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Unilateral pulmonary edema

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Access these episodes and more at clevelandclinic.org/neuropodcast.
Stellate ganglion block as a treatment for vasomotor symptoms: Clinical application

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Susan E. Williams, MS, RD, MD, CDE, FACE, FAND

Common skin signs of COVID-19 in adults: An update

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Samantha Polly, MD; Anthony P. Fernandez, MD, PhD

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Potential systemic benefits of shocking or blocking nerves

While hormone therapy is demonstrably effective for vasomotor symptoms for the vast majority of perimenopausal and postmenopausal women, for some patients it is not an acceptable choice. In this issue of the Journal, Lee et al discuss stellate ganglion block (SGB), the guided percutaneous injection of anesthetic to relieve vasomotor symptoms, as an alternative in women for whom estrogen replacement is not a good option or has failed along with other approaches to provide adequate symptom control.

Studies supporting the efficacy of SGB are fairly small and of short duration. The reported efficacy varies, perhaps indicating a need for patient selection criteria, and perhaps indicating a significant dependence on the skill of the proceduralist. My takeaway is that this is a potential niche therapy for women with few options to control their significant vasomotor symptoms and improve quality of life.

Digging deeper into the topic of nerve manipulation therapies brings to light fascinating heretofore fringe literature on this and other conceptually related approaches of neuromodulation. There are reports of SGB benefitting patients with various upper extremity and facial pain syndromes including migraine. Preclinical research has suggested that nerve fibers connect this sympathetic nerve way station to parts of the brain including the hypothalamus, potentially influencing the impact of hormones on the stress response and the immune system. Isolated reports suggest benefit of SGB in diverse syndromes including posttraumatic stress disorder, dysautonomia, and long-haul COVID-19. If true, the mechanism is likely far more complex than simply blocking regional sympathetic outflow to modulate regional vasoconstriction and dilation. SGB is used to treat other conditions and is featured on the websites of several medical centers.

What has really caught my attention is the expanding research on controlled regional neuromodulation and its impact on systemic physiology and inflammation. Using electrical current to directly affect function of nerve and muscle is well accepted and at least conceptually understandable (eg, electroconvulsive therapy for depression, deep brain stimulation for Parkinson disease, cardiac pacemaker and defibrillator input for heart rhythm control). It is far less readily conceptualized how nerve stimulation can exert effects on systemic inflammation and the immune response.

But fascinating are the studies on stimulating (not blocking as is done with SGB) the vagal nerve, which can be done percutaneously. Several distinct animal models, involving different organs and inflammatory triggers, have been used to demonstrate systemic anti-inflammatory effects stemming from stimulation of the vagal nerve and some of its branches. One hypothesis with some experimental support explains this effect via vagal stimulation of the splenic nerve, which causes acetylcholine release in the spleen. The acetylcholine binds to receptors on macrophages and likely other cells, resulting in downregulation of inflammatory cytokines such as tumor necrosis factor, and also in altered cell circulation.

A recent open-label study in human patients with rheumatoid arthritis receiving

doi:10.3949/ccjm.89b.03022
percutaneous vagal nerve stimulation generated promising (though very preliminary) beneficial results using well-accepted clinical, laboratory, and imaging techniques. Larger studies in patients with rheumatoid arthritis are ongoing. A seemingly successful site for percutaneous stimulation is the external ear, where there are branches of the vagal nerve, making this a far more accessible and acceptable approach compared with direct activation of the vagal trunk as used in some animal studies.

While I am not yet ready to accept that the electromagnetic aura of body magnets and copper bracelets may replace methotrexate, it is provocative to wonder whether controlled neuromodulation may in the future provide a useful nonpharmacologic adjunct to the treatment of pain and inflammation. A better understanding of it may even help explain some of the beneficial effects of acupuncture, a procedure that has also in some studies reduced menopausal hot flashes.

Brian F. Mandell, MD, PhD
Editor in Chief

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This course will provide up-to-date reviews of management strategies and research on the complications of diabetes. Key topic areas that will be addressed include a review of therapeutic options to manage both type 1 and 2 diabetes and their complications, including a pump update, smart pens review, continuous glucose monitoring interpretation and use in the hospital, importance of obesity management vs diabetes control, hypertension goals and management, new roles for GLP1 agonists and SGLT2 inhibitors, diabetes and pregnancy in type 1 and type 2 diabetes, and treatment of hypoglycemia. New this year is a discussion of bariatric surgery in patients with COVID-19 and use of stem cell therapy to treat type 1 diabetes and fatty liver and other ectopic fat problems. The goal of this symposium is to increase practitioners’ competence and clinical performance to treat diabetes and its complications and, ultimately, to improve patient outcomes.

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A 48-year-old man was transferred to our hospital for dyspnea. Although he had no significant medical history, he had been hospitalized for COVID-19 at a local healthcare facility 1 month earlier. Three weeks after discharge from that facility, he noted progressively worsening exertional dyspnea and fatigue. He returned to that facility, where he was afebrile at presentation and was diagnosed with bacterial pneumonia secondary to COVID-19 infection based on chest radiography and computed tomography that revealed a unilateral consolidation in the right lung and an inexplicable enlargement of the heart (Figure 1).

On admission to our facility, he presented with the following vital signs:
- Pulse rate 120 beats per minute
- Body temperature 36.1°C (96.9°F)
- Respiratory rate 24 breaths per minute
- Oxygen saturation 91% on oxygen delivered by nasal cannula at 2 L per minute.

Physical examination revealed mild right jugular venous distention and mild pitting edema of the lower extremities. Coarse crackles were noted in the right lung, but no abnormal heart sounds were documented.

Although electrocardiography was unremarkable except for sinus tachycardia with no ST-segment or T-wave abnormalities, we considered heart failure in the differential diagnosis given his findings on physical examination and imaging. Transthoracic echocardiography revealed diffuse left ventricular hypokinesis with an ejection fraction of 20% and moderate mitral regurgitation toward the posterior left atrial wall. Additionally, his serum N-terminal pro-
brain natriuretic peptide level was 6,469 pg/mL (reference range, 0–125 pg/mL). The patient was diagnosed with congestive heart failure and was placed on intravenous furosemide, nitrates, and noninvasive positive pressure ventilation. Initial therapy dramatically improved his dyspnea and chest radiograph within 72 hours after admission without the use of antibiotics (Figure 2). The patient made a full recovery and was discharged on hospital day 11.

### UNILATERAL PNEUMONIA WITH COVID-19

Approximately 1 out of every 10 patients with COVID-19 pneumonia presents with unilateral—as opposed to bilateral—pneumonia. Generally, one would consider viral or secondary bacterial pneumonia as the most likely diagnosis when a patient presents with unilateral consolidations on chest radiography. However, cardiogenic pulmonary edema accounts for 2.1% of unilateral pulmonary edema.

On imaging, cardiogenic pulmonary edema generally appears as an opacity involving the right lung and is frequently attributed to severe mitral regurgitation. The direction of the mitral regurgitation toward the posterior left atrial wall could selectively impede the right pulmonary venous system, and the regurgitant flow may focally elevate the pressure in the right pulmonary vein. Our patient had retrograde blood flow toward the posterior left atrial wall. However, we could not confirm “severe” mitral regurgitation. Other factors that would affect the distribution of pulmonary edema include decubitus position of the patient (gravitational effect), position of the pulmonary veins, and preexisting lung disease.

When encountering unilateral lung consolidations on chest imaging during the COVID-19 era, one should avoid the common pitfall of hastily attributing the finding to COVID-19 and instead should consider the full spectrum of differential diagnoses, including cardiogenic pulmonary edema.

### 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


Maybe. A detailed clinical history should be obtained directly from patients to determine their risk of penicillin allergy. Those deemed at low risk may not require a formal allergy evaluation. The recently validated PEN-FAST penicillin allergy clinical-decision rule\(^1\) may be useful for clinicians of all specialties to direct appropriate strategies and, for some patients, to potentially remove the “penicillin allergy” label from their medical record.

**HOW COMMON IS PENICILLIN ALLERGY?**

Beta-lactam antibiotics, which include the penicillins, are among the safest and most effective antibiotics and are widely used. However, 5% to 10% of the US population has reported allergies to penicillins, with a higher prevalence in older and hospitalized patients.\(^2\) Patients with a documented penicillin allergy are more likely to receive alternative broad-spectrum antibiotics, which can lead to higher healthcare expenditures, longer hospital stays, higher risk of adverse events, and development of drug-resistant pathogens.

Despite the high frequency of documented allergy, more than 95% of hospitalized patients labeled as having penicillin allergy can actually tolerate this class of drug without adverse reactions.\(^3\) This discrepancy between reported and actual penicillin allergy may be explained by the waning of penicillin-specific immunoglobulin E (IgE) antibodies over time. It is estimated that up to 80% of patients with a history of immediate clinical symptoms compatible with a penicillin allergy become tolerant of it after a decade if there has been no further exposure. After 20 years, fewer than 1% of patients continue to maintain their sensitivity.\(^2\)

Other factors contributing to the discrepancy between reported and clinically relevant allergy may include confounding symptoms related to the patient’s illness, misclassification of adverse reactions, or both. “Unknown” is a frequently documented type of reaction in electronic medical records, as are cutaneous reactions including rash and hives.\(^3\)

Although most patients may be able to tolerate penicillins safely, keep in mind that penicillins are the most common cause of drug-induced fatal and nonfatal anaphylaxis in the United States, particularly when they are given parenterally.\(^4\) As a general rule, IgE-mediated allergic reactions typically occur within minutes after receiving the drug and may present as anaphylaxis, urticaria, bronchospasm, angioedema, or hypotension. Penicillins have also been associated with other severe non-IgE-mediated reactions such as drug reaction with eosinophilia and systemic symptoms and Stevens-Johnson syndrome/toxic epidermal necrolysis.

**WHAT QUESTIONS SHOULD I ASK THE PATIENT?**

Components essential to an allergic history include how long ago the reaction occurred, symptom details, timing of symptom onset, duration of reaction, treatment of the reaction, and use of same or similar medication since. When relevant, concomitant medications, diagnoses, laboratory results, and imaging details should be reviewed.

While allergy specialists widely agree on these components of an allergic history, few decision tools are available for other clinicians to direct appropriate diagnosis and management of penicillin allergy. In addition, obtaining such a history may be difficult in many pa-

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Q: Does my patient need an allergy evaluation for penicillin allergy?

A: Maybe. A detailed clinical history should be obtained directly from patients to determine their risk of penicillin allergy. Those deemed at low risk may not require a formal allergy evaluation. The recently validated PEN-FAST penicillin allergy clinical-decision rule\(^1\) may be useful for clinicians of all specialties to direct appropriate strategies and, for some patients, to potentially remove the “penicillin allergy” label from their medical record.

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While allergy specialists widely agree on these components of an allergic history, few decision tools are available for other clinicians to direct appropriate diagnosis and management of penicillin allergy. In addition, obtaining such a history may be difficult in many pa-
tients who are unable to clearly recall the drug to which they reacted or details surrounding the reaction.

### HOW DO I STRATIFY A PATIENT’S RISK?

After the allergy history is determined, patients can be stratified as being at low, moderate, or high risk for penicillin allergy to determine if skin testing or drug challenge or both are appropriate. To date, there is no universally accepted definition of risk levels. The need for the development of validated tools to support clinical decision-making has been recognized. However, efforts have been limited by the lack of generalizability across various populations and effective implementation strategies.5

The PEN-FAST decision rule

PEN-FAST, a penicillin allergy decision rule, was recently developed to aid clinicians in point-of-care risk assessment.1 A prospective cohort of 622 penicillin allergy-tested patients from 2 primary Australian sites and 3 retrospective cohorts from Australia and the United States were subjected to internal and external validation, respectively. The following features associated with a positive penicillin test were used to create the mnemonic PEN-FAST:

- **PEN**icillin allergy reported (proceed with the assessment below)
- **F**ive years or less since a reaction, or unknown interval (2 points)
- **A**naphylaxis or angioedema, or **S**evere cutaneous reaction (2 points)
- **T**reatment was required for the allergy episode (1 point).1

A score of 0 indicates a very low risk of a positive penicillin allergy test (< 1%), a score of 1 or 2 indicates a low risk (5%), a score of 3 indicates a moderate risk (20%), and a score of 4 or 5 indicates a high risk (50%). A cutoff of less than 3 points was found to have a negative predictive value of 96.3%.1

PEN-FAST has been further validated in a large European cohort of adult patients reporting a reaction with amoxicillin.6 These studies suggest PEN-FAST may be an effective tool for non–allergy-trained clinicians to use in estimating risk in patients across various populations.

### WHAT TESTING IS AVAILABLE FOR EVALUATING PENICILLIN ALLERGY?

Figure 1 outlines our approach for a patient with reported penicillin allergy, starting with risk stratification using PEN-FAST.

A direct or graded amoxicillin challenge under medical observation may be performed in low-risk patients, ie, a PEN-FAST score of 2 or less.3,7,8 Before performing such a procedure, it is essential to obtain informed consent and ensure appropriate monitoring and access to medications used to treat allergic reactions. If no reaction occurs during the observation period, the patient can subsequently take any type of penicillin without restriction. For those with reported allergy to penicillin only, any other beta-lactam (including cephalosporins, carbapenems, and monobactams) can be given as indicated. Drug challenge with the culprit penicillin (if not amoxicillin) is also a reasonable option.

Penicillin skin testing is recommended for patients at moderate or high risk (PEN-FAST score ≥ 3) or with unknown history, current pregnancy, or hemodynamic instability. The skin test is the most reliable way to demonstrate penicillin-specific IgE antibodies. However, it does not predict the risk of non–IgE-mediated reactions or development of IgE-mediated allergic reactions upon future exposures to penicillins. For this reason, skin testing, drug challenge, and desensitization are not recommended in patients with a history of severe delayed reaction such as Stevens-Johnson syndrome-toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, interstitial nephritis, serum sickness, or hemolytic anemia.

Penicillin skin testing is performed using both major and minor antigenic determinants in a stepwise evaluation with percutaneous followed by intradermal testing. Medical providers, including clinicians, advanced practice practitioners, and registered nurses, who have been adequately trained, can perform penicillin skin testing.

Patients who have a positive skin test result are assumed to be allergic to penicillin and should not undergo a penicillin challenge test. However, they can undergo desensitization to penicillin if they truly need it to induce a state
Figure 1. Recommended approach to patients with reported penicillin allergy based on PEN-FAST risk stratification.

**PEN-FAST score** (see text for details)

<table>
<thead>
<tr>
<th>PEN-FAST score</th>
<th>Low or very low risk</th>
<th>Moderate or high risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2</td>
<td>Direct or graded penicillin challenge&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Penicillin skin testing&lt;sup&gt;e&lt;/sup&gt; (percutaneous and intradermal)</td>
</tr>
<tr>
<td></td>
<td>No reaction</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>Continue penicillin avoidance, and use equally effective alternative antibiotics</td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td>Has reaction</td>
<td>Has reaction</td>
</tr>
<tr>
<td></td>
<td>Proceed with full dosing&lt;sup&gt;c&lt;/sup&gt; Delete allergy from patient’s medical record</td>
<td>Direct or graded penicillin challenge</td>
</tr>
<tr>
<td></td>
<td>Consider desensitization performed by an allergist if no appropriate alternative agent exists</td>
<td>No reaction</td>
</tr>
<tr>
<td></td>
<td>Proceed with full dosing&lt;sup&gt;c&lt;/sup&gt; Delete allergy from patient’s medical record</td>
<td></td>
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<sup>a</sup>A drug challenge can be performed by a non-allergist or allergist under medical observation. Informed consent must be obtained from the patient.

<sup>b</sup>For a direct challenge in an adult patient, a single dose of 250 mg of amoxicillin followed by 60 to 120 minutes of observation is a common approach. Graded amoxicillin challenges are often performed by giving one-tenth of the full dose followed by the remaining dose with 30 to 60 minutes of observation between steps. In pediatric patients, amoxicillin challenges are performed using weight-based dosing. Drug challenge with the culprit penicillin could also be considered.

<sup>c</sup>Any type of penicillin can be given without restriction. For those with reported allergy to penicillin only, any other beta-lactam can be utilized as indicated.

<sup>d</sup>Skin testing should be performed only by adequately trained providers.

**THE BOTTOM LINE**

In patients with a reported penicillin allergy, obtaining a detailed allergic history directly from the patient is essential. Clinical-decision tools such as PEN-FAST may be useful to identify patients for whom the penicillin allergy label can be removed without a formal allergy evaluation, thus facilitating optimal antibiotic therapy and reducing drug costs.

**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


Address: Sandra J. Hong, MD, Department of Allergy and Clinical Immunology, Respiratory Institute, A90, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; hongs3@ccf.org
Microangiopathic hemolytic anemia in a female patient with systemic lupus erythematosus

A 34-year-old female patient with a history of systemic lupus erythematosus (SLE) presented to the emergency department after several days of worsening swelling of the lips and legs along with decreased oral intake. She also reported intermittent pleuritic chest pain and exertional dyspnea for the past 2 months.

The patient was previously diagnosed with SLE with cutaneous manifestations including malar rash and discoid lesions of the face and scalp, recurrent pericardial and pleural effusions, diffuse arthralgias, and positive serologic markers including positive antinuclear antibody, anti-dsDNA antibody, anti-Smith antibody, and low complement levels. A previous pericardial pleural effusion resulted in normalization of complement levels with corticosteroid therapy.

Medical history was significant for hypertension, controlled with amlodipine, as well as two unexplained consecutive first-trimester miscarriages and recurrent pulmonary embolism. However, prior investigations were not consistent with antiphospholipid antibody syndrome, with the absence of lupus anticoagulant, anticardiolipin immunoglobulin (Ig)G/IgM, and anti-B2 glycoprotein IgG/IgM on two separate occasions 6 months apart. Her home medications included the anticoagulant rivaroxaban, amlodipine, prednisone, hydroxychloroquine, methotrexate, and folic acid. However, the patient had been nonadherent for the previous 4 months owing to lack of insurance coverage and instead had been trying alternative remedies including herbal tea.

Laboratory testing revealed anemia, thrombocytopenia, and an elevated serum creatinine level of 1.82 mg/dL (increased from baseline of 0.8 mg/dL).

Urinalysis with microscopic examination yielded cloudy appearance with high hemoglobin, red blood cells, protein, granular casts, urine protein-to-creatinine ratio, and urine sediment with dysmorphic red blood cells and red blood cell casts. See Table 1 for laboratory results.

A chest radiograph showed significant increase of the cardiac silhouette compared with previous radiographs.
SOHAIL AND COLLEAGUES

cardiography demonstrated a large pericardial effusion.

**Possible diagnosis**

Patient presentation of new aphthous ulcers, deteriorating kidney function, pancytopenia with lymphocytopenia, and a new large pericardial effusion was suggestive of an active lupus flare. The lip-swelling was also concerning for angioedema, which has been reported as an unusual manifestation of SLE, with the

**TABLE 1**

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient value</th>
<th>Reference range</th>
</tr>
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<tbody>
<tr>
<td>Hemoglobin, g/dL</td>
<td>11.8</td>
<td>12.3–15.3</td>
</tr>
<tr>
<td>Hematocrit, %</td>
<td>36.0</td>
<td>36.0–46.0</td>
</tr>
<tr>
<td>White blood cell count, × 10⁹/L</td>
<td>2.62</td>
<td>3.70–11.0</td>
</tr>
<tr>
<td>Absolute lymphocyte count, × 10⁹/L</td>
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<td>ADAMTS13, %</td>
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**ADAMTS13 = a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13**
HEMOLYTIC ANEMIA

The proposed mechanism being acquired deficiency of C1 esterase inhibitor.1,2

Peripheral smear revealed abundant schistocytes and thrombocytopenia (Figure 1). Other testing showed a reticulocyte index of 0.69% (indicative of hypoproliferation), a negative direct Coombs test, and prothrombin and partial thromboplastin times within normal limits.

At this point, microangiopathic hemolytic anemia (MAHA) was suspected, which is a descriptive term for nonimmune or Coombs-negative hemolysis resulting from intravascular red blood cell fragmentation that produces schistocytes on peripheral blood smear.

Further laboratory test results included low C3, low C4, high dsDNA, positive Critthidia lucillae, negative lupus anticoagulant, negative anticardiolipin IgG and IgM, negative anti-B2 glycoprotein IgG and IgM, low ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) activity, and negative ADAMTS13 inhibitor.

IMPLICATIONS OF HEMOLYTIC ANEMIA WITH THROMBOCYTOPENIA

What is the implication of hemolytic anemia with thrombocytopenia in this patient?

- It may indicate possible development of thrombotic thrombocytopenic purpura (TTP)
- It is related to poorly controlled severe hypertension
- It is attributed to acquired complement-mediated thrombotic microangiopathy (TMA) associated with lupus nephritis
- It is attributed to Shiga toxin-mediated hemolytic uremic syndrome

The combination of characteristic laboratory data in our patient, including negative Coombs test, elevated lactate dehydrogenase (LDH), low haptoglobin, normal coagulation studies, and peripheral smear showing abundant schistocytes, were characteristic for MAHA. The combination with thrombocytopenia and worsening kidney function raised high suspicion for TMA.

TMA is a pathologic diagnosis determined by tissue biopsy in which abnormalities of arteriolar and capillary walls subsequently lead to microvascular thrombosis. As described previously, MAHA refers to Coombs-negative hemolysis resulting from intravascular red blood cell destruction, which may be caused by abnormalities in the microvasculature or even by intravascular devices such as prosthetic heart valves. Consequently, even though not all MAHA is caused by TMA, the diagnosis of TMA can be typically inferred in patients with MAHA and thrombocytopenia in the appropriate clinical setting.

CAUSES OF TMA

TMA syndrome encompasses many disorders that include TTP, Shiga toxin-induced hemolytic uremic syndrome, drug-induced TMA, radiation-induced TMA, and complement-mediated TMA, which is also referred to as atypical hemolytic uremic syndrome.

Systemic disorders that can cause TMA include scleroderma, severe hypertension, pre eclampsia/HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, and antiphospholipid syndrome, especially the most severe form of antiphospholipid syndrome known as catastrophic antiphospholipid syndrome, which is characterized by disseminated intravascular thrombosis resulting in multiorgan failure within a short period of time (usually within 1 week).
Other causes. TMA is also well described in transplant recipients, both as a manifestation of transplant rejection and as possible toxicity from immunosuppressive medications such as cyclosporine and tacrolimus. Rarely, this syndrome can be caused by disorders involving regulators of the coagulation cascade (mutations in the gene encoding diacylglycerol kinase epsilon and thrombomodulin) and the molecules responsible for vitamin \( B_{12} \) metabolism (mutations in the gene encoding methylmalonic aciduria and homocystinuria type C). Evaluation for the cause of TMA should initially focus on excluding the aforementioned systemic disorders associated with MAHA and thrombocytopenia. This should be followed by an investigation to distinguish among primary TMA syndromes, including the following:

- Assessment of exposure to drugs reported to cause TMA: chemotherapeutic agents (eg, gemcitabine, mitomycin), immunosuppressive agents (eg, cyclosporine, tacrolimus), vascular endothelial growth factor inhibitors (eg, bevacizumab), and illegal agents (eg, cocaine)
- Measurement of ADAMTS13 activity and ADAMTS13 inhibitor levels; elevations infer TTP
- Stool testing of Shiga toxin by immunoassay or polymerase chain reaction test to look for Shiga toxin-induced hemolytic uremic syndrome, especially in patients with diarrhea or known infectious diarrhea exposure
- Measurement of serum homocysteine and methylmalonic acid for cobalamin C deficiency-mediated TMA, which is caused by recessive (homozygous or compound heterozygous) mutations in the metabolism of the cobalamin-associated C (MMACHC) gene
- Complement testing for complement-mediated TMA, specifically, for antibodies against complement factor (CF) H protein (anti-CFH antibody) and for complement gene mutations, including evaluation of complement regulatory genes (CFH, CFI, or membrane cofactor protein [CD46]) and complement effector genes (CFB or C3).

Kidney biopsy is not helpful for determining cause of primary TMA syndromes and may not distinguish primary TMA syndromes from other disorders such as systemic sclerosis or severe hypertension, which can also manifest the typical pathologic features of TMA.

What was the cause of this patient’s TMA?

TTP is a primary TMA syndrome caused by severely reduced activity of the von Willebrand factor-cleaving protease ADAMTS13. When ADAMTS13 protease activity is reduced, large von Willebrand factor multimers can accumulate on the endothelial surface of small arterioles and capillaries, leading to potentially fatal platelet accumulation and subsequent mechanical red blood cell fragmentation. TTP can be acquired, from an autoantibody inhibitor to ADAMTS13, or it can be hereditary, owing to inherited mutations in ADAMTS13. Genetic testing of the ADAMTS13 gene is the definitive means of documenting the diagnosis of hereditary TTP in an individual with severe ADAMTS13 deficiency (activity < 10% of normal) without an inhibitor. On the other hand, acquired TTP can be confirmed by severe ADAMTS13 deficiency and the presence of an ADAMTS13 autoantibody inhibitor in the appropriate clinical setting (eg, a patient with MAHA and thrombocytopenia that responds to plasmapheresis). Hematologic recovery in TTP can be expected with plasmapheresis, as indicated by improvement in LDH (often within 1 day) and platelet count (within 2 to 3 days). TTP was ruled out in our patient on the basis of relatively normal ADAMTS13 activity, a negative ADAMTS 13 inhibitor, poor hematologic response to emergency plasmapheresis, and lack of hematologic recovery to suggest resolution of MAHA after 3 days of plasmapheresis.

Severe hypertension can also cause MAHA and thrombocytopenia with characteristic pathologic features of TMA in the kidneys. Grade III/IV retinopathy is more likely to be present, and recovery of kidney function and resolution of MAHA is typical with proper treatment of severe hypertension. Furthermore, severe hypertension may also occur in...
HEMOLYTIC ANEMIA

Plasma exchange was started without positive results; eculizumab was administered for suspected complement-mediated thrombotic microangiopathy.

primary TMA with severe renal involvement, so the temporal relationship is important. Although the patient did have funduscopic findings consistent with grade III hypertensive retinopathy, kidney function and MAHA did not improve despite appropriate management of blood pressure, prompting us to continue our investigation into other causes of TMA.

Shiga toxin-producing pathogens (eg, Escherichia coli O157:H7) can induce hemolytic uremic syndrome and are often related to exposure to improperly prepared foods, inadequately cooked meats, or farm animals. However, our patient did not report any severe abdominal pain or diarrhea with bloody stool, and DNA testing performed on the patient’s stool sample for Shiga-toxin genes was negative. Additional workup investigating non-Shiga-toxin-producing infectious organisms associated with MAHA and thrombocytopenia was also unrevealing, including tests for bacterial (eg, Clostridoides difficile, Legionella), viral (eg, cytomegalovirus, hepatitis viruses, human immunodeficiency virus, varicella-zoster virus, Epstein-Barr virus), and fungal (eg, Aspergillus) infections.

Complement-mediated TMA or atypical hemolytic uremic syndrome is a chronic, systemic, life-threatening disease characterized by TMA and severe multiple end-organ damage caused by dysregulation and uncontrolled activation of the alternative complement pathway. Complement regulatory proteins, including CFH, CFI, and CD46, prevent inappropriate activation of the complement cascade. The diagnostic workup for determining cause of complement-mediated TMA includes testing for inhibitory antibodies such as anti-CFH antibody, as well as genetic testing, including evaluation of the CFH, CFI, CD46, CFB, and C3 genes. On the other hand, testing for serum complement biomarkers such as CH50, C3, and C4 have no diagnostic role in complement-mediated TMA owing to low sensitivity and specificity. For instance, a low C3 level may only be appreciated in certain mutations such as variants in CFH, CFB, and C3.

Complement activation is also common in lupus nephritis, and a subset of these patients (17.5%) can present with complement-mediated TMA, described as a separate clinical entity that can be resistant to treatment with high-dose corticosteroids, immunotherapy, and plasmapheresis. The pathogenesis of renal TMA in lupus nephritis is yet to be determined and may be multifactorial, potentially attributable to antiphospholipid syndrome, malignant hypertension, or scleroderma.

Our patient had normal plasma levels of complement factors CFH and CFB, along with negative anti-CFH antibody. Complement genetic studies were not obtained, and the patient did not report a family history of TMA disorders suggestive of a hereditary cause. However, one should be mindful that most complement mutations associated with TMA are heterozygous, and many family members with heterozygous mutations are asymptomatic. If performed in this patient, complement genetic studies might have provided a more specific diagnosis.

Although complement testing was unrevealing in this patient, a presumptive clinical diagnosis of complement-mediated TMA was made in light of the progressive kidney dysfunction, MAHA, thrombocytopenia, and absence of an alternate explanation for these findings (eg, no known drug exposure associated with drug-induced TMA, no antiphospholipid syndrome or scleroderma, no response after adequate control of hypertension, no ADAMTS13 deficiency, no Shiga toxin in stool).

CASE CONTINUED: CONDITION WORSENED

The differential diagnosis for the patient’s acute kidney failure included lupus nephritis and TMA.

Plasmapheresis was performed for a total of 3 days, with no clinical improvement. Then, administration of eculizumab, a complement inhibitor, was commenced in light of the suspected diagnosis of complement-mediated TMA.

C5 inhibitors, including eculizumab and ravulizumab, prevent the cleavage of cell surface-bound complement protein C5 and inhibit generation of proinflammatory terminal complement proteins C5a and the membrane attack complex C5b-9, consequently reducing endothelial cell activation and thrombosis but also increasing the risk of developing menin-
cerebrospinal fluid, rendering an intrathecal infection less likely as the etiology of the patient’s acute encephalopathy and favoring the diagnosis of neuropsychiatric lupus.

**Acute kidney injury.** The patient’s kidney function continued to deteriorate, requiring kidney replacement therapy within 5 days of initial presentation to the hospital. Kidney biopsy was considered at this time but was ultimately not performed due to severe thrombocytopenia.

### WOULD KIDNEY BIOPSY HAVE HELPED?

*2 What would have been the value of kidney biopsy in this patient?*

- It would have been helpful in differentiating a specific type of TMA
- It would have been unlikely to affect patient management, as the therapeutic window was missed early in the disease course because of bleeding concerns related to thrombocytopenia
- It would have ascertained the extent of ischemic injury sustained in relationship to renal TMA to facilitate decision-making regarding next steps in therapy
- It was contraindicated in this patient owing to increased risk of bleeding complications from azotemia and thrombocytopenia

### Risk vs potential benefit of biopsy

Biopsy of the kidney may be performed for suspected TMA syndrome. However, kidney biopsy may not inform treatment decisions for a specific TMA as there is no consensus regarding features on kidney biopsy that definitively diagnose a specific TMA syndrome. Kidney biopsy is not usually done to evaluate patients with acute kidney injury, MAHA, and thrombocytopenia unless there is a specific management decision that would be influenced by the results.

Our patient’s clinical condition was an example of a situation in which a kidney biopsy may have been helpful: it may have identified the extent of ischemic injury sustained in relationship to potential TMA, as well as the degree of irreversible kidney injury to support decision-making for next therapeutic treatment steps. Kidney biopsy may have justified the maintenance or discontinuation of immunosuppressive therapy for lupus nephritis, especially as the patient had not yet developed other systemic manifestations of SLE (eg, pericardial effusion, neuropsychiatric SLE) at the time kidney biopsy was being considered. The presence of extensive interstitial fibrosis or glomerulosclerosis (class VI advanced sclerosis lupus nephritis), as opposed to focal or...
HEMOLYTIC ANEMIA

The patient was discharged to a rehabilitation facility on immuno-suppressive therapy with cyclophosphamide.

diffuse proliferative glomerulonephritis (class III and IV lupus nephritis, respectively), might have prompted discontinuation of immunosuppression.

Although the association between kidney dysfunction and bleeding is well recognized, major complications have been noted to be less than 1%.22 Our patient did not undergo kidney biopsy owing to persistent thrombocytopenia, as thrombocytopenia increases the risk of major complications with kidney biopsy in patients with SLE.23

SUBSEQUENT CLINICAL COURSE

Intravenous methylprednisolone and mycophenolate mofetil were initially employed as induction therapy for lupus nephritis. Mycophenolate mofetil was preferred over cyclophosphamide because mycophenolate mofetil has been shown to be more effective than intravenous cyclophosphamide in inducing remission of lupus nephritis.24 The patient’s race was a consideration as it has been demonstrated that African American patients with lupus nephritis respond better to mycophenolate mofetil than to intravenous cyclophosphamide (53.9 vs 40%; \( P = 0.39 \)).25

However, concern for neuropsychiatric SLE with antibody-mediated striatal encephalitis later prompted the discontinuation of mycophenolate mofetil in favor of cyclophosphamide, as cyclophosphamide is the only therapy that has demonstrated efficacy for neuropsychiatric SLE compared with methylprednisolone in a controlled clinical trial.26

Although high-dose glucocorticoids and intravenous cyclophosphamide remain the cornerstone for patients with neuropsychiatric SLE, rituximab or intravenous immunoglobulin may be used if response is not achieved.27 Furthermore, even without studies regarding efficacy of plasmapheresis in patients with lupus antibody-mediated striatal encephalitis, there is some evidence regarding its use in severe neuropsychiatric SLE.28,29 Consequently, plasmapheresis was briefly performed together with administration of cyclophosphamide, with subsequent improvement in the patient’s mental status.

Although the hemolytic anemia and thrombocytopenia resolved after 6 weeks of therapy with eculizumab, the patient’s kidney function did not recover for more than 2 months during hospitalization. Eventually the decision was made to stop eculizumab and continue immunosuppressive therapy with cyclophosphamide upon discharge to a rehabilitation facility. Although the patient did not undergo kidney biopsy to guide therapy, the rationale for continued treatment with immunosuppressive therapy at discharge was owing to evidence of other systemic manifestations of SLE during the course of hospitalization, including pericardial effusion and lupus antibody-mediated striatal encephalitis.

WHICH MANAGEMENT STRATEGY?

Which management strategy has been shown to improve kidney outcomes in patients with complement-mediated TMA associated with SLE?

- Therapeutic plasma exchange
- Immunosuppressive therapy specific for lupus nephritis
- Complement-inhibiting therapy with eculizumab
- Supportive management with red blood cell and platelet transfusions

Therapeutic plasma exchange

The immediate management decision for a patient with suspected TMA is whether to perform plasma exchange for a presumptive diagnosis of TTP or anticomplement therapy for a presumptive diagnosis of complement-mediated TMA.

Plasma exchange should be initiated in adults as soon as diagnosis of TMA is suspected. This helps remove ADAMTS13 autoantibodies, factor H autoantibodies, and hyperfunctioning complement components as well as replaces ADAMTS13 and faulty complement regulators.21

Immunosuppressive therapy specific for lupus nephritis

Unfortunately, TMA associated with lupus nephritis is usually refractory to treatment with corticosteroids, cyclophosphamide, immunomodulation, and plasma exchange.30,31 However, a 2018 series involving patients with complement-mediated TMA related to
SLE reported complete recovery of hematologic parameters in all patients and recovery of kidney function in 80% of patients treated with eculizumab.16

Complement inhibition with eculizumab or ravulizumab

Initial evidence for the efficacy of eculizumab for treating TMA came from a prospective, open-label case-series32 of patients with complement-mediated TMA in which eculizumab improved kidney and hematologic outcomes and reduced thrombotic microangiopathic events including requirement for plasma exchange or infusion, reduction in platelet counts, and initiation of hemodialysis.32

Although C5 inhibitors including eculizumab and ravulizumab are currently the only effective therapy designed to prevent the underlying mechanism of microvascular damage, which is dysregulation of the complement activation system, there are limited data on long-term outcomes in patients with TMA treated with terminal complement inhibition. There are also several unanswered questions regarding C5 inhibitor therapy, including optimal duration of therapy, appropriate strategies for monitoring therapeutic efficacy in patients with suboptimal response or during periods of infection or inflammation, and determining tailored therapeutic regimens in various groups of patients with TMA, including those with complement-mediated TMA.

At Cleveland Clinic, eculizumab therapy has been used broadly, not only for clinically suspected complement-mediated TMA, but also for other TMA syndromes. Owing to the lack of available information regarding management decisions for patients with TMA, investigation into management strategies for these patients is warranted as is research regarding kidney and hematologic outcomes after therapy.

■ TAKE-HOME POINTS

• Suspect complement-mediated TMA in patients with MAHA in whom other causes including TTP, antiphospholipid antibody syndrome, Shiga toxin-induced hemolytic-uremic syndrome, and uncontrolled hypertension have been excluded.

• Kidney biopsy does not help identify a specific type of TMA and therefore does not inform treatment decisions for specific TMA syndromes. However, kidney biopsy may assist in evaluating the extent of ischemic injury sustained in relation to TMA and thus may characterize the degree of irreversible kidney injury and facilitate decision-making regarding next therapeutic steps, especially in cases that are refractory to C5 inhibitor therapy.

• C5 inhibitors, including eculizumab and ravulizumab, currently represent the only effective therapy designed to prevent the underlying mechanism of microvascular damage in complement-mediated TMA, which is dysregulation of the complement activation system. However, data are limited on long-term outcomes in patients with TMA treated with terminal complement inhibition.

■ DISCLOSURES

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

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Breast cancer (BC) is the most commonly diagnosed cancer in women in the United States and the second most common cause of female cancer deaths.1 As such, many female patients present to primary care physicians for further guidance regarding their concerns and risks of developing BC. Risk assessment involves a significant amount of time to complete with many available risk calculation models, all of which have varied limitations.2–5

However, a personalized risk assessment for BC should be performed, to some degree, in all female patients using a combination of risk calculators and obtaining a complete medical history of BC risk factors. Approaching patients systematically; gathering basic information such as age, body mass index (BMI), family BC history, reproductive risk factors; and gathering specific risk factors such as known genetic mutations, prior chest radiation, or history of atypical hyperplasia or lobular carcinoma in situ (LCIS) can help determine which patients need more formal and in-depth evaluation. This can be undertaken by the primary care clinician or a high-risk BC specialist and lead to shared decision making regarding screening and risk-reduction strategies. Some patients need not undergo extensive BC risk calculation if already considered high risk. It is prudent to consider the patient’s personal values, individual risk factors, as well as differences in BC screening recommendations by societies and organizations (American Cancer Society [ACS], American College of Obstetrics and Gynecology, National Comprehensive Cancer Network [NCCN], and United States Preventative Services Task...
BREAST CANCER RISK EVALUATION

Force [USPSTF]). When individual risk is better understood, timing for appropriate initiation of screening, frequency of screening, implementation of lifestyle modifications for prevention, as well as recommendations for risk-reducing medications can be determined.

Patients who are found to be of high risk for BC, defined as an overall lifetime risk greater than 20%, are also candidates for enhanced BC screening. The ACS recommends that patients with elevated risk (based on family history risk calculations such as those from the International Breast Cancer Intervention study [IBIS]) should undergo annual magnetic resonance imaging (MRI) breast screening in addition to annual mammography, although this recommendation is not currently supported by USPSTF.

Recent American Society of Clinical Oncology, IBIS, and USPSTF recommendations, support the use of risk assessment to determine benefit of certain endocrine therapies (eg, tamoxifen, raloxifene, anastrozole) for postmenopausal female patients with one or more of the following: diagnosis of atypical (ductal or lobular) hyperplasia or LCIS, an estimated 5-year risk (National Cancer Institute [NCI] Breast Cancer Risk Assessment Tool [BCRAT]) ≥ 3%, 10-year risk (IBIS/Tyrer-Cuzick risk calculator) ≥ 5%, or relative risk of ≥ 4 times the population risk for their age group if 40 to 44 years old, or > 2 times the population risk if 45 to 69 years old. Despite consistent national guidelines, less than 4% of candidates for endocrine therapy are currently prescribed these medications.

In this article, we review BC risk factors, determinants of risk, and a pragmatic systematic approach to manage patients in the primary care setting.

■ KNOWN BREAST CANCER RISK FACTORS

Gene mutations/hereditary breast and ovarian cancer genetic syndromes

Approximately 8% to 10% of BCs are attributed to mutations in cancer susceptibility genes; more than 50% of germline mutations can be attributed to BRCA1 and BRCA2 mutations followed by mutations in genes such as checkpoint kinase 2 (CHEK2), ataxia-telangiectasia mutated (ATM), and partner and localizer of BRCA2 (PALB2). Despite the minority of BCs being attributable to genetics, BC attributable to mutations can be more lethal, and genetic counseling with discussion of genetic testing should be offered and available to patients with a significant family history of BC and/or ovarian cancer or known familial gene mutations, and in whom identifying a potential genetic mutation may change assessment and management options.

For instance, patients with BRCA1 and BRCA2 should seriously consider surgical options for risk reduction, whereas BC from mutations in genes such as ATM, CDH1, CHEK2, NBN, NF1, PALB2, or STK11 can be followed by enhanced screening with breast MRI in conjunction with mammography although this recommendation is not currently supported by USPSTF.

There are other gene mutations (such as BARD1, MSH2, MLH1, MSH6, PMS2, EPCAM, BRIP1, RAD51C, RAD51D) without clear evidence supporting increased lifetime risk of BC, and thus guidelines for screening in these populations are unclear at this time.

History of high-risk breast lesions

Atypical hyperplasia, which includes atypical ductal hyperplasia and atypical lobular hyperplasia as well as LCIS are characterized by dysplastic proliferation of epithelial mammary cells and differentiated based on histologic patterns and cytology seen on pathology. These patterns are significant risk factors for BC. Atypical hyperplasia is identified in around 10% of all benign breast biopsies.

In the Mayo Benign Breast Disease Cohort and the Nashville Breast Cohort, incidence of BC in patients with atypical hyperplasia without chemoprevention was found to be around 1% to 2% per year with a cumulative incidence of BC of 30% at 25 years. Younger age at diagnosis of atypical hyperplasia is associated with increased likelihood of developing BC, as is increased foci of atypical hyperplasia on pathology.

LCIS is associated with an increased risk of BC to varying degrees from 3- to 8-fold higher risk when compared with the general population, regardless of whether the primary lesion has been removed. Using data from the National Surgical Adjuvant Breast and Bowel Project P-1 Study, it was found that there was a 1.3% annual risk of development of invasive BC among patients with LCIS.
Personal history of thoracic radiation
Ionizing radiation is a recognized risk factor for development of BC; this has been observed in the past in people exposed to atomic explosions such as Hiroshima or Nagasaki as well as in patients exposed to radiation treatments for diseases such as Hodgkin disease. Risk is inversely associated with age at radiation exposure and increased in women exposed to radiation before age 20 years compared with patients without a history of exposure. Personal risk in these patients has been shown to be as high as 56.7-fold greater than in the general population.

Mantle radiation therapy is a form of extended field radiation and refers to radiation therapy that is administered to the mantle field that encompasses lymph nodes in the neck, chest, mediastinum, and axillary regions with the breast receiving about 3% to 15% of the administered dose.

Most studies demonstrate increased BC risk 10 to 15 years following radiation treatment with development of secondary BC being rare within 10 years of treatment. Current guidelines recommend that patients who underwent thoracic radiation treatment between the ages of 10 and 30 begin annual screening MRI in addition to mammogram beginning 8 to 10 years after undergoing radiation treatment.

Age/menopause
As more risk factors associated with BC are discovered, age remains one of the most significant. BC is most frequently diagnosed among women ages 65 to 74 with median age of diagnosis at 63. Based on data from 2015 to 2017, 12.9% of women will receive a diagnosis of BC at some point during their lifetime. Age-related BC risk according to the NCI Surveillance, Epidemiology, and End Results database between 2013 and 2017 shows increasing risk associated with each decade increase (Table 1).

Breast density
Dense breast tissue is very common, with 35% to 50% of the population being categorized as having dense breast tissue based on American College of Radiology Breast Imaging Reporting and Database System scoring. Increased breast density has been shown to be an independent risk factor for the development of BC. The presence of extremely dense breast tissue on mammogram purports a 4- to 6-fold increase in BC risk compared with almost entirely fatty breast tissue. Owing to this significantly increased risk, breast density has been added to the most recent IBIS risk calculator and has been shown to increase accuracy of the model. In addition to increased BC risk with increased density, mammographic sensitivity is significantly decreased; therefore, consideration of density as a component of risk, particularly in patients with other risk factors, is important.

First-degree relatives with breast cancer
Family history is a well-recognized risk factor for development of BC. A first-degree relative (eg, mother, sister, daughter) with BC increases an individual’s relative risk of developing BC to 1.7 when compared with patients without an affected first-degree relative; this relative risk increases to 5 when two first-degree relatives are affected. Risk is further increased with younger age of diagnosed family members.

The risk ratio for BC was analyzed on the basis of number of first-degree relatives being affected, with a risk ratio of 1.80 (99% floated confidence interval [FCI] 1.69–1.91) for patients with one affected first-degree relative having BC, 2.93 (99% FCI 2.36–3.64) for patients with two first-degree relatives, and 3.90

### Table 1

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<th>Age range (years)</th>
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Data from reference 16.
Breast cancer risk evaluation (99% FCI 2.03–7.49) for patients with three or more first-degree relatives. Overall, 12.9% of patients with BC reported having at least one first-degree relative having BC whereas 7.3% of controls reported having at least one affected first-degree relative. Thus, while having a family history of BC in at least one first-degree relative increases BC risk, most patients with a family history of BC will not go on to develop BC themselves.

Obesity

Obesity is known to be correlated with increased risk of several malignancies, including BC. The types of BC, namely hormone receptor (HR)-positive or HR-negative BC and the association with obesity can be further stratified by menopausal status. Obese premenopausal patients have not been shown to be at increased risk of HR-positive malignancy; however, they do appear to be at an increased risk of HR-negative/triple-negative and inflammatory cancers.

Obese postmenopausal patients, however, are at a significantly increased risk of HR-positive BC. The Million Woman Study followed 1.2 million women in the United Kingdom and demonstrated a 39% increased risk of HR-positive BC for postmenopausal women with a BMI ≥ 30. Others have demonstrated that increased waist circumference and waist-to-hip ratio are also indicative of an increased risk for estrogen receptor (ER)-positive/progesterone receptor (PR)-positive cancers. Similarly, data from the Women’s Health Initiative Observational Study showed that patients with a BMI > 31.1 had an increased relative risk of postmenopausal BC (relative risk 2.52, 95% CI 1.62–3.93) compared with women with a BMI < 22.6. This association is postulated to be secondary to increased circulating estrogen levels and secondary to peripheral conversion of estrogen precursors to estrogen in adipose tissue despite the menopausal state resulting in decreased estrogen levels. Furthermore, hyperinsulinemia secondary to weight gain may increase growth factors and cytokine activation resulting in a microenvironment favorable to tumor development. Accordingly, postmenopausal obesity is not as clearly associated with HR-negative BC.

Weight loss has been associated with lower BC risk. Weight loss after 18 years as well as after menopause have both independently demonstrated a decrease in postmenopausal BC risk. Additionally, bariatric surgery was shown to reduce BC incidence at 5 years postoperatively. These data can be used to counsel patients regarding current risk, as well as possible incentive to pursue weight loss in the future.

Methods to evaluate risk

Breast cancer risk calculators

Several BC risk calculators exist; however, few are used in clinical practice regularly. The two most commonly used BC risk calculators in the United States—and what we use regularly in our practice—are the National Cancer Institute BCRAT, also known as the Gail Model, and the IBIS/Tyrer-Cuzick Risk Model calculator. Both can be used to identify candidates for risk-reducing medications and for supplemental MRI screening.

The BCRAT (https://bcrisktool.cancer.gov) is validated for patients ages 35 and older in many different populations but is not as useful for patients with a biopsy diagnosis of atypia as it underestimates overall risk. BCRAT can be used to calculate an estimated 5-year and lifetime risk estimate for patients under the age of 85. In contrast to the BCRAT, the IBIS calculator can be used to “qualify” patients for supplemental BC screening with MRI. The IBIS risk assessment tool (http://www.ems-trials.org/riskevaluator) considers reproductive history, body composition, and extensive family history; the most recent version includes mammographic breast density. A 5-year, 10-year, and lifetime risk estimate is available for patients under the age of 85. In contrast to the BCRAT, the IBIS calculator can be used to “qualify” patients for supplemental BC screening with MRI. However, this model tends to overestimate risk for patients with a biopsy diagnosis of atypia, and therefore, should not be used in this population.

In the office setting, the BCRAT model offers a quick estimate of BC risk. However, the IBIS model is more comprehensive and includes a more in-depth family history. There are many models available including Claus, BRCAPRO and BOADICEA models.
A SYSTEMATIC APPROACH TO RISK EVALUATION

There is no standard approach to initiate BC risk assessment in a primary care office setting. We recommend that clinicians periodically reassess BC risk factors, beginning with the patient's initial evaluation. Risk should be re-evaluated if patients have a family history of BC or ovarian cancer, and/or breast biopsy or baseline mammogram that demonstrates dense breast tissue, or if they present with a new diagnosis of cancer in the family. Assessment should include reproductive risk factors, prior high-risk breast lesions, exposure to ionizing radiation, lifestyle (eg, smoking, alcohol, diet, physical activity), and family history of BC or ovarian cancer. Moreover, clinicians should consider high-risk gene testing for individuals with a strong family history of BC or ovarian cancer.

The following table outlines a step-by-step approach to categorize patients who require further stratification vs patients needing referral to breast specialist.

<table>
<thead>
<tr>
<th>High risk</th>
<th>Further stratification needed</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High-risk gene mutation carrier (BRCA1/2, PALB2, ATM, CHEK2, NF1, NBN, PTEN, STK11, TP53)</td>
<td>• Strong family history</td>
<td>• No family or personal history of breast cancer</td>
</tr>
<tr>
<td>• Personal history of</td>
<td>• Age of onset &lt; 50</td>
<td>• No known high-risk gene mutations</td>
</tr>
<tr>
<td>○ Atypical hyperplasia</td>
<td>• Breast and ovarian cancer in family</td>
<td>• Minimal alcohol use</td>
</tr>
<tr>
<td>○ LCIS</td>
<td>• Ashkenazi Jewish</td>
<td>• Normal BMI</td>
</tr>
<tr>
<td>○ Mantle radiation</td>
<td>• TNBC</td>
<td></td>
</tr>
<tr>
<td>• Consider referral to high-risk breast cancer specialist</td>
<td>• Male breast cancer</td>
<td></td>
</tr>
<tr>
<td>• Discuss enhanced surveillance/risk-reducing strategies</td>
<td>• Augmenting factors</td>
<td>• No risk assessment needed</td>
</tr>
<tr>
<td>○ Annual breast MRI</td>
<td>• Increased mammogram density</td>
<td>• Shared decision-making regarding age of onset and frequency of mammography</td>
</tr>
<tr>
<td>○ Risk-reducing medications</td>
<td>• Obesity</td>
<td>• Counsel on lifestyle modification</td>
</tr>
<tr>
<td>○ Prophylactic surgery</td>
<td>• Alcohol use</td>
<td>• Consider supplemental imaging (MBI, US, CEM) for dense breast tissue</td>
</tr>
<tr>
<td>• Calculated risk &gt; 20–25% lifetime risk (using IBIS model)</td>
<td>• IBIS (Tyrer-Cuzick) version 8</td>
<td></td>
</tr>
<tr>
<td>• Calculated BCRAT 5-year risk ≥ 3.0% or IBIS 10-year risk of ≥ 5%</td>
<td>• NCI BCRAT (Gail Model)</td>
<td></td>
</tr>
</tbody>
</table>

Data from references 6, 7, 9, 11, 29, and 31.
Breast Cancer Risk Evaluation

Patients who understand personal risks may have a higher perceived benefit to intervention and are more likely to use risk-reducing treatment. Patients can then be divided into 3 major risk categories, with subsequent evaluation and recommendations appropriate to their level of risk (Figure 1).6,7,9,11,29,31

The first step of evaluation should be to identify patients who have clearly significantly increased risk for BC and who would benefit from a referral to a high-risk BC specialist for counseling and surveillance. This would include patients with a known gene mutation, history of thoracic radiation, personal history of atypical hyperplasia or LCIS on a biopsy, and/or strong family history of breast and ovarian cancer suggestive of a gene mutation. Owing to known increased BC risk for patients with these conditions as well as inaccuracy of models regarding this risk, these patients would likely benefit from consultation with a high-risk BC specialist to determine the type and frequency of BC screening, to discuss options such as prophylactic mastectomy and preventive medications, and to review indications for genetic consultation and testing. It has also been shown that female patients at high risk are more likely to take risk-reducing medications after a referral to medical oncology/high-risk BC specialists.43

In patients without the above-mentioned high-risk factors, we recommend considering other risk factors. The USPSTF recommends applying the use of a risk assessment tool for any female patient with a family history of BC, ovarian, tubal, or peritoneal cancer or ancestral association with BRCA1/2 gene mutations, such as Ashkenazi Jewish heritage.3 Additionally, the American College of Radiation and Society of Breast Imaging have recently published guidelines recommending that African American women undergo risk evaluation with consideration for genetic testing by the age of 30 years,44 including a discussion on supplemental screening with breast MRI for risk evaluation of all patients.44

For all patients, cancers on both maternal and paternal sides should be included in the history with special attention to BC at a young age and particular subtypes such as triple negative BC, BC in male family members, cancers in multiple sites. NCCN guidelines have been expanded to include family history in first- and second-degree relatives and potentially include extensive involvement of third-degree relatives. Additional risk factors discussed above can potentially augment that risk. Patients at higher risk could benefit the most from undergoing more formal BC risk stratification using the many validated BC risk assessment tools discussed above.

For patients who do not have significant family history but are found to have a higher-risk lifestyle (eg, obesity, smoking, excessive alcohol use), extensive risk evaluation with use of risk calculators is not necessarily needed. But these patients would clearly benefit from counseling regarding mitigation of these risk factors and reducing BC risk.

Some patients will come without any significant family history of BC or ovarian cancer and without significant lifestyle factors that contribute to BC risk. In this situation, no further risk stratification is indicated. We do recommend discussing society guidelines for BC screening in patients with average risk and using a shared decision-making approach to determining at what age and frequency patients undergo BC screening.

In conclusion, a systematic approach to risk assessment will allow the primary care clinician to identify female patients at high risk for BC and provide an opportunity for shared decision making regarding screening, enhanced screening, referrals to a specialty clinic, genetic counseling, and counseling on risk-reduction strategies including lifestyle modifications and risk-reducing medications. With knowledge and understanding of personal risks, patients may have a higher perceived benefit to intervention and are more likely to use risk-reducing treatment.43

Disclosures
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Stellate ganglion block as a treatment for vasomotor symptoms: Clinical application

ABSTRACT

VASOMOTOR SYMPTOMS (VMS), also called hot flashes, hot flushes, and night sweats, are common symptoms of menopause. They are described as moments of intense heat, usually accompanied by sweating and flushing in the upper body, including the head, neck, and upper torso, and they are associated with poor health outcomes and decreased quality of life. While hormonal therapies are the mainstay of treatment for VMS, there is a clear need for safe and effective nonhormonal treatment options for women who choose not to use hormone therapy and for those in whom hormone therapy is not effective.

The authors first review current hormonal and nonhormonal therapies, then review evidence supporting the potential use of stellate ganglion block for managing vasomotor symptoms in perimenopausal and postmenopausal women.

KEY POINTS

Stellate ganglion block is a well-established treatment for pain.

Data indicate that stellate ganglion block reduces the frequency of vasomotor symptoms by 4% to 90%, with few adverse events.

Stellate ganglion block is currently recommended with caution owing to a lack of long-term clinical trial data on efficacy and safety.

THE EPIDEMIOLOGY OF VASOMOTOR SYMPTOMS

Approximately 60% to 80% of women experience VMS during the menopause transition, which averages 7 to 9 years, although some continue to have VMS in their 70s and 80s. These symptoms can be associated with a decrease in quality of life, often manifested as sleep disturbance, depression, and even mental exhaustion.

Demographic and socioeconomic factors can affect VMS frequency and intensity. The Study of Women Across the Nation revealed that Black women have the highest prevalence...
and longest duration of VMS and are the most bothered by the symptoms. Women in lower socioeconomic positions were more likely to experience VMS. Also, those with a history of abuse or neglect, depression, anxiety, smoking, and early premenopausal onset of VMS have more severe and longer lasting VMS.7

Menopause-related symptoms also have a financial cost. Direct costs to the patient often lead to higher annual costs than other medical concerns in women in midlife.8 A 2015 article reported that healthcare costs for women with VMS were $1,346 higher than for their VMS-free counterparts, and women with VMS experienced lower productivity, with an indirect cost via work absenteeism, costing roughly $770 per year.9

■ TREATMENTS FOR VASOMOTOR SYMPTOMS

The most effective treatment for VMS is hormone therapy, either estrogen alone or combined with a progestogen.10 A Cochrane systematic review found that this therapy reduces the frequency and intensity of hot flashes associated with VMS by 75% to 79%.11 Hormone therapy has also been shown to be highly effective in early postmenopausal women.12 However, some women with VMS cannot use or choose not to use hormone therapy. Health conditions that are considered relative or absolute contraindications to hormone therapy include breast cancer, uninvestigated endometrial hyperplasia, hormone-responsive gynecologic cancers, unprovoked venous thromboembolism or thrombophilia, decompensated liver disease, myocardial infarction, stroke, and dementia.10

Nonhormonal options

A number of nonhormonal therapies for VMS are available.13 Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors have been shown to reduce the frequency and severity of VMS in menopausal women.13,14 Specifically, paroxetine (the only nonhormonal medication for VMS approved by the US Food and Drug Administration), citalopram, and escitalopram have been shown to be effective and at lower doses than when used for anxiety and depression.14 Possible adverse effects include nausea and constipation, but these are less likely given the lower dose required to treat VMS.

Of note, women with a history of breast cancer who are also taking tamoxifen should not be prescribed SSRIs that inhibit CYP2D6 (eg, paroxetine, fluoxetine) because they can interfere with tamoxifen metabolism.14 Clonidine and gabapentin have also been shown to be effective in reducing VMS.15,16 Clonidine is limited in clinical use owing to a number of undesirable side effects such as weight gain, blurred vision, constipation, and orthostatic hypotension, and its modest rate of symptom improvement.17 Gabapentin may be most effective at treatment of nighttime symptoms since it can cause sleepiness. Oxybutynin, an antimuscarinic drug, has been found to be effective at reducing self-reported VMS frequency, with mild anticholinergic side effects such as dry mouth, constipation, and drowsiness.18 Neurokinin-3 receptor antagonists have also shown promise as nonhormonal therapy for VMS.19

Nonpharmaceutical options. The North American Menopause Society recommends the use of cognitive-behavioral therapy and hypnosis as evidence-based nonpharmacological options for VMS.13 Other options that have potential efficacy but lack definitive evidence include acupuncture20,21 and lifestyle changes such as wearing layered clothing, staying in cool atmospheres, and exercising.13,22 Herbal remedies and vitamin supplements (eg, black cohosh, vitamin E) have not been shown to be more effective than placebo.23 At present, there are more than 70 ongoing clinical trials of various treatments for VMS.24

■ STELLATE GANGLION BLOCK

SGB involves blockade of the sympathetic ganglia in the lower cervical and upper thoracic region using an anesthetic agent. It may also have a modulatory role in thermoregulatory areas of the brain.25

A range of indications

For more than 50 years, SGB has been a standard treatment for alleviating pain, including migraines, facial and upper-extremity pain, and complex regional pain syndrome.
affecting the head, neck, and upper extremities, as well as essential hypertension and hypotension, Behçet disease, Sjögren syndrome, myasthenia gravis, herpes zoster, gout, diabetes, and angina pectoris. SGB has also been used to treat pain and body temperature changes that do not traditionally respond to pain medication, hence the growing interest and research evaluating SGB in the treatment of VMS.

Current use for vasomotor symptoms in menopause

The North American Menopause Society currently recommends using SGB with caution as a nonhormonal treatment for moderate to severe VMS owing to its invasive nature and the lack of data from large long-term randomized trials. SGB is currently being used in women with severe VMS who cannot use hormone therapy or whose symptoms have not responded to other treatments. However, its use is limited by a lack of awareness, limited availability, and high cost (estimated to be $2,000 for a treatment course of 2 SGB injections).

The procedure

SGB involves injection of a local anesthetic such as lidocaine under fluoroscopic or ultrasonographic guidance. In clinical trials, both unilateral and bilateral approaches (including if refractory to unilateral treatment) have been used, although a right lateral approach seems

Figure 1. In stellate ganglion block, anesthetic is injected under ultrasonographic or fluoroscopic guidance into the stellate ganglion at the C6 or C7 vertebral level, targeting the sympathetic nerve chain that runs anterior to the transverse processes of the seventh cervical vertebra and the neck of the first rib.
# TABLE 1

**Studies of stellate ganglion block for vasomotor symptoms in female breast cancer survivors**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Outcome measures</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rahimzadeh et al, 2018&lt;sup&gt;35&lt;/sup&gt; RCT N = 40</td>
<td>SGB (10 mL 0.5% bupivacaine, laterality NR) vs paroxetine (7.5 mg)</td>
<td>Baseline to 6 weeks  &lt;br&gt; Hot flashes by Sloan scale  &lt;br&gt; Sleep disturbance measured via PSQI</td>
<td>Hot flash scores  &lt;br&gt; SGB group: 42.35 to 10.50 (P &lt; .001)  &lt;br&gt; Paroxetine group: 36.85 to 10.94 (P &lt; .001)  &lt;br&gt; Sleep quality  &lt;br&gt; Trend toward better sleep noted  &lt;br&gt; No significant differences between SGB and paroxetine groups in hot flash and sleep quality improvement  &lt;br&gt; Adverse events: None; 1 mild headache</td>
</tr>
<tr>
<td>Othman and Zaky, 2014&lt;sup&gt;36&lt;/sup&gt; RCT N = 40</td>
<td>SGB (10 mL 0.5% bupivacaine, right lateral) vs pregabalin (75 mg twice daily)</td>
<td>Baseline to 3 months  &lt;br&gt; VMS frequency by self-reported daily hot flash diary and monthly questionnaire  &lt;br&gt; Hot flashes using Sloan scale</td>
<td>VMS  &lt;br&gt; Mild VMS: 28.0 to 10.0 (P = .005)  &lt;br&gt; Moderate VMS: 83.2 to 8.0 (P = .005)  &lt;br&gt; Very severe hot flashes: 51.2 to 0 (P = .005)  &lt;br&gt; Hot flashes  &lt;br&gt; Total score: 239.2 to 30.0 (P = .005)  &lt;br&gt; No significant differences between SGB and pregabalin groups  &lt;br&gt; Adverse events: None</td>
</tr>
<tr>
<td>Walega et al, 2014&lt;sup&gt;17&lt;/sup&gt; RCT N = 40</td>
<td>SGB (5 mL 0.5% bupivacaine, right lateral) vs sham injection</td>
<td>Baseline to 4–6 months  &lt;br&gt; Daily ambulatory sternal skin conductance monitoring and VMS diaries</td>
<td>VMS  &lt;br&gt; Reduced frequency in SGB group, event rate ratio: 0.71 (95% CI 0.64–0.99; P &lt; .05)  &lt;br&gt; Reduced frequency (moderate to very severe) in SGB group, event rate ratio: 0.50 (95% CI 0.35–0.71; P &lt; .001)  &lt;br&gt; Adverse events: None</td>
</tr>
<tr>
<td>van Gastel et al, 2013&lt;sup&gt;32&lt;/sup&gt; Open-label, case-series N = 20</td>
<td>SGB (7 mL 0.5% bupivacaine, right lateral) (1 excluded for lack of Horner syndrome after SGB)</td>
<td>Baseline to 4 weeks  &lt;br&gt; Hot flashes by self-reported diary and hygrometric hot flash recorder  &lt;br&gt; Quality of life and sleep disturbance by HFRDIS, MENQOL, ESS, and PSQI</td>
<td>Hot flash score  &lt;br&gt; Mean score decreased 34% (95% CI 18%–49%; P &lt; .005)  &lt;br&gt; Quality of life  &lt;br&gt; Decrease in daily flush interference (HFRDIS)  &lt;br&gt; Sleep disturbance  &lt;br&gt; Decreased from 9.9 to 7.7 (P &lt; .05) (PSQI)  &lt;br&gt; Adverse events: redness of conjunctiva, minimal hoarseness in first hour after SGB</td>
</tr>
<tr>
<td>Haest et al, 2012&lt;sup&gt;31&lt;/sup&gt; Pilot and main study N = 34</td>
<td>SGB (10 mL 0.25% levobupivacaine up to 3 blocks, bilateral)</td>
<td>Baseline to 1–24 weeks  &lt;br&gt; Hot flashes by self-reported diary  &lt;br&gt; Sleep quality assessed by self-reported diary and PSQI</td>
<td>Hot flash score  &lt;br&gt; Reduced from baseline by 64% (95% CI 49%–74%)  &lt;br&gt; Sleep quality  &lt;br&gt; Improved from OR 3.4 (95% CI 1.6–7.2) at week 1 to 4.3 (95% CI 1.9–9.8) at week 24  &lt;br&gt; Adverse events: None</td>
</tr>
<tr>
<td>Pachman et al, 2011&lt;sup&gt;33&lt;/sup&gt; Open-label, case series N = 10 (8 evaluable)</td>
<td>SGB (7 mL 0.5% bupivacaine, right lateral)</td>
<td>Baseline to 6 weeks  &lt;br&gt; Hot flashes by self-reported daily diary and weekly symptom questionnaires</td>
<td>Hot flashes  &lt;br&gt; Frequency: 10.1 to 5.4  &lt;br&gt; Score: 17.6 to 9.8  &lt;br&gt; Adverse events: None</td>
</tr>
<tr>
<td>Lipov et al, 2008&lt;sup&gt;34&lt;/sup&gt; Open-label, pilot study N = 13</td>
<td>SGB (7 mL 0.5% bupivacaine, up to 2 blocks, right lateral)</td>
<td>Baseline to 12 weeks  &lt;br&gt; Hot flashes by self-reported daily diary for Sloan hot flash score  &lt;br&gt; Night awakenings by PSQI</td>
<td>Hot flash totals  &lt;br&gt; At 2 weeks: from mean 79.4 (SD 37.4) per week to 49.9 (SD 39.9) (P &lt; .0001)  &lt;br&gt; At 12 weeks: very severe near zero (P &lt; .0001)  &lt;br&gt; Adverse events: None</td>
</tr>
</tbody>
</table>

**Notes:**  
CI = confidence interval; ESS = Epworth Sleepiness Scale; HFRDIS = Hot Flash Related Daily Interference Scale; HT = hormone therapy; MENQOL = Menopause Specific Quality of Life; NR = not reported; OR = odds ratio; PSQI = Pittsburgh Sleep Quality Index; RCT = randomized clinical trial; SD = standard deviation; SGB = stellate ganglion block; VMS = vasomotor symptoms
to be preferred. Generally, the anesthetic is injected at the C6 or C7 vertebral level (Figure 1), targeting the sympathetic nerve chain that runs anterior to the neck of the first rib. The procedure takes about 30 minutes, with same-day patient discharge. Abatement of symptoms is highly variable in onset and impact.30

WHAT HAVE STUDIES SHOWN?

Data on the efficacy of SGB for VMS have come from case reports, pilot studies, and randomized clinical trials. Table 1 presents detailed results from studies evaluating SGB for VMS in breast cancer survivors.17,31–36

The first randomized, sham-controlled trial of fluoroscopy-guided SGB, published in 2014 by Walega et al,17 noted a 52% reduction in frequency of moderate to severe VMS symptoms from baseline to months 4 to 6 in the active-treatment group vs 4% in the control group (P < .001). The control group had an initial notable reduction in the frequency of VMS, but the SGB group had a significantly more sustained and effective impact. This reduction in frequency and intensity of VMS with SGB was similar to that described in previous nonrandomized intervention studies, with reductions varying from 34% to 90% over 4 weeks to several months after the procedure.31–34

In a 2018 clinical trial by Rahimzadeh et al,35 a group of 40 breast cancer survivors were randomly assigned to ultrasonography-guided SGB with 10 mL of 0.5% bupivacaine or to 6 weeks of oral therapy with 7.5 mg of paroxetine. A significant decrease in hot flash score (self-reported on the Sloan hot flash scoring scale)37 and sleep disturbance index (measured the Pittsburgh Sleep Quality Index)38 was identified in both groups, with no noticeable difference between the groups in efficacy, and with minimal (and fewer) side effects noted in the SGB group.

In a 2014 randomized controlled trial by Othman and Zaky,36 40 survivors of breast cancer were divided into 2 treatment groups, 1 group receiving SGB with 10 mL of 0.5% bupivacaine, and the other receiving 75 mg of pregabalin orally twice daily. Data were collected from baseline to 3 months, with VMS frequency reported via daily hot flash diary and monthly questionnaire. Hot flashes were self-reported on the Sloan hot flash scoring scale. This study showed a significant improvement in mild, moderate, and very severe hot flashes, and a decrease in frequency for both treatment groups. There were no significant differences shown between SGB and pregabalin, with no adverse events reported in either group.36

Case studies have also indicated tentative success with SGB for VMS. In a report of 6 patients by Lipov et al in 2005,39 SGB substantially decreased self-reported VMS. The initial SGB was shown to be successful based on 2 indicators: a positive test for Horner syndrome (ie, disrupted nerve pathway from brain to face and eye) and development of anhidrosis (ie, inability to sweat normally). However, results from this study describing 90% to 100% improvement in hot flashes have not been replicated in later studies.40

Other studies have reported a wide variation in hot flash improvements ranging from a 34% decrease in van Gastel et al32 to a 64% decrease in Haest et al,31 as well as in the methods used to measure improvement. The wide variability in hot flash reduction across studies may be explained by when the hot flashes were assessed (treatment effects can vary substantially over time), repetition and readministration of the treatment for increased efficacy, placebo effect, or the limitation-of-recall bias for self-reported hot flash diaries.

COMPLICATIONS ARE RARE BUT POTENTIALLY SIGNIFICANT

Complications of SGB are rare but can be significant and include central nervous system complications (eg, convulsions), vascular puncture, neural puncture, esophageal and tracheal puncture, spread of local anesthetic, pneumothorax, and allergic reactions.30 The published incidence of complications, predating the use of imaging guidance, is 1.7 per 1,000 procedures and correlates mostly with the intravascular injection of anesthesia that may lead to temporary seizures.30 With the increased use of imaging guidance, complications are less likely, although still relevant considering the critical structures in the injection area (eg, vertebral artery, internal carotid artery, inferior thyroid artery, other spinal nerves).30 Guidance with fluoroscopy or ultrasonography, monitoring of cardiovascular function, and having resuscitative equipment available can minimize the risk of complications.
HOW DOES STELLATE GANGLION BLOCK WORK?

The underlying mechanism for how SGB improves VMS is unclear. Lipov et al proposed that the mechanism likely involves peripheral vasodilation but noted that the wide range of indications for SGB (eg, pain treatments for migraines, atypical facial pain, upper extremity pain, complex regional pain syndrome, and, in Japan, diseases of the immune and endocrine systems) may indicate a more complicated mechanism of action. In a rat study, Westerhaus and Loewy used pseudorabies virus injections to find the neural pathway of stellate ganglion block and uncovered connections to the hypothalamus and amygdala, supporting hypotheses that the stellate ganglia are intricately involved with modulating temperature and factors that influence pain. The unifying mechanism may be through nerve growth factor, which is involved in cell differentiation, survival, and apoptosis, increasing brain norepinephrine in various illnesses and conditions, as well as through a possible reduction in the concentration of nerve growth factor and norepinephrine to deactivate these states. Others have hypothesized that SGB results in changes in voltage-gated sodium channels of peripheral nerves and central response by spinal feedback loops, thus decreasing VMS. More research is needed to clarify the mechanisms by which SGB treats VMS.

THE BOTTOM LINE

VMS is common and is associated with decreased quality of life in perimenopausal and postmenopausal women. Nonhormonal treatment options for VMS that are safe and effective are important for women who cannot use or choose not to use hormone therapy. SGB is a promising treatment. Based on existing data, it can be considered with caution in patients with severe VMS whose symptoms are refractory to conservative care, who can afford the treatment, and who have access to this service. Although cost data are limited, preliminary analyses indicate that SGB could balance out the cost of hormone therapy, and some insurance companies cover the cost of SGB in VMS.

DISCLOSURES

Dr. Kling reports consulting for Procter & Gamble and for Triangle Insights Group. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.
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Vitamin D supplementation: Pearls for practicing clinicians

ABSTRACT
Vitamin D supplementation is common in the United States, with about one-fifth of the adult population taking a daily supplement in one form or another. Although the detrimental effects of insufficient sun exposure in childhood were established centuries ago, the beneficial effects of vitamin D sufficiency have only recently been established, given the myriad investigations associating vitamin D deficiency with numerous chronic diseases. But it is far less clear precisely how to replete low 25-hydroxyvitamin D (25(OH)D) levels, how long treatment should be continued, if there are potential hazards in doing so, and how to assess and counsel patients regarding the use of vitamin D. This article provides a brief historical review, examines how to assess and counsel patients on the use of vitamin D, presents scenarios that clinicians are likely to encounter, and reviews the literature on recommendations for vitamin D supplementation.

KEY POINTS
Typical vitamin D replacement requires at least 2,000 IU/day, with some authors recommending 5,000 IU/day.

The richest food sources of vitamin D, consumed in manageable portions, provide only a small percentage of the recommended daily intake of 800 IU.

Several mechanisms contribute to the ability of vitamin D₃ to attain and maintain goal serum concentrations of 25(OH)D more efficiently than vitamin D₂, including that vitamin D₂ has a lower affinity for D binding protein and D 25-hydroxylase converts D to 25(OH)D₃ substantially faster.

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Vitamin D deficiency is common in the United States and around the globe. The most common cause of deficiency is insufficient intake (oral or dermal). In a study using National Health and Nutrition Examination Survey (NHANES) data from 2011 to 2014, almost 20% of the US population had serum 25-hydroxyvitamin D (25(OH)D) values categorized as “at risk for inadequacy” (defined as 30 to 49 nmol/L or 12 to 19 ng/mL), and 5% were categorized as “at risk for deficiency” (< 30 nmol/L or 12 ng/mL). These reference ranges may be lower than what most clinicians consider to be deficient. For example, numerous studies have found a recommended threshold of 50 nmol/L (20 ng/mL) for bone health to be insufficient for fall or fracture risk reduction.

**Immunologic effects**

Vitamin D supplementation to prevent and treat immune-related diseases including COVID-19 was reviewed by Charoenngam et al. In an extensive examination of the immunologic effects of vitamin D supplements, the authors described the immunomodulatory hormonal effects of vitamin D, noted significant biologic effects on the innate and adaptive immune systems, cited the immunomodulatory and antiviral effects of the active form of vitamin D (1,25 dihydroxyvitamin D), and suggested that vitamin D supplementation might reduce the risk and severity of COVID-19 infection. They concluded that although the optimal level of vitamin D remains unclear, maintaining a serum 25(OH)D level of 100 to 150 nmol/L (40 to 60 ng/mL) is recommended.

As reported at an American Academy of Dermatology conference in 2005, repeated exposure to ultraviolet (UV) light activates both the innate and adaptive arms of the immune system, and UV light from solar radiation has dose-dependent effects on cells, with cellular and DNA damage that can cause immunosuppression.

**Guidelines for replacement**

In 2011, the Endocrine Society issued clinical practice guidelines that defined vitamin D deficiency as less than 30 ng/mL and recommended minimum replacement dosages (Table 1).

The guidelines identify minimum requirements to maximize bone health and muscle function. However, achieving blood levels above 30 ng/mL (which is considered below normal or low-normal in most laboratory reference ranges) may require more than 2,000

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Minimum requirement</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 19–50</td>
<td>600 IU/day</td>
<td>Increasing and maintaining the 25(OH)D level consistently above 30 ng/mL may require at least 1,500–2,000 IU/day</td>
</tr>
<tr>
<td>Age 51–70</td>
<td>600 IU/day</td>
<td>To maximize bone health and muscle function</td>
</tr>
<tr>
<td>Age ≥ 65</td>
<td>800 IU/day</td>
<td>For the prevention of falls and fractures</td>
</tr>
<tr>
<td>Pregnant and lactating female patients</td>
<td>600 IU/day</td>
<td>At least 1,500–2,000 IU/day may be needed to maintain a blood level of 25(OH)D above 30 ng/dL</td>
</tr>
<tr>
<td>Adults with obesity</td>
<td></td>
<td>Give at least 2 to 3 times more vitamin D to meet bodily requirements</td>
</tr>
</tbody>
</table>

*With the recommendation not to exceed 4,000 IU daily maintenance dose.
IU = international units; 25(OH)D = 25-hydroxyvitamin D

Based on information in reference 10.
VITAMIN D SUPPLEMENTATION

TABLE 2
Vitamin D content of selected foods

<table>
<thead>
<tr>
<th>Food</th>
<th>Micrograms per serving</th>
<th>International units per serving</th>
<th>Percent of daily valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cod-liver oil, 1 tablespoon</td>
<td>34.0</td>
<td>1,360</td>
<td>170</td>
</tr>
<tr>
<td>Trout (rainbow), farmed, cooked, 3 ounces</td>
<td>16.2</td>
<td>645</td>
<td>81</td>
</tr>
<tr>
<td>Salmon (sockeye), cooked, 3 ounces</td>
<td>14.2</td>
<td>570</td>
<td>71</td>
</tr>
<tr>
<td>Mushrooms, white, raw, sliced, exposed to ultraviolet light, ½ cup</td>
<td>9.2</td>
<td>366</td>
<td>46</td>
</tr>
<tr>
<td>Milk, 2% milkfat, vitamin D fortified, 1 cup</td>
<td>2.9</td>
<td>120</td>
<td>15</td>
</tr>
<tr>
<td>Soy, almond, and oat milks, vitamin D fortified</td>
<td>2.5–3.6</td>
<td>100–144</td>
<td>13–18</td>
</tr>
<tr>
<td>Ready-to-eat cereal, fortified with 10% of the daily valuea for vitamin D, 1 serving</td>
<td>2.0</td>
<td>80</td>
<td>10</td>
</tr>
<tr>
<td>Sardines (Atlantic), canned in oil, drained, 2 sardines</td>
<td>1.2</td>
<td>46</td>
<td>6</td>
</tr>
<tr>
<td>Egg, 1 large, scrambledb</td>
<td>1.1</td>
<td>44</td>
<td>6</td>
</tr>
<tr>
<td>Liver, beef, braised, 3 ounces</td>
<td>1.0</td>
<td>42</td>
<td>5</td>
</tr>
<tr>
<td>Tuna (light), canned in water, drained, 3 ounces</td>
<td>1.0</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>Cheese, cheddar, 1 ounce</td>
<td>0.3</td>
<td>12</td>
<td>2</td>
</tr>
</tbody>
</table>

a Daily value (DV) was developed by the US Food and Drug Administration to help consumers compare the nutrient contents of foods and dietary supplements within the context of a total diet. The DV for vitamin D is 20 μg (800 IU) for adults and children age 4 years and older. Foods providing 20% or more of the DV are considered to be high sources of a nutrient, but foods providing lower percentages of the DV also contribute to a healthful diet.
b The vitamin D is in the yolk.

Based on information in reference 1.

IU daily. Patients with obesity may require several times that dose to attain and maintain a normal level. The Endocrine Society guidelines, in addressing the issue of assay variability, note that in the clinical setting, achieving a level of 40 ng/mL will not result in toxicity but will ensure that an individual’s true value is greater than 30 ng/mL.10

Investigators have considered whether a predictive equation could help clinicians select the correct replacement dose of vitamin D for their patients. Singh et al11 addressed this question with a retrospective observational study. After reviewing the response to vitamin D supplementation in more than 1,300 ambulatory and nursing home patients and employing multiple regression analyses, they published a series of equations that predict the dose of vitamin D needed to achieve a given change in the serum concentration of 25(OH)D in these patient populations. Their equation for calculating the dose in international units (IU) that incorporates body mass index (BMI) was as follows11:

\[
\text{Dose in IU} = \left[ (8.52 - \text{desired change in } 25\text{(OH)D}) + (0.07 \times \text{age}) - (0.20 \times \text{BMI}) + (1.74 \times \text{serum albumin}) - (0.62 \times \text{starting } 25\text{(OH)D concentration}) \right] / (-0.002)
\]

Singh et al speculated that lack of sun exposure explained the need for higher doses of vitamin D in nursing home patients, since their analyses concluded that increased age alone was not a negative factor in response to vitamin D treatment.11 Their analyses did not address the duration of treatment, but Singh et al acknowledged that many patients require long-term maintenance therapy. They further observed that 5,000 IU per day is usually needed to correct deficiency, and a typical maintenance dose should be at least 2,000 IU daily.11
HOW TO REPLACE VITAMIN D

Vitamin D dietary supplements are widely available, and in 2020, the industry’s estimated market value exceeded $1.1 billion, projected to reach close to $1.6 billion by 2025.12 The annual growth rate is more than 7% due to people paying more attention to their nutrition and their health in general.

The popularity of vitamin D supplements has been fueled at least in part by campaigns educating the public about the risks of skin cancer due to excess sun exposure, the association of vitamin D deficiency with many chronic diseases, and the association of vitamin D levels with optimal immune function.

Vitamin D supplements are available by prescription, over-the-counter, and online. In 2021, the cost per 100 tablets of 2,000 IU vitamin D3 was around $0.05 per tablet, while 100 capsules of 50,000 IU vitamin D2 or D3 started at $0.25 per capsule.

Is it possible to get sufficient vitamin D exclusively from diet?

Despite fortification of commonly consumed products such as milk, food sources of vitamin D are few, and even the richest sources consumed in manageable portions provide only a small percentage of the recommended daily intake (Table 2).1

CLINICAL SCENARIO 1: VITAMIN D2 OR D3?

An otherwise healthy 30-year-old woman with a BMI of 37 kg/m2 was referred for vitamin D deficiency “unresponsive to D repletion.” Her initial 25(OH)D level was 14 ng/mL. After taking vitamin D3 at a dose of 50,000 IU once weekly with her morning coffee for 4 weeks, her 25(OH)D level remained at 21 ng/mL, still below the normal range.

The clinical challenges with this patient are to consider whether vitamin D2 (ergocalciferol) or D3 (cholecalciferol) makes a difference, and whether taking it on an empty stomach is optimal for absorption.

Several recent articles have addressed the question of whether D2 and D3 supplements are equivalent in raising serum 25(OH)D.13–15 Houghton and Vieth13 questioned assumptions about their equivalency and proposed several mechanisms that may contribute to the ability of vitamin D3 to maintain higher serum concentrations over time, including the following:

- Supplementation with vitamin D2 produces serum 25(OH)D2, but its lower affinity for D binding protein results in a shorter half-life than that of 25(OH)D3.
- Mitochondrial vitamin D 25-hydroxylase converts vitamin D3 to 25(OH)D3 five times faster than it converts vitamin D2 to 25(OH)D2.

In a systematic review and meta-analysis, Tripkovic et al14 concluded that supplementation with vitamin D3 had a significant and positive effect in the raising of serum 25(OH)D concentrations compared with the effect of D2 (P = .001). In a study that explored the relative potency of vitamin D2 and vitamin D3, Armas et al15 found the 2 forms to be equivalent in absorption. Further, they both produced similar increases in serum 25(OH)D in the first 72 hours, but the 25(OH)D level continued to rise in the D3-treated patients, peaking at day 14. Their calculated area under the curve at 28 days indicated that D3 was 9.5 times more potent than D2.

Any difference in how it is taken?

Does it matter if the supplement is taken on an empty stomach vs with a meal? In a small study, Mulligan and Licata16 found that taking either vitamin D2 or D3 with the largest meal of the day increased the average serum 25(OH)D level by 50.2% (± 13.4%).

Similarly, a systematic review by Silva and Furlanetto17 included randomized controlled trials examining the response to a single dose of vitamin D taken with a fat-free meal vs meals that contained 15 g or more of fat. Mean serum 25(OH)D concentrations were higher in those who took the supplement with a meal that included at least 15 g of fat.

Recommended treatment for this patient

This 30-year-old female patient, deemed unresponsive to vitamin D repletion, was treated with vitamin D3 50,000 IU weekly for 8 weeks taken with dinner. Her 25(OH)D level rose to 42.8 ng/mL.

CLINICAL SCENARIO 2: PHOTOTHERAPY TO COUNTER MALABSORPTION?

A 38-year-old man with a history of fistulization thresholds for vitamin D deficiency vary among organizations.
ing Crohn disease had undergone multiple small-bowel resections and had become dependent on parenteral nutrition. His 25(OH)D level was 12 ng/mL despite taking vitamin D2 50,000 IU daily. In an effort to overcome his malabsorption issue, he would bite into the gel cap to release the contents before swallowing the supplement.

Dual x-ray absorptiometry was notable for an extraordinarily low hip Z-score of −3.4, his long bones were painful to palpation, and his parathyroid hormone level was significantly elevated at 248 pg/mL (reference range 15–65 pg/mL). Osteomalacia is not uncommon in this patient population, but treating the vitamin D deficiency can be very challenging.

In addition to Crohn disease, other conditions can interfere with vitamin D absorption, including a history of malabsorptive-type bariatric surgery, celiac disease, cystic fibrosis, steatorrhea, short bowel disease, inflammatory bowel disease, and severe cholestasis. A vitamin D challenge test is one way to confirm the absorptive capability for vitamin D supplementation in these patients.

When vitamin D is taken orally, it is incorporated into the chylomicron fraction, and about 80% of the dose is absorbed into the lymphatics. The blood level of 25(OH)D will peak about 12 hours after a single dose of 50,000 IU. Knowing this about oral absorption of vitamin D allows for provocative testing in patients with suspected malabsorption of the vitamin.

To test for malabsorption, a blood sample is drawn immediately before administering a 50,000-IU oral dose of vitamin D. The blood draw is repeated in 12 to 24 hours. If no increase in 25(OH)D is noted, the patient has “complete” malabsorption of vitamin D. Incidentally, if this is the finding, then the patient may need testing for deficiencies of other fat-soluble vitamins such as vitamin A.

In addition to supplementation, vitamin D synthesis can take place when the skin is exposed to UV-B light. The therapeutic benefits of phototherapy are recognized for a wide variety of skin conditions, and with careful skin-typing and carefully metered exposure to UV-B light, phototherapy can also achieve normal 25(OH)D levels.

This 38-year-old patient was referred to dermatology for phototherapy. UV-B light was administered 3 days per week under the close supervision of an experienced dermatologist, and his 25(OH)D level rose to 48 ng/mL within a few weeks.

Sunbathing and tanning booths: A word of caution

Sunbathing and tanning booths are not therapies for vitamin D deficiency. Sunshine is composed of approximately 95% UV-A and 5% UV-B, but only UV-B is required for vitamin D synthesis. UV-A is the predominant or sole light source used in tanning beds, and the dose of UV-A in tanning beds can be up to 12 times that provided by the sun.

Skin cancers comprise one-half of all cancers, and UV-A and UV-B are both implicated. UV-A is thought to damage skin and increase the risk of melanoma by causing oxidative stress-induced DNA damage. UV-B damage is more direct, with photoproducts that are implicated in skin carcinogenesis. Skin type and age are factors in the response to UV exposure, but in general, exposing 5% of the body surface twice weekly for 20 minutes during the summer months may be equivalent to 430 IU of vitamin D per day, with a plateau being reached after 20 minutes.

Clinical Scenario 3: Vitamin D Deficiency with Hypercalcemia

A 78-year-old otherwise healthy woman with primary hyperparathyroidism also has vitamin D deficiency, with a 25(OH)D level of 15 ng/mL in the presence of an elevated serum calcium level of 11.4 mg/dL (reference range 8.5–10.2 mg/dL), high parathyroid hormone of 128 pg/mL (reference range 15–65 pg/mL), low phosphorus of 1.7 mg/dL (reference range 3.0–4.5 mg/dL), and high 24-hour urine calcium of 472 mg (reference range 100–300/day).

In a meta-analysis of 10 studies that included 340 patients with primary hyperparathyroidism, Shah et al assessed the effect of 25(OH)D replacement in patients with coexistent vitamin D deficiency. The studies included the use of vitamin D2 and D3 supplements, and the time span of administration ranged from 1 to 12 months. Interestingly, this study noted a nonsignificant but modest
decline in serum calcium after vitamin D replacement. Only 2.2% developed more severe hypercalcemia (> 12 mg/dL) that responded to stopping the supplement or to reducing the dose. The authors concluded that vitamin D replacement in patients with primary hyperparathyroidism does not worsen hypercalcemia.

This patient was placed on 5,000 IU of vitamin D3 daily, taken with her largest meal, and was maintained on that dose following parathyroid surgery. At her 3-month postoperative visit, the 25(OH)D level was normal at 52 ng/mL, and her parathyroid hormone and serum calcium levels were also normal.

A word of caution: Vitamin D toxicity

Vitamin D toxicity can result from overcorrection of vitamin D deficiency. Case reports have implicated manufacturing errors, overdosing by patients or prescribers, or a combination of these factors.21 Perhaps no report is more poignant than the report by Zhou et al22 of an 80-year-old man who presented with signs and symptoms consistent with vitamin D toxicity including confusion, dysarthria, and ataxic gait, and was found to have a serum calcium of 14.4 mg/dL in the presence of a parathyroid hormone level of 11 pg/mL and 25(OH)D of 365 ng/mL. He had been prescribed a weekly 50,000-IU vitamin D tablet, but at some point, he began to take it daily with his other medications. All of his symptoms resolved after a brief hospital stay, during which the vitamin D supplement was stopped and the hypercalcemia was addressed.

CLOSING THOUGHTS

Vitamin D deficiency is relatively common. The detrimental effects of vitamin D deficiency have been well documented, dating to the 1600s, but only during the early 1900s did we discover and implement palatable fortification of milk and other foods that led to the eradication of rickets in children. However, fortification of milk alone failed to eliminate vitamin D deficiency.

Fortunately, vitamin D supplements are easily prescribed, inexpensive, and available over the counter. It is important for clinicians to be attentive to the likelihood of vitamin D deficiency, especially in patients with certain diseases and conditions; to advise patients on the best ways to attain and maintain an adequate 25(OH)D level; to counsel patients taking supplements on avoiding oversupplementation; to advise against inappropriate reliance on sun exposure and tanning beds for vitamin D supplementation; and to recognize symptomatic vitamin D toxicity.

DISCLOSURES

The author reports no relevant financial relationships which, in the context of her contributions, could be perceived as a potential conflict of interest.

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VITAMIN D SUPPLEMENTATION


Address: Susan E. Williams, MS, RD, MD, CDE, FACE, FAND, Endocrinology and Metabolism Institute, F20, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; willias9@ccf.org
Common skin signs of COVID-19 in adults: An update

ABSTRACT

Cutaneous findings can be clues to diagnosis and infection severity in viral illnesses, including COVID-19. The authors provide an update on the diagnostic and prognostic value of the 5 most common cutaneous abnormalities associated with COVID-19 in adult patients: morbilliform rash, urticaria, vesicles, pseudo-chilblains, and vaso-occlusive lesions.

KEY POINTS

The common cutaneous abnormalities that occur in COVID-19 patients were recognized early in the pandemic, and evidence concerning their pathogenesis and clinical relevance continues to accumulate.

Urticarial and vesicular eruptions may precede other COVID-19-associated symptoms and, along with morbilliform rashes, are typically associated with overall high survival rates.

The association of pseudo-chilblains with COVID-19 remains controversial, and no definitive evidence linking them to SARS-CoV-2 infection has been reported.

The most worrisome manifestations are vaso-occlusive skin lesions, which most often occur in hospitalized patients with COVID-19 and are associated with a poorer prognosis than other skin lesions.

As experience with caring for patients with COVID-19 has accumulated since the onset of the pandemic, so has our understanding of its associated cutaneous manifestations and their clinical implications.

It is beneficial to watch for cutaneous manifestations of COVID-19, both in and out of the hospital. For example, a study of more than 330,000 community-based patients in the United Kingdom1 found that patient-reported skin rash was associated with positive COVID-19 testing and was more predictive than fever. Additionally, an analysis of 296 hospitalized patients with COVID-19 in the United States2 found that mucocutaneous findings were associated with the need for mechanical ventilation, even when adjusted for age, body mass index, and comorbidities.

COVID-19-associated cutaneous abnormalities are often grouped into 5 major categories (Table 1):

- Morbilliform rash (containing macules and papules, resembling measles)
- Urticaria (itchy red welts)
- Vesicles (small blisters)
- Pseudo-chilblains (also known as “COVID toes,” painful inflammation of the digits in response to cold)
- Vaso-occlusive lesions (due to thrombosis and occlusion of small arteries, with subsequent ischemia).

MORBILLIFORM RASH: THE MOST COMMON SKIN MANIFESTATION

Morbilliform eruptions are common in many viral illnesses and were reported in patients with COVID-19 early in the pandemic.3,5 International registry data indicate that mor-
SKIN SIGNS OF COVID-19

Billiform eruptions are the most common cutaneous manifestation in patients with laboratory-confirmed COVID-19. Typical clinical features include a generalized, symmetric maculopapular rash with pruritus (Figure 1).

Patients with COVID-19-associated morbilliform eruptions have an excellent prognosis, with survival rates of 96.9% to 97.5%.

### URTICARIA CAN BE THE FIRST SIGN OF COVID-19

Urticaria is also common in COVID-19. The clinical features do not appear to differ from those of idiopathic urticaria and typically consist of generalized pruritic wheals. On average, urticaria lasts less than 1 week and is associated with relatively mild disease and survival rates of 97.8% to 98.2%.

Histologic features also mimic those of idiopathic urticaria and thus limit the value of skin biopsy. However, urticarial vasculitis has been described in association with COVID-19, suggesting that biopsy should be considered in patients with persistent urticarial plaques with associated purpura.

Interestingly, in a systematic review of 895 patients with COVID-19, 105 (12%) had urticarial lesions, and in 17 (16%) of these 105 the urticaria began before the onset of the other COVID-19 symptoms, suggesting that it can be a clue to diagnosis in appropriate clinical settings and can help

---

**TABLE 1**

**Major categories of cutaneous eruptions in COVID-19**

<table>
<thead>
<tr>
<th>Category</th>
<th>Presentation</th>
<th>Onset rates</th>
<th>Survival rates</th>
<th>Additional notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morbilliform</td>
<td>Pink-erythematous blanching macules and papules, commonly on trunk and lasting &lt; 1 week</td>
<td>Usually within 2 weeks of COVID-19 symptom onset</td>
<td>High&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Most common cutaneous finding in confirmed COVID-19 cases</td>
</tr>
<tr>
<td>Urticarial</td>
<td>Transient, pruritic edematous papules and plaques lasting about 1 week</td>
<td>Can be before COVID-19 symptoms</td>
<td>High&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Reported association with gastrointestinal symptoms</td>
</tr>
<tr>
<td>Vesicular</td>
<td>Minimally pruritic vesicular eruption that can be localized or diffuse</td>
<td>Can be before COVID-19 symptoms</td>
<td>High&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Reported association with neurologic symptoms</td>
</tr>
<tr>
<td>Pseudo-chilblains</td>
<td>Younger, healthy patients with tender red-purple papules affecting toes more than fingers</td>
<td>Usually within 2–4 weeks after COVID-19 symptom onset</td>
<td>High&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Association with SARS-CoV-2 infection is debated</td>
</tr>
<tr>
<td>Vaso-occlusive</td>
<td>Hospitalized patients with retiform purpura, livedo racemosa, acral necrosis, or sacral ulcers</td>
<td>Usually within 2 weeks of COVID-19 symptom onset</td>
<td>Lower&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Linked to systemic vascular thrombosis</td>
</tr>
</tbody>
</table>

<sup>a</sup>More than 95%.
<sup>b</sup>About 80%.

Based on information in reference 3.
guide early testing (Figure 2). Additionally, an analysis of 200 patients with COVID-19 with cutaneous manifestations found a significant association between urticaria and gastrointestinal symptoms, which could assist clinicians in their anticipatory management.

■ **VESICLES CAN ALSO BE THE FIRST SIGN OF COVID-19**

Initially described as “varicella-like,” vesicular eruptions in COVID-19 have been described in both localized and diffuse distributions. The localized pattern is characterized by monomorphic vesicles in the same stage of evolution that are confined to the trunk (Figure 3). But the diffuse pattern may be more common. A cohort study reported that it accounted for 18 (75%) of 24 cases. The diffuse pattern consists of polymorphic papules, vesicles, and pustules that develop simultaneously on the trunk and spread distally, sometimes involving the palms and soles. Lesions tend to resolve after about 8 days without scarring.

An analysis of 200 patients with COVID-19 with cutaneous manifestations found a significant association between urticaria and gastrointestinal symptoms.
Lesional skin biopsies reveal histologic features consistent with viral exanthems, namely vacuolar degeneration of the basal epidermal layer with occasional dyskeratotic keratinocytes and superficial dermal inflammation. However, some reports describe prominent keratinocyte acantholysis contributing to formation of intraepidermal vesicles, which is a relatively unusual histologic finding. Additionally, while there have been reports of SARS-CoV-2 spike proteins detected with immunohistochemistry in sweat glands and dermal endothelial cells in skin biopsies from COVID-19 patients, 2 studies of COVID-19-associated vesicular rashes detected no SARS-CoV-2 in vesicular fluid by reverse transcriptase polymerase chain reaction testing.

Like urticaria, vesicular eruptions were also commonly noted before other COVID-19 symptoms (in 8.5% to 15% of cases of COVID-19-associated urticaria) in multiple studies, and therefore may similarly provide an indication for COVID-19 testing and isolation in the appropriate clinical context. Additionally, a systematic review reported a possible link between vesicular eruptions and neurologic symptoms including headache, dysgeusia, irritability, and confusion. Like those with morbilliform rash or urticaria, patients with COVID-19 with vesicular eruptions have high survival rates (96.1% to 96.6%).

### Pseudo-chilblains: Link to COVID-19 Debated

Although pernio-like acral lesions (Figure 4) were the first cutaneous manifestations to generate significant attention, whether they are truly linked to COVID-19 has been debated.

Challenging the link are strikingly low rates of positive COVID-19 testing in affected patients, as well as results of several studies that suggest these lesions are most consistent with typical perniosis, with an increased incidence related to changes in daily routine (eg, quarantining, working from home) during the pandemic rather than infection with SARS-CoV-2. Additionally, a systematic review found that pre-existing rheumatologic conditions were more common in patients with presumed COVID-19-related pernio-like lesions, raising the possibility that underlying diagnoses contributed to development of the acral lesions.

However, proponents of the association with COVID-19 point to “outbreaks” of chilblain-like lesions corresponding to COVID-19 waves and propose that an efficient, type I interferon-driven antiviral response could induce pernio-like lesions and suppress both symptoms and confirmatory testing.

Interestingly, information is accumulating about pernio-like lesions in “long-hauler” COVID-19 patients, with a significant association reported between persistent cutaneous and extracutaneous symptoms.

While the debate continues, if these lesions are truly a COVID-19 manifestation, they are fortunately associated with high survival rates (96.4% to 98.7%) and few or no systemic symptoms.

### Vaso-occlusive Lesions Are Associated with Higher Risk

Vaso-occlusive lesions (Figure 5) have been reported in patients with COVID-19 with varied clinical presentations, including fixed livedo racemosa, retiform purpura, and acral...
ischemia, which may be clinically confused with COVID toes. These lesions are most commonly seen in hospitalized patients with moderate to severe COVID-19 and are associated with higher risks of severe pneumonia and intensive care unit admission and relatively low survival rates (78.9% to 81.8%).

Similar patterns of microvascular thrombosis have been found in skin biopsies and pulmonary tissue of COVID-19 patients with vaso-occlusive cutaneous lesions, suggesting that this manifestation could be a marker of systemic microvascular injury. Additionally, systemic thrombotic events including deep vein thrombosis and pulmonary embolism have been reported in patients with retiform and necrotic lesions, with rates as high as 64%. Whether early recognition of these lesions can prompt treatment decisions that decrease systemic thrombotic events or increase overall survival requires further research.

OTHER CUTANEOUS FINDINGS

Other cutaneous findings that have been reported with COVID-19 include oral lesions; reactivation of viral infections; rash resembling symmetrical drug-related intertriginous and flexural exanthema; small-vessel vasculitis; cutaneous hyperesthesia; papulosquamous eruptions; and erythema nodosum-like lesions.

Oral lesions. A study of 666 patients reported various oral mucosal findings in 78 (26%) of 304 patients who had mucocutaneous manifestations, and the authors hypothesized that lesions in the mouth may be underreported due to contact precautions and assisted ventilation that limits examination of the oral mucosa.

Reactivation of herpes simplex virus (HSV) and varicella-zoster virus (VZV) infections has been reported in conjunction with COVID-19 infection. A cross-sectional study of nearly 900 patients with COVID-19 found a significantly higher prevalence of HSV-1 and VZV than in the hospital population, even when adjustments were made for numerous comorbidities. Some reports suggest that HSV reactivation may be associated with more severe COVID-19 infection, including acute respiratory distress syndrome and viremia, but the prognostic implications of treating these reactivations has not yet been robustly investigated.

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DISCLOSURES

Dr. Fernandez reports consulting for Abbvie Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Mallinckrodt, Novartis, and UCB; teaching and speaking (non-promotional) for Abbvie Pharmaceuticals, Kyowa Kirin, Mallinckrodt, and Novartis; research/vendependent contracting for Abbvie Pharmaceuticals, Mallinckrodt, Novartis, and Pfizer; and work as advisor or review panel participant for Abbvie Pharmaceuticals. Dr. Polly reports no relevant financial relationships which, in the context of her contributions, could be perceived as a potential conflict of interest.

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

CREDIT DESIGNATION

American Medical Association (AMA)

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

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

Certificate of Participation

A certificate of participation will be provided to other healthcare professionals for requesting credits in accordance with their professional boards and/or associations.

**MOC/CC PART II ACCREDITATION:**

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

- **ABA MOC:** 1.0 Lifelong Learning MOC points in the ABA MOCA 2.0® Maintenance of Certification in Anesthesiology Program®.
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- **ABS MOC:** 1.0 Accredited CME & Self-Assessment credits toward ABS Continuous Certification Program.

It is the CME activity provider’s responsibility to submit participant completion information to ACCME for the purpose of granting ABA, ABIM, ABPath, ABP, and ABS credit.

Credit will be reported within 30 days of claiming credit.

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

**Estimated time to complete each activity: up to 1 hour**

**March 2022 CME/MOC activities**

**Vitamin D supplementation:** Pearls for practicing clinicians

Release date: March 1, 2022

Expiration date: February 28, 2023