 on a scale of 0–5; inability to work or perform usual activities)9
  - Fever, with a temperature greater than 100.5 °F (38.0 °C) for at least 2 weeks without other evidence of infection
  - Night sweats for at least 1 month without evidence of infection.

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

■ CASE CONTINUED
As noted above, the patient’s second episode of anemia was determined to be due to pure red cell aplasia. A trial of steroids was ineffective, and the patient was subsequently started on ibrutinib with rituximab to treat his CLL. The anemia resolved, but the patient developed severe neutropenia that resolved after withdrawing the rituximab. The patient remained well for more than 2 years while taking ibrutinib alone, with resolution of anemia and no additional complications of CLL.

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

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

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

---

**Table 2**
The patient’s complete blood cell count in the emergency department in his third episode of anemia

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

---

Biopsy revealed pure red cell aplasia as the cause of the second episode.
The patient did well for 2 years on ibrutinib, but then the anemia returned.

**TABLE 3**
The patient’s basic metabolic panel in the emergency department in his third episode of anemia

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

**WHAT IS THE NEXT STEP?**

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

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

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

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

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

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

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

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

**CASE CONTINUED: UNEXPECTED BIOPSY FINDINGS**

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

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

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

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

### EFFECT OF PROSTATE CANCER ON THE PERIPHERAL BLOOD SMEAR

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

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

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

### CASE CONCLUDED

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

The patient’s CLL continues to be managed with ibrutinib. He was started on anti-androgen therapy with leuprolide, a gonadotropin-releas-

---

**TABLE 4**

**Further laboratory findings in the patient’s third episode of anemia**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient’s value</th>
<th>Reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reticulocyte count</td>
<td>9.9 x 10^9/L (0.6%)</td>
<td>90–130 x 10^9/L (1%–2%)</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>90.5 fL</td>
<td>78–95 fL</td>
</tr>
<tr>
<td>Red cell distribution width</td>
<td>15.9%</td>
<td>11.5%–15.1%</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>231 U/L</td>
<td>135–225 U/L</td>
</tr>
<tr>
<td>Direct antiglobulin test</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>362 mg/dL</td>
<td>30–200 mg/dL</td>
</tr>
<tr>
<td>Indirect bilirubin</td>
<td>0.7 mg/dL</td>
<td>0.0–1.0 mg/dL</td>
</tr>
<tr>
<td><strong>Peripheral smear</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Red blood cells</td>
<td>Normocytic, normochromic, rare schistocytes, no nucleated red blood cells, no teardrop cells</td>
<td></td>
</tr>
<tr>
<td>White blood cells</td>
<td>No immature white blood cells noted, neutrophil predominance, small mature lymphocytes</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>Increased in number, few giant platelets noted</td>
<td></td>
</tr>
</tbody>
</table>
CLL is generally considered an incurable, chronic disease. The current treatment strategy is to manage the complications of the disease, which can include cytopenias. It is therefore essential to understand the multiple mechanisms of anemia in patients with CLL, how to diagnose them, and how to manage them.

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

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

**REFERENCES**


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

**DISCLOSURES**

Dr. Gonsky reports ownership interest in Abbvie Pharmaceuticals, Johnson & Johnson, and Pfizer. Dr. Ghanem reports no relevant financial relationships which, in the context of his contributions, could be perceived as a potential conflict of interest.

**TAKING-HOME POINTS**

- CLL is generally considered an incurable, chronic disease. The current treatment strategy is to manage the complications of the disease, which can include cytopenias.
- It is therefore essential to understand the multiple mechanisms of anemia in patients with CLL, how to diagnose them, and how to manage them.
- Every new episode of anemia does not automatically imply disease progression, and each should be evaluated completely. The initial evaluation should include at least the reticulocyte count to assess bone marrow response, the mean corpuscular volume, the red cell distribution width, and review of the peripheral smear with further testing as needed.
- This case also highlights the importance of avoiding anchoring bias, as each new episode of anemia had a different cause that called for different treatment.

**Figure 2.** Focal bone marrow infiltration by solid nests of tumor cells (arrows) in the patient’s third episode of anemia (hematoxylin and eosin, × 20).
Hypercalcemia and vitamin A: A vitamin to keep in mind

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

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

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

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

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

do:10.3949/ccjm.89a.21056
Preformed vitamin A retinoids are derived from animal products; carotenoids occur in plant-based foods.

- **PREFORMED VS PRECURSOR VITAMIN A**

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

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

---

**TABLE 1**

Results of initial laboratory tests

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

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

### THE ROLE OF ABSORPTION IN VITAMIN A TOXICITY

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

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

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

### TABLE 2

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

<table>
<thead>
<tr>
<th>Food product or supplement</th>
<th>Form of vitamin A</th>
<th>Vitamin A content (μg RAE)</th>
<th>Percentage of RDI for adult men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef liver, 3 ounces</td>
<td>Activated (preformed)</td>
<td>6,582</td>
<td>731</td>
</tr>
<tr>
<td>Cod-liver oil, 1 tablespoon</td>
<td>Activated</td>
<td>4,080</td>
<td>453</td>
</tr>
<tr>
<td>Sunmark One Daily Women’s Multivitamin, 1 tablet</td>
<td>Mixed (80% activated, 20% provitamin A)</td>
<td>2,500</td>
<td>277</td>
</tr>
<tr>
<td>Sweet potato, 1 whole</td>
<td>Provitamin A</td>
<td>1,403</td>
<td>156</td>
</tr>
<tr>
<td>Centrum Silver Adults, 1 tablet</td>
<td>Mixed (60% activated, 40% provitamin A)</td>
<td>750</td>
<td>83</td>
</tr>
<tr>
<td>One A Day, Women’s Complete Multivitamin*</td>
<td>Mixed (90% activated, 10% provitamin A)</td>
<td>700</td>
<td>78</td>
</tr>
<tr>
<td>Spinach, ½ cup</td>
<td>Provitamin A</td>
<td>573</td>
<td>64</td>
</tr>
<tr>
<td>Ricotta cheese, part skim, 1 cup</td>
<td>Activated</td>
<td>263</td>
<td>31</td>
</tr>
<tr>
<td>Egg, boiled, 1 large</td>
<td>Activated</td>
<td>75</td>
<td>8</td>
</tr>
<tr>
<td>Broccoli, ¼ cup</td>
<td>Provitamin A</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>Yogurt, 1 cup</td>
<td>Activated</td>
<td>32</td>
<td>4</td>
</tr>
<tr>
<td>Chicken meat, ½ breast piece</td>
<td>Activated</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

*Product used by our patient at the time of presentation.
RAE = retinol activity equivalents; RDI = recommended daily intake

Based on information in references 5, 17, 18, 19, and 20.
luminal border, and this results in poor absorption efficiency, in the range of 9% to 22%. In addition, upon ingestion of excessive amounts of carotenoids, the efficiency of luminal diffusion decreases, which further protects against toxicity from over-ingestion. Based on this, OTC vitamins containing carotenoids may be safer for patients than those containing preformed vitamin A.11 The patient described in our case scenario was taking a supplement with vitamin A content that was above the recommended daily intake (RDI).

Once absorbed, most vitamin A is stored in the liver and released into the bloodstream, where retinol-binding protein transports it to its target tissues.12 If the body’s supply of vitamin A changes, the liver modifies the release of retinol into the serum to maintain normal plasma retinol levels. However, a normal plasma retinol level does not always indicate normal total body levels of vitamin A, and low or high retinol levels can indicate a significant abnormality of the body’s vitamin A stores.12,13 The half-life of vitamin A is estimated to be 128 days, so it can take many months for retinol levels to normalize after vitamin A toxicity.4

### Challenges to Appropriate Vitamin A Intake

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

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

### Consequences of Excessive Vitamin A Intake

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

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**TABLE 3**

**Recommended daily intake of vitamin A**

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

*Value extrapolated from vitamin A content of consumed breast milk by healthy infants.

RAE = retinol activity equivalents

Based on information in references 4 and 5.
Acute ingestion (ie, a single dose) of more than 200,000 μg RAE of preformed vitamin A is required to cause acute hypervitaminosis A syndrome in adults.6 This condition is uncommon and was seen historically in Atlantic explorers who inadvertently ate large amounts of animal livers containing preformed vitamin A.5,10

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

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

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

### VITAMIN A AND THE SKELETON: BONE RESORPTION AND HYPERCALCEMIA

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

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

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

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

### TREATMENT RELIES ON ANECDOTAL EXPERIENCE

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

### TAKE-HOME MESSAGE: CONSIDER VITAMIN A IN HYPERCALCEMIA

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

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**Absorption of preformed vitamin A through gut transport proteins is highly efficient**
HYPERCALCEMIA AND VITAMIN A

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

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

REFERENCES


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Anaphylaxis: Highlights from the practice parameter update

ABSTRACT

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

KEY POINTS

Epinephrine is first-line pharmacotherapy for anaphylaxis.

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

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

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

THE UPDATED GUIDELINES on the prevention and treatment of anaphylaxis1 from the Joint Task Force on Practice Parameters address key issues in the prevention and management of anaphylaxis, including diagnostic criteria for anaphylaxis; therapeutic use of epinephrine, antihistamines, and glucocorticoids; prevention of recurrent anaphylaxis; and follow-up care including patient education on trigger avoidance and use of self-injectable epinephrine. This update to the 2015 guidelines2 was a collaborative effort of the American Academy of Allergy, Asthma, and Immunology and the American College of Allergy, Asthma, and Immunology.

GENERAL CONSIDERATIONS OF THE UPDATE

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

- Acute onset of symptoms involving the skin or the mucous membrane, or both, including hives, itching, flushing, or swelling; plus the acute onset of respiratory symptoms, with or without hypotension or other symptoms of target-organ dysfunction
- Involvement of 2 or more organ systems that occurs rapidly after exposure to a likely allergen, including skin or mucosal membrane symptoms, respiratory symptoms, hypotension or other symptoms of target-organ dysfunction, and sudden gastrointestinal symptoms
Hypotension occurring acutely after exposure to a known or established allergen for that patient. In patients who meet the anaphylaxis criteria, epinephrine is recommended. However, the updated guidelines recognize that epinephrine treatment may still be appropriate in some patients who do not meet anaphylaxis criteria, such as a patient exposed to a likely allergen who develops symptoms in a single organ system. Anaphylaxis is considered to be severe if respiratory failure or cardiovascular collapse occurs.

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

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

**ANAPHYLAXIS TREATMENT**

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

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

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

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

Second-line therapy with beta-2 agonists such as albuterol, antihistamines (histamine-1 and histamine-2 receptor antagonists), and corticosteroids may be considered. Glucagon may be helpful for patients who are receiving beta-adrenergic blocking agents.2 Unlike epinephrine, these second-line medications will not work in patients with beta-blocker-induced bradycardia or heart block.

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**TABLE 1**

**Diagnostic criteria for anaphylaxis**

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

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

Based on information from reference 1.
not effectively treat cardiovascular symptoms such as hypotension and should not be administered in place of epinephrine.\textsuperscript{1}

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

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

■ BIPHASIC ANAPHYLAXIS

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

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

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

■ PREVENTING BIPHASIC ANAPHYLAXIS

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

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

■ ADDRESSING THE POTENTIAL CAUSES OF ANAPHYLAXIS

Chemotherapy

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

Radiocontrast media

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

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

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

WHAT’S DIFFERENT FROM THE 2015 GUIDELINES?
The Joint Task Force used the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) analysis to rigorously evaluate the certainty of the literature to answer key questions, whereas the 2015 guidelines task force classified recommendations by the strength of the recommendations and the quality of the evidence.

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

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

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

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

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

TABLE 2

Key clinical practice recommendations from the 2020 anaphylaxis guidelines

Treatment of anaphylaxis

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

Do not delay the administration of epinephrine for anaphylaxis.

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

Biphasic anaphylaxis

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

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

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

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

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

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

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

Based on information from reference 1.

WHAT’S THE EXPECTED CLINICAL IMPACT?

The updated guidelines will likely improve outcomes in patients with anaphylaxis by emphasizing early treatment with epinephrine and identifying risk factors for severe and biphasic anaphylaxis. Premedication with antihista-

mines and glucocorticoids may be utilized less to prevent recurrent radiocontrast media anaphylaxis, especially in patients with comorbidities that increase their risk of adverse effects from these premedication agents. These patients would include those with diabetes mellitus who are at high risk for hyperglycemia from high-dose glucocorticoids. On the other hand, premedication may become more standard practice for certain chemotherapy protocols.

DO OTHER SOCIETIES AGREE OR DISAGREE?

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

HOW WILL THE GUIDELINES CHANGE DAILY PRACTICE?

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

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

WHEN DO THE GUIDELINES NOT APPLY?

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

DISCLOSURES

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

REFERENCES


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