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Review

SGLT-2 inhibitors in heart failure and chronic kidney disease: A review for internists

This review summarizes recent data and guidelines regarding SGLT-2 inhibitors in heart failure and chronic kidney disease and provides practical guidance for their use.

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Review

Lymphedema vs lipedema: Similar but different

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Preventing herpes zoster in immunocompromised patients: Current concepts

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Letters to the Editor

Severe hyponatremia: Are you monitoring the urine output?

Anup Katyal, MD; Ashwani Joshi, MD

In reply: Severe hyponatremia: Are you monitoring the urine output?

Elias Bassil, MD; Georges N. Nakhoul, MD, MEd; Jonathan J. Talierno, DO; Ali Mehdi, MD, MEd

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SGLT-2 inhibitors: Diabetes and CKD and CHF (and gout?), oh my!

Hyperglycemia is the hallmark characteristic of diabetes mellitus. Blood glucose and hemoglobin A1c are guideline-driven markers useful for diagnosis and monitoring treatment. But blood glucose is but 1 part of this systemic metabolic disease that also has inflammatory components. “Successful” aggressive control of blood sugar has had limited success in preventing the onset and progression of cardiovascular and renal damage. Many of our patients still struggle with ischemic heart disease, heart failure, peripheral arterial disease, and kidney disease. There have been several new US Food and Drug Administration (FDA)–approved medications to treat type 2 diabetes, some of which use unique physiologically targeted mechanisms to lower blood glucose.

The FDA drug approval process has mandated that increased attention be given to studying the effects of potential diabetes drugs on the systemic components of diabetes mellitus, not just on their hypoglycemic activity. The initial focus was on excluding unanticipated detrimental cardiovascular effects. Studies were large, with prospectively planned collection of detailed cardiovascular and renal data, and cardiovascular events were carefully adjudicated. As a result, it was demonstrated that some of the newer drugs capable of lowering the glucose by novel mechanisms were not only cardiac safe, but somewhat surprisingly were able to reduce several cardiac (and renal) morbidities. Jaswaney et al1 in this issue of the Journal discuss the use of the sodium-glucose cotransporter 2 (SGLT-2) inhibitors in patients with heart failure and chronic kidney disease, including those without type 2 diabetes.

These drugs are effective adjuncts in lowering glucose and A1c levels. Designed to work by inducing glucosuria with anticipated reductions in circulating insulin levels in patients with type 2 diabetes, there was reason to think that they could reduce some of the metabolic components of type 2 diabetes that might be exacerbated by hyperinsulinemia. It was a welcome surprise (and a bit confusing) to many of us not practicing primarily in the diabetes arena that the clinical trials for multiple drugs in this class demonstrated efficacy in decreasing heart failure admissions (for patients with reduced as well as maintained ejection fraction), all-cause and cardiovascular mortality, and progression of chronic kidney disease. And, these benefits were also found in patients without type 2 diabetes. Perhaps also surprisingly, the incidences of myocardial infarction and stroke apparently were not significantly reduced,2 raising further questions about mechanism of action. But it seems quite unlikely that these benefits are from the induced glucosuria and the resultant relative hypoglycemia.

So how does gout enter into this discussion? Gout is a prototypic autoinflammatory disease that may occur in patients with long-standing hyperuricemia (generally defined as a level above urate’s estimated in vivo saturation point of 6.8 mg/dL), which can result in the deposition of monosodium urate in and around joints and sometimes in organs, including the kidney. The physiologic basis for hyperuricemia in most patients is inefficient intestinal and renal excretion, the latter being due to excess reabsorption of uric acid in the proximal tubules. Although it is the dramatic

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acutely gout flare that gets attention from patients and clinicians alike, patients with gout and hyperuricemia share many metabolic comorbidities with patients who have diabetes mellitus: chronic kidney disease, cardiovascular disease, metabolic dysfunction–associated steatotic liver disease, and hypertension. The frequent presence of these comorbidities (as well as diabetes mellitus) in patients with gout often creates therapeutic challenges when treating acute flares as well as hyperuricemia. Like the glucose control and cardiovascular disease story, successful treatment of hyperuricemia has not been rigorously demonstrated to beneficially impact the comorbidities of cardiovascular and kidney disease.

Nonetheless, it was a welcome observation that all the SGLT-2 inhibitors reduce the serum urate level, perhaps as much as 1.5 mg/dL, providing another therapeutic option to treat hyperuricemia and gout. Exploring the clinical and biological features of this effect has led to other interesting observations.

The SGLT-2 inhibitors lower the serum urate rapidly, and this effect persists as long as the drug is taken. The major, but likely not only, mechanism of action is to stimulate uricosuria. The hypouricemic effect is somewhat less in patients with type 2 diabetes, perhaps because the hyperinsulinemia is associated with increased expression of URAT1, the urate transporter primarily responsible for urate reabsorption in the proximal tubule (which may counteract the uricosuric effect of the SGLT-2-active drugs). More relevant to clinical practice, prospective studies with controls as well as observational studies have demonstrated that the SGLT-2-targeted drugs decrease the gout flare rate. These drugs are effective in the presence or absence of xanthine oxidase inhibitors like allopurinol.

A provocative observation has been that the decreased incidence of gout flares can be demonstrated fairly soon after initiation of treatment. This is in contradiction to the frequently observed increase in gout “mobilization flares” that accompanies the initiation of traditional urate-lowering drugs such as allopurinol or probenecid. That the SGLT-2 inhibitors don’t trigger mobilization flares suggests that they may also exert an anti-inflammatory effect, functionally akin to the prophylactic effect of colchicine on decreasing these early gout flares. Anti-inflammatory effects of SGLT-2 inhibitors have been demonstrated in separate experimental studies, and perhaps it is their anti-inflammatory effects on cytokine generation and macrophage polarization that explain not only their anti-gout activity, but also their beneficial effects on some of the heretofore treatment-resistant cardiovascular aspects of diabetes that were not successfully impacted by other glucose-lowering therapies. Perhaps it is the multipronged anti-inflammatory activities of these drugs that account for their diverse beneficial effects. Lowering the blood glucose may be just an extra benefit.

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Severe hyponatremia: Are you monitoring the urine output?

To the Editor: We read with great interest the article by Bassil and colleagues on severe hyponatremia in the April issue. The authors state that in patients with chronic hyponatremia the rate of sodium correction should not exceed 6 to 8 mmol/L in the first 24 hours because of the risk of osmotic demyelination syndrome (ODS).

Two recent studies argue against slow correction, i.e., 6 to 8 mmol/L per 24 hours. The first study looked at 22,858 patients with hyponatremia admitted to 5 Canadian hospitals. Rapid correction was common, occurring in 3,632 (17.7%) patients. Only 12 patients (0.05%) developed ODS, and of these, 7 did not have rapid correction of serum sodium.

The second study included 3,274 patients with severe hyponatremia who presented to 2 US hospitals with sodium levels of less than 120 mmol/L. A correction rate greater than 10 mmol/L per 24 hours was associated with lower in-hospital mortality and shorter hospital length of stay in multivariate analysis. Seven patients developed ODS, and in 5 of these the correction rate was 8 mmol/L per 24 hours or less.

Given the rarity of ODS and poor correlation with rapid correction, limiting correction to 6 to 8 mmol/L in the first 24 hours leads to frequent monitoring of electrolytes. Overcorrection leads to use of intravenous desmopressin and hypotonic fluids, which invariably leads to increased intensive care unit length of stay and possibly increased mortality. In light of the above evidence, shouldn’t the goals of correction in severe hyponatremia in the first 24 hours be liberalized?

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REFERENCES

In Reply: We appreciate the letter from Drs. Katyal and Joshi regarding our Symptoms to Diagnosis article. They point out 2 recent studies casting doubt on the long-held concept that rapidly correcting hyponatremia may contribute to the development of osmotic demyelination syndrome (ODS). These papers also suggested that a conservative rate of correction increases intensive care unit length of stay and may even increase mortality. As such, Drs. Katyal and Joshi pose an excellent question of whether the goals of hyponatremia correction should be liberalized in the first 24 hours. We sincerely appreciate their comments and discuss below why such a generalized conclusion should not be inferred based on these studies.

MacMillan et al. conducted a multicenter retrospective study in Toronto examining the association of hyponatremia with ODS. While the inclusion of 22,858 admissions with 17,254 unique patients is certainly laudable, about 87% of the cohort had a plasma sodium level of 120 mmol/L or greater and therefore had a negligible risk of ODS. In fact, only 265 patients had a plasma sodium below 110 mmol/L, which would confer a real risk of ODS. The authors reported a 0.05% total incidence of ODS, a reflection of the overall low risk of the entire cohort. However, of the patients with a plasma sodium below 110 mmol/L, 2.6% of them developed ODS, an incidence 52-fold higher than the entire cohort’s and more in line with other studies.

Patients with blood glucose levels up to 450 mg/dL were included. When examining translocational hyponatremia (hyperglycemia-mediated hyponatremia), a correction factor of 1.6 is commonly employed. However, a sodium decrease of 2.4 mmol/L for every 100 mg/dL increase in glucose concentration is more accurate, especially at higher glucose concentrations. For example, a patient with a measured plasma sodium level of 109 mmol/L and a blood glucose level of 300 mg/dL corrects to a plasma sodium of about 114 mmol/L. MacMillan et al. did not account for this, which likely inflated the cohort of patients with a true plasma sodium of less than 110 mmol/L, further decreasing the number of patients truly at risk for ODS. In addition, hyperglycemia treatment would increase the sodium levels independently, thus potentially inflating the reported “overcorrection” rates.

The adjudication of ODS in the MacMillan study also has been called into question. The diagnosis was solely based on neuroimaging, but only 64% of patients underwent imaging. Symptoms of ODS vary, and milder manifestations may not have warranted neuroimaging; as such, these milder cases may be missed. Furthermore, when examining overcorrection (defined by the authors as an increase in sodium...
levels > 8 mmol/L in a 24-hour period), the authors fail to mention whether they adjudicated for sodium relowering. Sodium relowering after an overcorrection has been shown to reverse ODS in animal models,7 and, more importantly, MacMillan et al.8,9 did not find harm or adverse events associated with addressing sodium overcorrection by relowering. Of note, patients with an identified overcorrection appropriately underwent more corrective rescue strategies (desmopressin and free water utilization) to relower sodium levels, further mitigating their ODS risk.

Katyal and Joshi note that 7 out of 12 patients with identified ODS did not undergo rapid sodium correction. However, most of these patients overcorrected all the way to hypernatremia within 2 to 11 days after admission. The reported serum sodium level in this patient subset ranged from 153 to 164 mmol/L over 7 to 11 days. This is highly unusual but highlights the role of changes in sodium levels in ODS pathophysiology.

Given the above limitations, the applicability of these results to the population of interest (patients at legitimate risk of ODS) is severely limited. To illustrate this, we note a nationwide study from Sweden examining the incidence of ODS in which 75% of identified ODS cases had a serum sodium of 110 mmol/L or less, with a median sodium of 104 mmol/L.10 About 90% of patients with identified ODS had a sodium correction exceeding 8 mmol/L in 24 hours.10

The second cited paper, Seethapathy et al.,3 suggests that a slow correction of hyponatremia leads to increased mortality. The authors indeed found improved outcomes when sodium correction rates exceeded 10 mmol/L daily compared with rates less than 6 mmol/L daily. However, the population’s baseline characteristics (Table 1 of Seethapathy et al.) reveal an interesting pattern. The cohort with sodium correction rates less than 6 mmol/L per 24 hours had a significantly higher prevalence of cirrhosis, congestive heart failure, malignancy, and metastatic cancer. It is well known that hyponatremia is an indicator of disease severity predicting adverse outcomes in cirrhosis,11 heart failure,12 and malignancy.13 Therefore, it is highly plausible that the higher mortality observed corresponds to the underlying disease process, as opposed to the rate of correction.

The rarity of ODS is repeatedly cited as a reason to forego conservative correction goals. While ODS is rare overall, it can be catastrophic. ODS manifestations can be as severe as locked-in syndrome, with prolonged symptoms lasting a year before independence in activities of daily living is regained.14 In this context, we pose the question: Does rarity negate significance? In the words of Dr. Richard Sterns, “We do not treat acutely hyponatremic patients aggressively because they WILL die of cerebral edema but because they CAN die from it. We should apply the same standard to our efforts to avoid osmotic demyelination in patients with chronic hyponatremia,” specifically in those at highest risk.15 Conservative correction rates will inherently require more time, which may include longer intensive care unit lengths of stay. However, until this approach is conclusively identified as a driver of mortality and morbidity, it should remain the standard of care for patients at high risk of ODS.

We realize that ODS in the setting of hyponatremia remains poorly understood and is likely a multifactorial phenomenon encompassing more than just nadir sodium levels or correction rates. We and other authors cite many of these contributing risk factors, reinforced by the findings of both cited cohorts. Conceivably, not every hyponatremic patient requires strict correction goals, but the 2 cited studies do not warrant abandoning our long-held strategy for patients considered at high risk for ODS.

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Varicose veins

A 60-year-old man weighing 154 lb (70 kg) presented to his primary care physician with a 20-year history of slowly worsening prominent veins in both lower limbs (Figure 1). He described intense pruritis and swelling of the ankles and pretibial areas at the end of the day that improved with leg elevation overnight. He denied pain, history of venous thrombosis, leg trauma, or other medical problems. Family history was notable for varicose veins in his mother and 2 siblings. He had tried wearing compression stockings (20 to 30 mm Hg) but discontinued using them because he found them inconvenient to put on and uncomfortable. He no longer wore short pants in public due to embarrassment about the bulging veins as well as occasional comments from others asking him what was wrong with his legs.

Figure 1. Extensive bilateral varicose veins.

Figure 2. Marked improvement of varicose veins following radiofrequency ablation in both legs.
Due to cosmetic concerns, he was referred to a vascular surgeon. Venous duplex ultrasonography showed notable femoral and saphenous vein dilation and reflux without evidence of deep venous thrombosis. The surgeon performed bilateral radiofrequency ablation of the varicose veins. The patient had marked postoperative improvement (Figure 2). Follow-up Doppler ultrasonography 1 week after radiofrequency ablation did not show evidence of deep vein thrombosis.

## LOWER-LIMB VARICOSITIES

Varicose veins are a common clinical manifestation of chronic venous disease. In the lower limbs this condition is characterized by subcutaneous dilated veins greater than or equal to 3 mm in diameter. It typically involves the great and small saphenous veins and their branches.1,2

Lower-limb varicocities are thought to result from elevated venous pressure in the extremities due to incompetent valves that allow reflux of blood backward, obstruction, or a combination of reflux and obstruction, thereby impairing adequate venous return.3 Risk factors for developing varicose veins include occupation requiring prolonged standing or walking and history of venous thrombosis, among others.4

Chronic venous disorders are graded using the Clinical, Etiologic, Anatomical, Pathophysiologic (CEAP) classification; in this system, the visible signs of chronic venous disease range from C0 (no visible or palpable disease) to C6 (venous ulcer), with varicose veins considered class C2.1

### Evaluation

Patients with varicose veins can be asymptomatic or can present with clinical features including leg pain, heaviness, swelling, dryness, itching, skin changes, and ulceration.1 When examining patients with varicose veins, it is important to evaluate the varicosity pattern. In patients with symptomatic varicose veins and suprapubic or abdominal wall varicosities and in patients with leg heaviness, fullness, swelling, and claudication, evaluation for iliofemoral venous obstruction with Doppler ultrasonography is indicated to find the source of reflux.1 In those with medial thigh or vulvar varicosities and symptoms of pelvic venous congestion (eg, chronic pelvic pain, dysmenorrhea, dyspareunia, and urinary urgency), evaluation of pelvic venous pathology with Doppler ultrasonography is needed given the association between pelvic venous insufficiency and these varicosity patterns.1 Scrotal varicosities can suggest gonadal vein incompetence, nutcracker syndrome (left renal vein compression between the superior mesenteric artery and aorta), inferior vena cava lesions, or renal carcinoma.5

Color duplex ultrasound is the first diagnostic test recommended for patients presenting with varicose veins to confirm the absence of deep and superficial venous thrombosis.

Differential diagnoses to consider for chronic venous insufficiency include lymphedema, congestive heart failure, and renal disease.6

### Treatment options

Untreated varicose veins can cause venous ulcers, pain, or, most commonly, aesthetic concerns, which is often why treatment is sought. Treatment of lower-extremity chronic venous disease depends on the CEAP classification and the severity of disease based on the Venous Clinical Severity score.1,6

Treatment of varicose veins often begins with conservative measures using moderate-pressure compression stockings (20–30 mm Hg) and lifestyle modifications such as weight loss and leg elevation.7 Compared with no stockings, compression stockings can improve symptoms, control edema, and improve orthostatic venous pressure.7 However, there is insufficient evidence to support their effectiveness as the primary treatment of varicose veins.1 When considering compression stockings, it is crucial to ensure that the patient does not have coexisting arterial insufficiency, which compression can worsen. Also, in practical terms, compression stockings have low compliance rates (as low as 37%) due to discomfort.1

Referral to vascular surgery for endovenous therapy (laser or radiofrequency ablation and sclerotherapy) or open venous surgical intervention (ligation or phlebectomy [or venous stripping]) may be indicated for patients with varicose veins refractory to conservative treatment or symptomatic varicose veins with axial reflux in the great or small saphenous vein.1 The type of surgical intervention is based on the size, location, and extent of venous involvement.4

Cosmetic improvement following radiofrequency ablation is around 70%, with optimal results occurring when patients wear compression stockings for 7 to 10 days after treatment6 and ambulate early. Complications of radiofrequency ablation include deep vein thrombosis, heat-induced thrombus extension, or, rarely, pulmonary embolism.1,2,8 Postprocedural duplex scanning within 1 week is routinely recommended.1

## DISCLOSURES

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


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Q: Do patients with sepsis benefit from intravenous albumin?

My hospitalized adult patient with sepsis is hypotensive despite adequate resuscitation with intravenous (IV) crystalloid fluid. Should I administer a bolus of IV albumin?

A: In hospitalized patients with sepsis who do not need vasopressors, administration of IV albumin affords no morbidity or mortality benefit compared with IV crystalloid therapy alone.

■ HOW DO WE DEFINE SEPSIS?

Sepsis is a clinical definition designed to identify patients at high risk of death due to infection. In modern practice, sepsis is most commonly defined as the presence of 2 or more of the following systemic inflammatory response syndrome criteria plus a suspected or confirmed infectious source:

- Heart rate greater than 90 beats per minute
- Respiratory rate greater than 20 breaths per minute
- Temperature above 38°C or below 36°C
- White blood cell count greater than 12 × 10⁹/L or less than 4 × 10⁹/L.¹

Severe sepsis is defined as sepsis plus evidence of end-organ dysfunction, hypotension, or hypoperfusion; septic shock is defined as severe sepsis with hypotension requiring vasopressors despite adequate fluid resuscitation.¹ Treatment is guided by the Surviving Sepsis Campaign 2021 guidelines,² with IV fluid resuscitation being a key component of effective management.

■ WHAT ARE THE TYPES OF IV FLUIDS?

IV fluids can be divided into crystalloid solutions, which are composed of small solutes (ie, electrolytes and glucose) dissolved in water, and colloid solutions, which are composed of large solutes (ie, proteins) dissolved in water. The most commonly used crystalloid solutions include normal saline, lactated Ringer’s solution, Plasma-Lyte A, and 5% dextrose in water. The most commonly used colloid solutions include human serum albumin, plasma products, and whole blood.³

■ WHAT IS HUMAN SERUM ALBUMIN, AND HOW DOES IT WORK?

Human serum albumin is a purified human blood product derived from pooled plasma donations. It consists of concentrated large proteins (albumin) dissolved in water. Theoretically, it serves to draw fluid into the blood vessel, thereby increasing IV colloid osmotic pressure and expanding effective circulating volume.⁴ However, physiologic studies have shown that these theoretical effects do not consistently translate into the expected clinical effects. For example, in postsurgical cardiac surgery patients, IV albumin is a more effective plasma volume expander than normal saline. Despite this, normal saline has similar effects as albumin on interstitial fluid volume, suggesting that fluid balance is a complex process dependent on mechanisms beyond plasma volume expansion alone.⁵

In the United States, human serum albumin is available in a 5% formulation, with the remainder of the solution composed of 95% normal saline, and in a 25% formulation, with the remainder of the solution composed of 75% normal saline.⁶ When the therapeutic goal is to raise the plasma albumin concentration while minimizing infusion of additional sodium and fluid volume, 25% albumin is the preferred formulation. Alternatively, when the goal is to provide patients with additional plasma fluid volume, 5% albumin is preferred.⁶

As a blood product, albumin carries risks, including transfusion-related acute lung injury, transmission of...
SEPSIS AND IV ALBUMIN

The utility of albumin in patients with sepsis remains controversial. Multiple randomized controlled trials have investigated albumin as a resuscitation fluid in sepsis dating back to 2004, after consistent implementation of the Surviving Sepsis guidelines. None of these trials has proven albumin to be superior to crystalloid.

The first of these trials was the 2004 Saline versus Albumin Fluid Evaluation (SAFE) study. This study explored whether albumin improved outcomes in all comers to the intensive care unit (ICU) compared with normal saline. Nearly 7,000 patients, 20% of whom had sepsis, were randomized to receive all ICU fluid resuscitation with either 4% albumin or normal saline for up to a 28-day period. Patients admitted for burns, liver transplantation, and cardiac surgery were excluded. The study found no difference between the albumin and saline groups in mortality, hospital length of stay, ICU length of stay, duration of mechanical ventilation, or duration of renal replacement therapy. The SAFE study established that albumin does not improve outcomes in undifferentiated ICU patients. However, a subgroup analysis of patients admitted for severe sepsis identified a trend toward decreased mortality in patients treated with albumin compared with patients treated with normal saline.

The Albumin Italian Outcome Sepsis (ALBIOS) trial sought to address the question of albumin efficacy in sepsis. ALBIOS was a 2014 multicenter, open-label, randomized controlled trial in which 1,818 patients admitted to the ICU for severe sepsis were randomized to either 20% albumin plus crystalloid resuscitation or crystalloid resuscitation alone. Patients in the albumin group received up to 300 mL of 20% albumin daily for up to 7 days to maintain a serum albumin level of at least 3 g/dL, which ensured consistent and adequate replacement of albumin. Of note, IV albumin was not provided specifically as a fluid bolus for early fluid resuscitation. As in the SAFE study, patients admitted for burns, liver transplantation, and cardiac surgery were excluded. Despite these additional steps, this trial found no significant difference in mortality, organ dysfunction, ICU length of stay, or hospital length of stay in the albumin group compared with the crystalloid group. A post hoc analysis in 1,121 patients with septic shock found a 6.3% absolute reduction in 90-day mortality in patients who received albumin. However, the authors cautioned readers about the generalizability of this result and recommended further confirmation.

Two recent meta-analyses examined the question of colloid vs crystalloid fluid resuscitation. Martin and Basset found that undifferentiated critically ill patients who received colloid fluid had higher central venous pressure, mean arterial pressure, and cardiac index compared with patients who received crystalloid fluid alone. There was no statistically significant difference in mortality. This meta-analysis suggests that resuscitation with colloid fluid may afford improved hemodynamics compared with crystalloid fluid; however, the applicability of these results to patients with sepsis is limited by the study's broad inclusion criteria. Geng et al found that patients with septic shock who were given 20% albumin had lower 90-day mortality compared with those treated with crystalloid fluid alone. However, there was no statistically significant difference in mortality among patients with sepsis or severe sepsis. While this suggests a potential benefit of colloid fluid in appropriate patients with septic shock, it reaffirms that colloid fluid does not confer mortality benefit in septic patients without shock.

Given the lack of consensus and randomized controlled trial data to support the use of albumin as a first-line resuscitation fluid in sepsis, the Surviving Sepsis Campaign guidelines suggest using a balanced crystalloid solution such as lactated Ringer’s or Plasma-Lyte A. These guidelines are based on the Isotonic Solutions and Major Adverse Renal Events Trial (SMART), which showed a mortality benefit in a subset of patients with sepsis who were treated with balanced crystalloid solutions instead of normal saline.

ARE THERE OTHER INDICATIONS FOR ALBUMIN?

While not clearly indicated for patients with sepsis, there are some evidence-based indications for administration of human serum albumin. For example, it has US Food and Drug Administration approval for use after large-volume paracentesis in patients with cirrhosis, as it has been shown to decrease postprocedural hemodynamic shifts and improve mortality. In patients with cirrhosis, human serum albumin has been shown to decrease rates of kidney injury and mortality in both spontaneous bacterial peritonitis and hepato renal syndrome. When human serum albumin is used for these indications, the goal is to reduce the deleterious effects of abnormal hepatic physiology on
the circulatory system, thereby conferring renal protection and improving hemodynamics.

**THE BOTTOM LINE**

In the vast majority of patients hospitalized with sepsis, fluid resuscitation with IV albumin confers additional risk associated with transfusion of human blood products, substantially higher cost, and no proven morbidity or mortality benefit compared with IV crystalloid fluid. Hypotensive patients with sepsis should receive fluid resuscitation with crystalloid fluids alone. Patients who remain hypotensive despite adequate fluid resuscitation should receive vasopressors without delay.

**DISCLOSURES**

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

**REFERENCES**


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Q: Does my patient with acute variceal hemorrhage need a transjugular intrahepatic portosystemic shunt?

A: Preemptive TIPS insertion should be considered within 72 hours of initial endoscopy in this patient as he is at high risk for rebleeding (Child-Pugh class C [score ≥ 10 points]). Preemptive TIPS insertion would reduce his rebleeding risk, and preemptive TIPS has been shown to improve overall mortality in patients with variceal hemorrhage.

Variceal hemorrhage is a common decompensating event and a dreaded complication in patients with cirrhosis. Varices are portosystemic collateral vessels that form in the gastrointestinal tract because of clinically significant portal hypertension. This is typically defined as a hepatic venous pressure gradient of 10 mm Hg or greater. In patients with cirrhosis, varices most commonly form in the distal esophagus and the proximal stomach.

VARICEAL HEMORRHAGE MANAGEMENT

Variceal hemorrhage is associated with a 6-week mortality rate of up to 15%. If not appropriately treated at the time of initial presentation, variceal hemorrhage can recur in up to 60% of patients. Treatment goals in acute variceal hemorrhage include adequate hemostasis and prevention of rebleeding, the combination of which has been shown to reduce 6-week mortality. In more than 90% of cases, variceal hemorrhage can be controlled with endoscopic and pharmacologic interventions. Endoscopic variceal ligation and medications that reduce portal venous pressure, such as nonselective beta-blockers, are used in both primary and secondary prophylaxis strategies for variceal hemorrhage management.

Placement of a TIPS, which reduces the hepatic venous pressure gradient by diverting blood from the portal venous system to the systemic circulation, is another potential treatment strategy for variceal hemorrhage. It can be used as salvage therapy to control bleeding when endoscopic management fails and as a means of secondary prophylaxis in selected patients. Because TIPS insertion is an invasive procedure with potential serious side effects, it is not routinely considered as a primary prophylactic strategy to prevent variceal hemorrhage.

HOW IS A TIPS PLACED?

A TIPS is an endovascular shunt that connects the portal vein to the systemic circulation; TIPS insertion is usually performed by an interventional radiologist. Under fluoroscopic guidance, the hepatic vein is accessed through the jugular vein. Once the hepatic vein is cannulated, a needle is used to puncture the portal vein and an expandable polytetrafluoroethylene-covered stent is placed in the portal vein. The stent is then connected to a catheter placed in the hepatic vein. This creates an shunt that diverts blood from the portal vein to the hepatic vein, reducing portal pressure and preventing rebleeding.

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS
is deployed, creating a direct connection between the portal vein (portal circulation) and the hepatic vein (systemic circulation). This effectively produces a porto-caval shunt and reduces the hepatic venous pressure gradient.2 During the procedure, the pressure gradient is measured before and after TIPS insertion to ensure that the portal venous system has been successfully decompressed with placement of the shunt.2 The target post-TIPS hepatic venous pressure gradient is less than 12 mm Hg or a 50% decrease in the pre-TIPS gradient.2

Once placed, the permanent endovascular TIPS does not require routine intervention except in the event of dysfunction.

WHEN TO CONSIDER TIPS INSERTION AFTER ACUTE VARICEAL HEMORRHAGE

Once the presence of a variceal hemorrhage is confirmed, TIPS insertion should be considered in the following scenarios.

Uncontrolled bleeding
Salvage TIPS should be pursued if hemostasis cannot be achieved during endoscopy.3,5 In this setting, TIPS insertion is considered an emergency procedure. Even though it is successful in controlling bleeding in more than 80% of cases, 6-week mortality remains high as patients experience increased rates of liver failure, renal failure, and infection.6 In a retrospective analysis of 83 patients treated with a salvage TIPS, 6-week survival was 100% in those with an arterial lactate level of 2.5 mmol/L or less and a MELD score of 15 or less, but 5% in those with a lactate level of 12 mmol/L or higher and a MELD score of 30 or higher.6 Hence, salvage TIPS is not recommended in patients with a Child-Pugh score of 14 or higher, a MELD score greater than 30, or an arterial lactate level greater than 12 mmol/L unless liver transplantation is an option.5

Recurrence of bleeding within 5 days
If a patient with variceal hemorrhage rebleeds within 5 days of an index bleed, they are considered to have failed first-line management and salvage TIPS is recommended.3,5

High risk for rebleeding
Preemptive TIPS insertion should be done within 72 hours of variceal hemorrhage in patients considered to be at high risk for rebleeding, with high risk defined as Child-Pugh class C (≥ 10 points) cirrhosis and Child-Pugh class B (7–9 points) cirrhosis with active bleeding at the time of endoscopy (Table 1).2,3,5,7

The efficacy of this intervention was demonstrated in the landmark multicenter, randomized controlled trial by García-Pagán et al8 in 2010. Sixty-three patients with Child-Pugh class C or class B cirrhosis with active variceal bleeding on endoscopy were randomized to TIPS placement within 72 hours of diagnostic endoscopy vs standard of care (endoscopic therapy plus nonselective beta-blockers). The 1-year probability of remaining free of failure to control bleeding and of variceal rebleeding was 97% in the preemptive TIPS group vs 50% in standard-of-care group (number needed to treat = 2.1).8 Survival at 6 weeks and 1 year was significantly higher in the preemptive TIPS group than in the standard-of-care group (number needed to treat = 3.3 and 4, respectively). Moreover, there was not a significant difference in serious adverse events among the 2 groups.8

Several studies since 2010 have shown the survival benefit of preemptive TIPS. In an individual-patient data meta-analysis of 8 studies and 1,389 patients,9 preemptive TIPS significantly improved 1-year survival compared with standard of care in patients with acute variceal hemorrhage (hazard ratio 0.43, 95% confidence interval 0.32–0.60, number needed to treat = 6), providing strong evidence in support of preemptive TIPS. The recently published Baveno VII guidelines5 state that acute-on-chronic liver failure, hepatic encephalopathy, and hyperbilirubinemia at admission should not be contraindications to preemptive TIPS.

Preemptive TIPS has primarily been studied in patients with bleeding from esophageal varices. There is limited evidence from an underpowered study showing improved rebleeding-free survival in patients with gastric fundal variceal hemorrhage.10

Secondary prophylaxis
Elective TIPS insertion is recommended in patients in whom first-line secondary prophylaxis measures
Suspicion of acute variceal bleed in a patient with cirrhosis who presents with an upper gastrointestinal bleed

Start preendoscopic management

Resuscitation
- Conservative transfusion strategy with a target hemoglobin of 7 to 8 g/dL
- Fresh frozen plasma and platelet transfusions are not recommended as they do not correct coagulopathy and can lead to volume overload

Location
- Intensive care unit or step-down unit
- If patient is actively vomiting or has altered mentation, intubation before endoscopy is required

Initial medical management
- Start vasoactive drugs (somatostatin, octreotide, or terlipressin) and continue for 2 to 5 days
- Start antibiotic prophylaxis with intravenous ceftriaxone 1 g daily for 5 days
- Start intravenous proton pump inhibitors empirically, as peptic ulcer disease is common in patients with cirrhosis

Perform endoscopy within 12 hours of presentation

Variceal hemorrhage confirmed or suspected
- Bleeding from a varix or presence of a “white nipple” (a sign of recent bleeding)
- Presence of varices and blood present in the stomach, or varices present without blood in the stomach if esophagogastroduodenoscopy was performed 24 hours after the hemorrhage

Evaluate for indications for TIPS
- Uncontrolled bleeding → salvage TIPS
- Rebleeding within 5 days → salvage TIPS
- High risk for rebleeding: Child-Pugh class C or class B (see Table 1) plus active bleeding → preemptive TIPS
- Secondary prophylaxis → elective TIPS
  - First-line prophylaxis failed
  - First gastric variceal bleed
  - Recurrent ascites

Assess for contraindications to TIPS
- Heart failure
- Severe hepatic encephalopathy
- Pulmonary hypertension
- Uncontrolled sepsis

Indication for TIPS not present or contraindication to TIPS present
- Start a nonselective beta-blocker, preferably carvedilol
- Perform serial endoscopic variceal ligation until eradication

Figure 1. Initial management of patients with cirrhosis presenting with signs of acute variceal hemorrhage.

TIPS = transjugular intrahepatic portosystemic shunt

Based on information from reference 2.
VARICEAL HEMORRHAGE

**Table 2**

Reported rates of complications from transjugular intrahepatic portosystemic shunts

<table>
<thead>
<tr>
<th>Complications</th>
<th>Reported rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td></td>
</tr>
<tr>
<td>Hemoperitoneum</td>
<td>3</td>
</tr>
<tr>
<td>Biliary peritonitis</td>
<td>0.5</td>
</tr>
<tr>
<td>Stent malposition</td>
<td>1</td>
</tr>
<tr>
<td>Hemobilia</td>
<td>2</td>
</tr>
<tr>
<td>Renal failure requiring dialysis</td>
<td>0.25</td>
</tr>
<tr>
<td>Hepatic infarction</td>
<td>0.5</td>
</tr>
<tr>
<td>Hepatic artery injury</td>
<td>1</td>
</tr>
<tr>
<td>Liver failure</td>
<td>3</td>
</tr>
<tr>
<td>Minor</td>
<td></td>
</tr>
<tr>
<td>Medically controlled encephalopathy</td>
<td>15–25</td>
</tr>
<tr>
<td>Transient pulmonary edema</td>
<td>1</td>
</tr>
<tr>
<td>Fever</td>
<td>2</td>
</tr>
<tr>
<td>Entry-site hematoma</td>
<td>2</td>
</tr>
</tbody>
</table>

Based on information from reference 19.

(eg, endoscopic variceal ligation plus nonselective beta-blockers) have failed. This recommendation is supported by evidence from randomized controlled trials in which patients who underwent TIPS insertion had significantly lower rates of rebleeding compared with those who did not undergo TIPS insertion. Of note, these trials showed no difference in survival among the TIPS vs non-TIPS groups, and the incidence of hepatic encephalopathy was higher in the TIPS group.

Current guidelines recommend TIPS insertion as the first-line form of secondary prophylaxis following an acute bleed from gastric fundal varices. These varices are less common than esophageal varices but tend to bleed more severely. Because gastric fundal variceal hemorrhage is less common, studies evaluating the role of TIPS after variceal hemorrhage in this location are limited. In a randomized controlled trial that included 72 patients with cirrhosis and acute gastric variceal bleeding, variceal rebleeding occurred less often in patients who received a TIPS for secondary prophylaxis compared with those who received cyanoacrylate injections.

The Baveno VII guidelines include a new recommendation to consider TIPS insertion for first-line therapy after a variceal hemorrhage in patients with recurrent ascites, defined as 3 or more large-volume paracenteses in a year. Of note, regardless of whether variceal hemorrhage occurs, TIPS insertion should be considered in patients with recurrent ascites.

**Figure 1** outlines the initial management of patients with cirrhosis presenting with signs of acute variceal bleeding.

**Considerations for TIPS**

Pre-TIPS evaluation requires contrast-enhanced cross-sectional imaging to evaluate the vasculature as part of procedure planning. In emergent situations, bedside Doppler ultrasonography of the liver may suffice. Because a TIPS diverts blood directly to the systemic circulation, echocardiography is needed to assess the ejection fraction, right heart function, and potential for pulmonary hypertension; severe preexisting abnormalities can precipitate circulatory dysfunction after TIPS insertion.

Absolute contraindications to TIPS include American Heart Association heart failure stage C or D, ejection fraction of less than 50%, severe pulmonary hypertension (mean pulmonary artery pressure > 45 mm Hg), and severe tricuspid regurgitation. Similarly, because blood is bypassed into the systemic circulation without being filtered through the liver, a history of severe uncontrolled hepatic encephalopathy is a strong contraindication, as is uncontrolled systemic infection.

Relative contraindications are untreated severe biliary obstruction, severe uncontrollable coagulopathy, polycystic liver disease, and hepatocellular carcinoma.

There is no specific MELD score cutoff, but trials for elective and preemptive TIPS procedures have excluded patients with a Child-Pugh score of 14 or higher and a MELD score of 18 or more, as higher MELD scores are associated with a worse prognosis. MELD scores higher than 30, Child-Pugh scores of 14 or greater, and lactate levels above 12 mmol/L typically render salvage TIPS attempts futile.

Prophylactic rifaximin can be prescribed to reduce the risk of hepatic encephalopathy, as supported by a randomized controlled trial in which rifaximin started 14 days before TIPS placement resulted in a 19% absolute risk reduction in post-TIPS hepatic encephalopathy.

The decision to insert a TIPS should be made by a multidisciplinary team involving at least a hepatologist and interventional radiologist.

**TIPS-related complications**

Procedural complications include injury to the vasculature causing intraperitoneal bleeding, hemobilia, hepatic infarct, immediate TIPS thrombosis, cardiac arrhythmias, and sepsis. Procedure-related deaths occur in less than 1% of patients who undergo TIPS placement. Increases in total bilirubin and international normalized ratio can be seen after TIPS insertion.
but have not been associated with negative outcomes. Long-term complications include hepatic encephalopathy, cardiac overload, and deterioration of liver function. Table 2 lists rates of complications related to TIPS insertion.

### POST-TIPS CARE

After TIPS insertion, if the hepatic venous pressure gradient drops below 12 mm Hg, nonselective beta-blockers (eg, carvedilol) may be discontinued. Doppler ultrasonography evaluation is routinely performed within 1 to 4 weeks to screen for TIPS dysfunction and assess patency, and is repeated at regular intervals thereafter.

### REFERENCES


### 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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SGLT-2 inhibitors in heart failure and chronic kidney disease: A review for internists

ABSTRACT

Despite current therapies, heart failure and chronic kidney disease continue to be major causes of morbidity and mortality. Sodium-glucose cotransporter 2 (SGLT-2) inhibitors have recently become standard-of-care therapy for these conditions. This review summarizes important randomized controlled trials of SGLT-2 inhibitors and guidelines for using these agents in patients with heart failure and chronic kidney disease in both clinic and hospital settings.

KEY POINTS

- SGLT-2 inhibitors decrease the risk of cardiovascular events in patients with heart failure regardless of ejection fraction and the presence of diabetes.
- SGLT-2 inhibitors decrease the risk of chronic kidney disease progression in patients with chronic kidney disease regardless of the presence of diabetes.
- SGLT-2 inhibitors are relatively safe and generally well tolerated.

Heart failure and chronic kidney disease are common diseases that lead to considerable morbidity and mortality. Modern medical therapy has substantially reduced the burden associated with both conditions. A recent addition to the standard of care is therapy with sodium-glucose cotransporter 2 (SGLT-2) inhibitors. Though initially approved for glycemic control in type 2 diabetes, SGLT-2 inhibitors use novel mechanisms that further improve outcomes for individuals with these conditions.

This review summarizes recent data and guidelines regarding the use of SGLT-2 inhibitors in heart failure and chronic kidney disease and provides practical guidance for their use in both the general medical clinic and hospital ward.

SGLT-2 INHIBITORS IN HEART FAILURE

Chronic heart failure with reduced (≤ 40%) ejection fraction

A 68-year-old man with hypertension and hyperlipidemia was admitted to the hospital for acute decompensated heart failure. During the hospitalization, echocardiography revealed a reduced ejection fraction of 35%, and he was started on a low-dose beta-blocker, sacubitril-valsartan, spironolactone, and daily furosemide before discharge. Two weeks after discharge, he presented to the clinic with a blood pressure of 105/68 mm Hg and heart rate of 69 beats per minute. Serum creatinine was normal. He was still experiencing some exertional dyspnea but otherwise felt well and was euvolemic on examination. He asked about any additional therapy that would improve his prognosis.
SGLT-2 INHIBITORS

The beneficial effect of SGLT-2 inhibition in the management of heart failure with reduced ejection fraction (HFrEF) was first noted after reduced rates of incident heart failure hospitalization were observed in the initial trials of SGLT-2 inhibitors in patients with diabetes and increased cardiovascular risk. Mechanisms of this benefit are complex and unclear and appear to involve improved diuretic effect, myocardial metabolism, and vascular function. Several randomized controlled trials were eventually conducted to investigate the benefits of SGLT-2 inhibitors in heart failure regardless of the presence of diabetes.

The Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure (DAPA-HF) trial randomized 4,744 patients with reduced ejection fraction (≤ 40%) and symptomatic heart failure to receive dapagliflozin 10 mg or placebo, in addition to otherwise-prescribed guideline-directed medical therapy. Patients with severe renal disease, acute decompensated heart failure, recent myocardial infarction, recent percutaneous coronary intervention, recent coronary artery bypass grafting, type 1 diabetes, or life expectancy less than 2 years were excluded from the trial. In this trial, the primary composite outcome of worsening heart failure (unplanned hospitalization or urgent visit for heart failure) or death from cardiovascular causes occurred at a lower rate in patients receiving dapagliflozin compared with placebo (16.3% vs 21.2%; P < .001; number needed to treat = 21). Notably, compared with placebo, dapagliflozin treatment demonstrated a reduction in the risk of each component of the primary end point, fewer serious safety events, and improved quality of life scored via the Kansas City Cardiomyopathy Questionnaire.

Another randomized controlled trial, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction (EMPOWER-Reduced), randomized 3,730 patients with symptomatic HFrEF (ejection fraction ≤ 40%) and with or without diabetes to empagliflozin 10 mg daily or placebo in addition to other guideline-directed medical therapies. This trial also reported a significant reduction in the primary composite outcome of hospitalization for heart failure or cardiovascular death in the empagliflozin group (19.4% vs 24.7% in the placebo group; number needed to treat = 19).

The DAPA-HF and EMPORER-Reduced trials led to a paradigm shift in the use of SGLT-2 inhibitors in patients with HFrEF. The 2022 guideline for the management of heart failure from the American Heart Association (AHA), American College of Cardiology (ACC), and Heart Failure Society of America (HFSA) provides Class 1a (highest level of benefit and highest level of evidence) recommendations for SGLT-2 inhibition for the management of symptomatic chronic HFrEF (ejection fraction ≤ 40%), regardless of diabetes status. Maximizing doses of all 4 guideline-directed medical therapy classes (beta blockade, renin-angiotensin inhibition, mineralocorticoid receptor antagonism, and SGLT-2 inhibition) maximizes clinical benefit.

In our case, the patient continued with maximum-tolerated doses of beta blockade, renin-angiotensin inhibition with a neprylisin inhibitor, and mineralocorticoid inhibition. SGLT-2 inhibitor therapy was considered with either dapagliflozin 10 mg daily or empagliflozin 10 mg daily. Given that the patient appeared to be euvolemic, it was likely that furosemide could be safely discontinued, as the natriuretic effects of the SGLT-2 inhibitor would offset the loss of the loop diuretic.

Chronic heart failure with mildly reduced or preserved (≥ 50%) ejection fraction

A 48-year-old man with obesity and hypertension was hospitalized owing to progressive shortness of breath. At admission, his examination was notable for elevated jugular venous pressure and mild lower-extremity edema. His echocardiogram demonstrated an ejection fraction of 55% and grade 2 diastolic dysfunction. He was treated with intravenous furosemide, which improved his symptoms. At the time of his clinic follow-up visit, the patient inquired about any therapies that would reduce his risk of returning to the hospital.

Heart failure with preserved ejection fraction accounts for approximately half of all hospitalizations for acute decompensated heart failure. Unlike HFrEF, many trials involving these patients have been unsuccessful in demonstrating the benefit of traditional heart failure therapies including beta-blockers, mineralocorticoid inhibitors, or renin-angiotensin inhibitors.

In response to the benefit observed with SGLT-2 inhibitors in patients with HFrEF, the Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction (EMPOWER-Preserved) was designed to test the hypothesis that empagliflozin benefits patients with heart failure with preserved ejection fraction. This randomized controlled trial assigned 5,988 patients with New York Heart Association class II to IV heart failure and ejection fraction greater than 40% to either empagliflozin 10 mg or placebo. Notable exclusion criteria were acute decompensated heart failure, atrial fibrillation or flutter, history of infiltrative cardiomyopathy, severe valvular disease, chronic severe pulmonary disease,
impaired renal function with an estimated glomerular filtration rate less than 20 mL/minute/1.73 m², or severe anemia. This study found a significant reduction in the primary composite end point of hospitalization for heart failure and cardiovascular death in the empagliflozin group (13.8% vs 17.1% in the placebo group; P < .001; number needed to treat = 31). This finding was primarily driven by a 29% relative risk reduction in the rate of hospitalization for heart failure. Notably, subgroup analyses demonstrated a consistent effect across all prespecified ejection fraction ranges, including an ejection fraction of greater than 50%. Subsequently, the Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure (DELIVER-HF) trial investigated the benefit of dapagliflozin in patients with symptomatic heart failure with preserved ejection fraction. In this trial, 6,263 patients with symptomatic heart failure with preserved ejection fraction were randomized to dapagliflozin 10 mg or placebo. The trial reported a significant reduction in the primary composite end point of worsening heart failure and cardiovascular death (16.4% vs 19.5%; number needed to treat = 32), also driven by a reduction in worsening heart failure.

The results from the DELIVER-HF trial were not incorporated into the 2022 ACC/AHA/HFSA guideline, which gives SGLT-2 inhibitors a class 2a recommendation (likely benefit with moderate quality evidence). The 2023 ACC expert consensus statement, however, suggested using SGLT-2 inhibitors in patients with heart failure with preserved ejection fraction given the results of the DELIVER-HF and EMPORER-Preserved trials. In our case, the patient appeared to be stable with residual symptomatic heart failure with preserved ejection fraction. An SGLT-2 inhibitor was indicated, either empagliflozin 10 mg or dapagliflozin 10 mg daily.

Acute heart failure
A 55-year-old man with hypertension presented to the hospital with shortness of breath. He had not been to his primary care physician for several years and had stopped taking his antihypertensive medication. In the hospital, his blood pressure was 190/110 mm Hg with jugular venous distention, bilateral rhonchi, and pitting edema on examination. Echocardiography demonstrated an ejection fraction of 40%, and he was informed of his diagnosis of congestive HFpEF. He was given intravenous diuretic therapy that significantly improved his symptoms. He asked whether any therapies could be suggested to take in the hospital to improve his prognosis.

Acute decompensated heart failure accounts for about 1.2 million hospitalizations in the United States. Management of this serious condition is challenging, and often relies on diuretic therapy. SGLT-2 inhibition in acute heart failure exacerbation has been suggested as a possible adjunctive therapy to current care.

To examine this question, the Study to Test the Effect of Empagliflozin in Patients Hospitalized for Acute Heart Failure Who Have Been Stabilized (EMPULSE) randomized 530 patients regardless of ejection fraction to either empagliflozin 10 mg daily or placebo at the time of clinical stability. The primary outcomes were a hierarchical assessment of time to all-cause death, number of heart failure events, and change in Kansas City Cardiomyopathy Questionnaire total symptom score. The trial demonstrated significant benefit in all 3 elements of the primary composite outcome for patients administered empagliflozin. The Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial evaluated sotagliflozin, a combined SGLT-1/2 inhibitor, in patients soon after recent hospitalization for worsening heart failure. Despite loss of sponsorship leading to limited enrollment, this trial found that patients receiving sotagliflozin had a significant reduction (P < .001) in the primary composite end point of total number of deaths from cardiovascular causes and hospitalizations and urgent visits for heart failure compared with patients receiving placebo.

It is important to note that the 2022 ACC/AHA/HFSA guideline does not specifically recommend SGLT-2 inhibitors in treating acute decompensated heart failure. However, it does suggest the continuation and optimization of guideline-directed medical therapy, as initiation of these therapies at maximum doses before discharge can help reduce adverse outcomes.

Based on the results of the EMPULSE trial, it would be reasonable to initiate empagliflozin 10 mg daily in our patient, after he was stable and before he was discharged.

Clinical trials of SGLT-2 inhibitors in heart failure are summarized in Table 1.
As with heart failure, recent trials\textsuperscript{21–24} have shown that SGLT-2 inhibitors reduce the risk of kidney disease progression and death among individuals with chronic kidney disease. A recent systematic review and meta-analysis of 12 randomized controlled trials that included 38,949 participants with an estimated glomerular filtration rate less than 60 mL/minute/1.73 m\textsuperscript{2} found that use of an SGLT-2 inhibitor was associated with a 23% lower incidence of chronic kidney disease progression compared with placebo (relative risk 0.77; 95% confidence interval 0.68–0.88).\textsuperscript{21}

### TABLE 1

**Trials of sodium-glucose cotransporter 2 inhibitors in heart failure**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Intervention</th>
<th>Primary composite end point</th>
<th>Primary composite results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heart failure with reduced ejection fraction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAPA-HF (2019)\textsuperscript{8}</td>
<td>4,744 adults</td>
<td>Dapagliflozin 10 mg</td>
<td>Cardiovascular death or worsening heart failure</td>
<td>16.3% vs 21.2% (NNT = 21)</td>
</tr>
<tr>
<td>EMPORER-Reduced (2020)\textsuperscript{9}</td>
<td>3,730 adults</td>
<td>Empagliflozin 10 mg</td>
<td>Cardiovascular death or worsening heart failure</td>
<td>19.4% vs 24.7% (NNT = 19)</td>
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<tr>
<td><strong>Heart failure with preserved ejection fraction</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPORER-Preserved (2021)\textsuperscript{15}</td>
<td>5,988 adults</td>
<td>Empagliflozin 10 mg</td>
<td>Cardiovascular death or hospitalization for heart failure</td>
<td>13.8% vs 17.1% (NNT = 31)</td>
</tr>
<tr>
<td>DELIVER-HF (2022)\textsuperscript{16}</td>
<td>6,263 adults</td>
<td>Dapagliflozin 10 mg</td>
<td>Cardiovascular death or worsening heart failure</td>
<td>16.4% vs 19.5% (NNT = 32)</td>
</tr>
<tr>
<td><strong>Acute decompensated heart failure</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPULSE (2022)\textsuperscript{19}</td>
<td>530 adults</td>
<td>Empagliflozin 10 mg</td>
<td>All-cause death, heart failure events,\textsuperscript{a} Kansas City Cardiomyopathy Questionnaire score</td>
<td>53.4% vs 39.7% (Win ratio\textsuperscript{b} 1.36 (95% confidence interval: 1.09–1.68))</td>
</tr>
<tr>
<td>SOLOIST-WHF (2021)\textsuperscript{20}</td>
<td>1,222 adults</td>
<td>Sotagliflozin 200 or 400 mg</td>
<td>Events of cardiovascular deaths, hospitalizations and urgent visits for heart failure</td>
<td>51% vs 76.3% (NNT = 4)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}EMPULSE: heart failure events include heart failure hospitalizations, urgent heart failure visit, unplanned outpatient heart failure visit, and worsening symptoms or intensification of therapy.

\textsuperscript{b}Win ratio in favor of empagliflozin; the primary outcome analysis defined a “win” as when, in the common follow-up time, the patient did not die, have an increased number of exacerbations, have an earlier time to first exacerbation, or have a change in Kansas City Cardiomyopathy Questionnaire score < 5 points in hierarchal fashion. If any end point was achieved, it was considered a loss. The “wins ratio” was calculated for each group as the ratio of “wins” to “losses.”

DAPA-HF = Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure; DELIVER-HF = Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure; EF = ejection fraction; eGFR = estimated glomerular filtration rate; EMPORER-Preserved = Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction; EMPORER-Reduced = Empagliflozin Outcome Trial in Patients with Chronic Heart Failure and a Reduced Ejection Fraction; EMPULSE = Empagliflozin in Patients Hospitalized With Acute Heart Failure Who Have Been Stabilized; HF = heart failure; NNT = number needed to treat; SOLOIST-WHF = Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure
A pivotal randomized controlled trial focused on chronic kidney disease has been conducted for each of the 3 SGLT-2 inhibitors on the US market: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation (CREDENCE),24 Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease (DAPA-CKD),22 and Study of Heart and Kidney Protection with Empagliflozin (EMPA-KIDNEY).23 Although all participants had chronic kidney disease, eligibility for these trials varied in terms of estimated glomerular filtration rate and urine albumin-to-creatinine ratio limits. Also, the CREDENCE trial24 was restricted to participants with type 2 diabetes, whereas the DAPA-CKD trial22 and EMPA-KIDNEY trial23 included participants with and without diabetes. Importantly, patients were required to be taking an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker unless a contraindication or intolerance was documented. Major common exclusion criteria of these trials included a history of polycystic kidney disease or kidney transplantation.

All 3 trials22–24 showed benefit in reducing the risk of chronic kidney disease progression or cardiovascular death, with relative risk reductions ranging from 28% to 39%. This effect did not vary by the presence or absence of diabetes at baseline. Because the lower limits of the estimated glomerular filtration rate ranged from 20 to 30 mL/minute/1.73 m², there are different minimum estimated glomerular filtration rate thresholds for approved use of SGLT-2 inhibitors for indications other than type 2 diabetes (Table 3).8–10,15,16,19–27

Of note, the glucosuric effect of SGLT-2 inhibition declines with the estimated glomerular filtration rate.28 Therefore, at estimated glomerular filtration rates below 30 to 45 mL/minute/1.73 m², SGLT-2 inhibitors have minimal effect on blood glucose levels. However, in recognition of the compelling trial data, the American Diabetes Association recommends that an SGLT-2 inhibitor be used to reduce the risk of chronic kidney disease progression and cardiovascular events in patients with type 2 diabetes, diabetic kidney disease with a urinary albumin-to-creatinine ratio of 200 mg/g or greater, and an estimated glomerular filtration rate as low as 20 mL/minute/1.73 m², as in the patient presented in our case.29

**The estimated glomerular filtration rate dip**

Despite slowing the decline of the estimated glomerular filtration rate over time, SGLT-2 inhibitors decrease the estimated glomerular filtration rate by about 5 mL/minute on average within 1 to 2 weeks of

### TABLE 2
**Trials of sodium-glucose cotransporter 2 inhibitors in chronic kidney disease**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patients</th>
<th>Intervention</th>
<th>Primary composite end point</th>
<th>Primary composite results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CREDENCE (2019)24</td>
<td>4,401 adults eGFR 30–89 mL/minute/1.73 m² and UACR 301–5,000 mg/g</td>
<td>Canagliflozin 100 mg</td>
<td>End-stage kidney disease,⁴ double serum creatinine, or cardiovascular or renal death</td>
<td>43.2 vs 61.2 events/1,000 patient years (NNT = 22)</td>
</tr>
<tr>
<td>DAPA-CKD (2020)²²</td>
<td>4,304 adults eGFR 25–75 mL/minute/1.73 m² and UACR 200–5,000 mg/g With or without diabetes mellitus</td>
<td>Dapagliflozin 10 mg</td>
<td>≥ 50% sustained decline in eGFR, end-stage kidney disease,⁵ or cardiovascular or renal death</td>
<td>9.2% vs 14.5% (NNT = 19)</td>
</tr>
<tr>
<td>EMPA-KIDNEY (2023)²³</td>
<td>6,609 adults eGFR 20–44 mL/minute/1.73 m² or eGFR 45–89 mL/minute/1.73 m² and UACR ≥ 200 mg/g With or without diabetes mellitus</td>
<td>Empagliflozin 10 mg</td>
<td>Kidney disease progression⁶ or cardiovascular death</td>
<td>13.1% vs 16.9% (NNT = 26)</td>
</tr>
</tbody>
</table>

⁴CREDENCE: dialysis for at least 30 days, kidney transplantation, or eGFR < 15 mL/minute/1.73 m².
⁵DAPA-CKD: maintenance dialysis ≥ 28 days, kidney transplantation, or eGFR < 15 mL/minute/1.73 m².
⁶EMPA-KIDNEY: initiation of maintenance dialysis, receipt of kidney transplant, eGFR < 10 mL/minute/1.73 m²; sustained decrease in eGFR ≥ 40%, or renal death.
CREDENCE = Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation; DAPA-CKD = Dapagliflozin and Prevention of Adverse Outcomes in Chronic Kidney Disease; eGFR = estimated glomerular filtration rate; EMPA-KIDNEY = Study of Heart and Kidney Protection with Empagliflozin; NNT = number needed to treat; UACR = urine albumin-to-creatinine ratio
drug initiation. Subsequently, the estimated glomerular filtration rate returns to baseline over the next 3 to 9 months. Because this temporary dip in the estimated glomerular filtration rate is not associated with kidney injury—the risk of acute kidney injury is actually decreased with SGLT-2 inhibitor use—and these drugs do not cause electrolyte abnormalities, we agree with the opinion that routine monitoring of serum creatinine after SGLT-2 inhibitor initiation is not necessary unless a patient is at high risk of volume depletion (blood pressure < 120/70 mm Hg, orthostatic symptoms, taking high-dose diuretics).

**PRACTICAL PRESCRIBING CONSIDERATIONS**

**Initiation and titration**

Table 3 shows indications, doses, and estimated glomerular filtration rate thresholds for SGLT-2 inhibitors approved by the US Food and Drug Administration. The recommended dosage for both empagliflozin and dapagliflozin for the indications of reducing cardiovascular event risk and chronic kidney disease progression is 10 mg daily without titration. They are also indicated for chronic kidney disease with persistently elevated urinary albumin excretion (≥ 200 mg/g) in patients on other first-line therapies for albuminuria. Canagliflozin has an indication for patients specifically with diabetic kidney disease with urinary albumin excretion greater than 300 mg/day at a dose of 100 mg daily without titration, although 300 mg may be used for additional glycemic control.

The cost of empagliflozin and canagliflozin is about $600 per month. Currently, there is a generic form of dapagliflozin that costs $200 per month. A variety of patient-assistance programs are available for patients to reduce the cost of these medications depending on income level and insurance coverage.

No current guideline offers a specific sequence to initiate or titrate guideline-directed medical therapy. When starting these medications in patients with type 2 diabetes, it may be necessary to down-titrate insulin or insulin secretagogues (eg, sulfonylureas) to decrease the risk of hypoglycemia. We suggest this down-titration if blood glucose levels are often less than 100 mg/dL.

**TABLE 3**

<table>
<thead>
<tr>
<th>Indications, doses, and estimated glomerular filtration rate thresholds for sodium-glucose cotransporter 2 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sodium-glucose cotransporter 2 inhibitor</strong></td>
</tr>
<tr>
<td><strong>Indication</strong></td>
</tr>
<tr>
<td>Glycemic control in type 2 diabetes</td>
</tr>
<tr>
<td>Major adverse cardiovascular events risk in type 2 diabetes and cardiovascular disease</td>
</tr>
<tr>
<td>CVE risk in heart failure</td>
</tr>
<tr>
<td>Heart failure hospitalization in type 2 diabetes and cardiovascular disease or cardiovascular risk</td>
</tr>
<tr>
<td>Chronic kidney disease progression or CVE risk in type 2 diabetes and diabetic kidney disease</td>
</tr>
<tr>
<td>Chronic kidney disease progression or CVE risk in chronic kidney disease</td>
</tr>
<tr>
<td><strong>Minimum estimated glomerular filtration rate (mL/minute/1.73 m²)</strong></td>
</tr>
<tr>
<td>For type 2 diabetes</td>
</tr>
<tr>
<td>For other indications</td>
</tr>
</tbody>
</table>

CVE = cardiovascular events (cardiovascular death, hospitalization for heart failure, urgent heart failure visits)

*aMay continue therapy.*

Data from references 8–10,15,16,19–27.
Anecdotally, some clinicians use a urine glucose test to confirm adherence to and the effect of the medication. As SGLT-2 inhibitors increase urinary glucose excretion, urine glucose tests may remain positive while on the drug. Volume status is another consideration. Before starting an SGLT-2 inhibitor, assess volume status and renal function in elderly (≥ 75 years) patients, those with renal impairment or low systolic blood pressure, and those on diuretics. At the time of initiation, it may be necessary to down-titrate diuretics to maintain euvoelma, and volume status should be monitored during therapy. Conversely, it is reasonable to consider increasing or restarting diuretics if an SGLT-2 inhibitor should need to be stopped.

The effect of SGLT-2 inhibition on blood pressure is minimal and mediated mostly by volume depletion. Lastly, starting therapy below drug-specific estimated glomerular filtration rate thresholds is not recommended, and these drugs provide little glycemic benefit at lower estimated glomerular filtration rates. Close collaboration with cardiology, endocrinology, and nephrology clinicians may be helpful in the initiation and use of SGLT-2 inhibitors.

Major drug interactions for canagliflozin include uridine 5’-diphospho-glucuronyltransferase inducers such as rifampin, phenytoin, and ritonavir. Canagliflozin area under the curve is reduced with these agents, which may reduce efficacy. Co-administration of canagliflozin and digoxin can lead to increased mean peak drug concentrations of digoxin. Digoxin levels should be monitored appropriately when co-administered with canagliflozin. There are no major drug interactions listed for empagliflozin or dapagliflozin.

**Adverse effects**

SGLT-2 inhibitors are generally well-tolerated, with most side effects being mild or moderate. A common mild side effect is increased urination. Some, but not all, meta-analyses of clinical trials of SGLT-2 inhibitors report a significant increase in the risk of genitourinary infections, with risk of genital mycotic infection greater than risk of urinary tract infection. SGLT-2 inhibitors should therefore be avoided in patients with a history of recurrent genitourinary infections. There have been some reports of urosepsis and pyelonephritis; thus, patients with urinary tract infection symptoms should be evaluated and treated promptly.

In our opinion, it is reasonable to continue an SGLT-2 inhibitor through a single occurrence of an uncomplicated urinary tract infection and to discontinue therapy if more severe infection or multiple infections occur.

Some studies have revealed an increased risk of diabetic ketoacidosis with use of SGLT-2 inhibitors in patients with type 2 diabetes. These agents should therefore be avoided in patients with a history of diabetic ketoacidosis, pancreatic insufficiency, or alcohol abuse. Additionally, euglycemic diabetic ketoacidosis has been reported with SGLT-2 inhibitor use, which can lead to diagnostic delay. Patients on SGLT-2 inhibitor therapy should be counseled regarding common symptoms of diabetic ketoacidosis (nausea, vomiting, abdominal pain, malaise, dyspnea), and patients with these symptoms should have ketone levels measured even in the absence of hyperglycemia. SGLT-2 inhibitors should be discontinued if ketosis is confirmed. Clinicians should consider counseling patients to stop these medications in situations known to predispose patients to ketoacidosis, such as prolonged fasting, gastrointestinal illness, and surgery. Current US Food and Drug Administration guidance is to consider holding these drugs for at least 3 days before scheduled surgery to reduce the risk of ketoacidosis.

There are some less common and more severe side effects of note. All 3 approved SGLT-2 inhibitors have been associated with necrotizing fasciitis of the perineum (Fournier gangrene). Canagliflozin has been associated with an increased risk for lower-limb amputation as well as bone fracture, and alternative SGLT-2 inhibitors should be considered in patients with risk factors for these conditions.

**Contraindications**

SGLT-2 inhibitors are not approved by the US Food and Drug Administration for patients with type 1 diabetes as they increase the risk for diabetic ketoacidosis. These drugs are also not appropriate for patients on dialysis.

**CONCLUSION**

SGLT-2 inhibitors are standard care for heart failure and chronic kidney disease as they decrease the risk of cardiovascular events in patients with heart failure regardless of ejection fraction and presence of diabetes, decrease the risk of chronic kidney disease progression regardless of the presence of diabetes, and are relatively safe and generally well tolerated.

**DISCLOSURES**

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


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Lymphedema vs lipedema: Similar but different

ABSTRACT
Lymphedema and lipedema are chronic debilitating disorders that most commonly affect the upper and lower extremities. Although they can appear similar, they differ in important ways, which the authors of this article review and contrast.

KEY POINTS
Lymphedema can be primary (ie, inherited), but far more often it is secondary to damage to the lymphatic system, notably from cancer treatment.

Lymphedema is a progressive lymphatic disorder that is often underdiagnosed because many clinicians are not familiar with it. Delay in its diagnosis can lead to infection (cellulitis) or chronic complications such as loss of function and movement and psychological issues with body image and self-esteem.

Lymphedema is often confused with lipedema, lifestyle-induced obesity, lipodystrophy, or lipohypertrophy. Its management must be multifaceted to support and improve the quality of life of the patient.

Lipedema is a chronic, painful progressive disease characterized by an abnormal distribution of fat that affects the abdomen, buttocks, hips, legs, and arms disproportionately. The fat distribution is resistant to weight loss or limb elevation.

Although lymphedema and lipedema are traditionally seen as incurable, a better understanding of their pathophysiology and better diagnostic and therapeutic tools are challenging this view.

Ms. Smith, a 35-year-old woman with class 3 obesity, type 2 diabetes, hypertension, hyperlipidemia, and obstructive sleep apnea, presented to our lymphedema-lipedema center with bilateral lower-extremity edema (Figure 1). She said her quality of life was poor because of swelling, heaviness, and pain in her legs. She also reported a history of varicose veins. What is your diagnosis?

SIMILAR BUT DIFFERENT
Lymphedema, lipedema, and even simple obesity in the extremities can resemble each other superficially and are often confused for one another, but they differ in important ways (Table 1). Here, we review the pathophysiology, diagnosis, and treatment of lymphedema and lipedema.

IS THIS LYMPHEDEMA?
Lymphedema is a progressive lymphatic disorder that is often underdiagnosed because many clinicians are not familiar with it. Delay in its diagnosis can lead to infection (cellulitis) or chronic complications such as loss of function and movement and psychological issues with body image and self-esteem.

The pathophysiology of lymphedema is complex and not completely understood. However, a current view is that “all edema is lymphedema.” This view emphasizes that the vascular and integumentary systems are connected through the lymphatic system and fluid is regulated by the endothelial glycocalyx layer. Accumulation of interstitial fluid, proteins, and glycosaminoglycans within the skin and subcutaneous tissue stimulates collagen production.
LYMPHEDEMA VS LIPEDEMA

by fibroblasts and disruption of elastic fibers. This subsequently creates skin-thickening fibrosis.8

Primary lymphedema: Rare inherited disorders
Primary lymphedema (Table 2)9 is a group of inherited conditions that affect the structure or function of the lymphatic system through hypoplasia, aplasia, or hyperplasia of the lymphatic vessel. The global prevalence of primary lymphedema is 1 in 100,000 individuals, and it is more common in women than men.10 Genetic causes are found in 36% of patients with familial disease and 8% of patients without a family history.11

The subtypes of primary lymphedema can be grouped by age of onset: congenital (age < 2 years), praecox (2–35), and tarda (> 35). Congenital and praecox lymphedema can be further classified as syndromic (affecting other parts of the body) or nonsyndromic (not associated with an anomaly or other symptoms).9

As for the congenital subtypes, Milroy lymphedema is nonsyndromic and is associated with mutations in the FTL4 gene.9 Its symptoms are present at birth or are recognized within the first 2 years of life. The other 2 types of nonsyndromic primary lymphedema are Milroy-like lymphedema and hereditary lymphedema type 1B.

Lymphedema praecox encompasses 6 conditions. Meige disease, or hereditary lymphedema type 2, is the most common primary lymphedema and is the only lymphedema praecox condition that is non-syndromic.9 Lymphedema praecox has autosomal-dominant inheritance, affects women more than men, and has a variable onset.9 At onset, patients present with inflammation and symptoms that can include distichiasis (eyelashes growing from the meibomian glands on the posterior lamella of the eyelid), ptosis (drooping eyelids), and yellow nails. The 5 other conditions are hereditary lymphedema type 1C, lymphedema-distichiasis syndrome, yellow nail syndrome, and hypotrichosis-lymphedema-telangiectasia syndrome. These all have distinct features (Table 2).9

Lymphedema tarda manifests after age 35 and is due to underdevelopment of the lymphatic pathways. It may present with unilateral or bilateral edema, and it is believed to be triggered by an infection or trauma.9 Lymphedema praecox and lymphedema tarda have been associated with mutations in the FOXC2 gene.

Secondary lymphedema is more common
Secondary lymphedema is triggered by disruption or overload of the lymphatic system. It is more common than primary lymphedema, affecting approximately 1 in 1,000 Americans.10 Risk factors include cancer treatment such as radiation therapy and lymphatic resection for cancer of the breast, head, or neck and other malignancies; soft-tissue infection (bacterial, parasitic, and cellulitis); chronic venous insufficiency; injury; trauma; and surgery.12

The incidence has been most studied in patients with cancer. The risk of lymphedema after breast cancer treatment varies widely, with estimates ranging from 14% to 40%.11 There are no specific clinical features that can distinguish those who will develop lymphedema from those who will not, but several factors have been associated with an increased risk: dissection of the axillary nodes, with or without extensive breast surgery; radiotherapy to the breast or the axillary, subclavicular, or internal mammary lymph nodes; infection or postoperative complications related to surgical wounds or drains; ipsilateral venous compromise; advanced or recurrent cancer; traumatic insult to the arm; taxane-based chemotherapy; number of positive lymph nodes; and capsular invasion by a tumor.13,14

Figure 1. The patient had bilateral leg swelling with sparing of the feet. Note the ankle cutoff, or cuff sign. Her thighs also had a mattress-like appearance with numerous painful, palpable nodules.
TABLE 1
Lipedema, lymphedema, and obesity compared

<table>
<thead>
<tr>
<th></th>
<th>Lymphedema</th>
<th>Lipedema</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex affected</td>
<td>Both men and women</td>
<td>Almost exclusively women</td>
<td>Both men and women</td>
</tr>
<tr>
<td>Family history</td>
<td>Present in primary lymphedema, absent in secondary</td>
<td>Present</td>
<td>Present or absent</td>
</tr>
<tr>
<td>Edema</td>
<td>Nonpitting (early) or pitting, unilateral or bilateral</td>
<td>Nonpitting, bilateral</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Swollen feet</td>
<td>Present</td>
<td>Absent unless patient has lipolymphedema or phlebolymphedema</td>
<td>Present</td>
</tr>
<tr>
<td>Increased fatty tissue</td>
<td>Absent</td>
<td>Present and usually nodular</td>
<td>Present</td>
</tr>
<tr>
<td>Abnormal distribution of adipose tissue</td>
<td>Possible</td>
<td>Present in arms, abdomen, buttocks, and legs</td>
<td>Possible</td>
</tr>
<tr>
<td>Tenderness and pain</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Tendency to develop hematomas</td>
<td>Absent</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Cuff sign(^a)</td>
<td>Negative</td>
<td>Positive</td>
<td>Positive</td>
</tr>
<tr>
<td>Stemmer sign(^b)</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Weight-loss treatment</td>
<td>Recommended to reduce lymphatic harm</td>
<td>May not reduce size of affected region but is recommended to minimize complications and if metabolic syndrome is present</td>
<td>Recommended</td>
</tr>
</tbody>
</table>

\(^a\)Tissue enlargement stops abruptly at the ankle or wrists (arms affected in up to 80% of patients).

\(^b\)Inability to pinch a fold of skin at the base of the second toe compared with the opposite foot.

Based on information from references 1–6.
Among survivors of head and neck cancer, more than 90% experience lymphedema internally (larynx and pharynx), externally (face or neck), or both in the first 18 months after treatment. Other cancers associated with lymphedema include sarcoma, gynecologic cancers, and malignant melanoma.

Another common cause of lymphedema, especially in poor, tropical countries, is filariasis due to the parasitic roundworm *Wuchereria bancrofti* occupying the lymphatic vasculature.

Chronic venous insufficiency can also lead to secondary lymphedema, as extracellular fluid cannot return to the venous system and overloads the lymphatic system. In fact, according to clinical practice guidelines, all patients with chronic venous insufficiency should be considered to have lymphedema. If untreated, it can permanently damage the lymphatic architecture, resulting in flow-obstructive lymphedema with worsening swelling.

The risk of lymphatic dysfunction also increases with body mass index, as obesity decreases the uptake of lymphatic fluid by the lymphatic vessels, resulting in buildup of subcutaneous deposits.

Relevant and rigorous epidemiologic studies are lacking, limiting a true estimate of the prevalence of secondary lymphedema. A retrospective analysis of hospital admissions for lymphedema in the United States from 2012 to 2017 showed that 92% of the 165,055 total admissions reported were for cellulitis, and 77% of the patients were admitted via the emergency department. The median age was 62 years, and the inpatient mortality rate was 0.03%. Although the mortality rate is low, the numbers indicate that secondary lymphedema affects a significant number of patients and imposes a financial burden on hospital systems.

### TABLE 2
**Primary lymphedema: Genetic basis and key features**

<table>
<thead>
<tr>
<th>Gene affected</th>
<th>Key features</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital</strong></td>
<td></td>
</tr>
<tr>
<td>Milroy lymphedema (hereditary lymphedema type 1A)</td>
<td>FTL4 (VEGFR3)</td>
</tr>
<tr>
<td>Hereditary lymphedema type 1B</td>
<td>Unknown</td>
</tr>
<tr>
<td>Milroy-like lymphedema (hereditary lymphedema type 1D)</td>
<td>VEGFC</td>
</tr>
<tr>
<td>Congenital lymphedema syndromes</td>
<td>Varies</td>
</tr>
<tr>
<td><strong>Lymphedema praecox</strong></td>
<td></td>
</tr>
<tr>
<td>Meige disease (hereditary lymphedema type 2)</td>
<td>Unknown</td>
</tr>
<tr>
<td>Lymphedema distichiasis syndrome</td>
<td>FOXC2</td>
</tr>
<tr>
<td>Primary lymphedema with myelodysplasia (Emberger syndrome)</td>
<td>GATA2</td>
</tr>
<tr>
<td>Hereditary lymphedema type 1C</td>
<td>GJC2</td>
</tr>
<tr>
<td>Hypotrichosis-lymphedema-telangiectasia</td>
<td>SOX18</td>
</tr>
<tr>
<td>Yellow nail syndrome</td>
<td>Unknown</td>
</tr>
<tr>
<td>Lymphedema tarda</td>
<td>FOXC2</td>
</tr>
</tbody>
</table>

Adapted from reference 9.
LYMPHEDEMA IS USUALLY DIAGNOSED CLINICALLY

A thorough history and physical examination can often point to the correct diagnosis.\textsuperscript{20,21} When collecting a history, it is crucial to ascertain the onset and location of the swelling and any of the following:

- Axillary or inguinal injury
- Surgical procedures, particularly lymph node dissection
- Radiation therapy
- Chemotherapy
- Trauma to the affected area
- History of bacterial or parasitic infection or cellulitis
- Travel to an area with endemic filariasis
- History of malignancy
- Family history of congenital lymphedema.

Clinical signs of lymphedema

Lymphedema progresses through stages:

- Stage 0 (latency)—patient is considered at risk; disease is latent or subclinical; swelling is not evident despite impaired lymph transport
- Stage 1 (spontaneously reversible)—spontaneous early accumulation of fluid high in protein content; pitting may occur; swelling is reduced with limb elevation
- Stage 2 (spontaneously irreversible)—pitting may be present depending on degree of fibrosis; limb elevation does not reduce swelling
- Stage 3 (lymphostatic elephantiasis)—trophic skin changes are present; acanthosis, fat deposits, and warty overgrowth often develop.\textsuperscript{20}

Thus, there is soft pitting edema early on (Figure 2), and fibrosis and induration in later stages. Clinical signs include *peau d’orange* skin changes, lymphorrhea, lymphangioma, papillomatosis, hyperkeratosis, cellulitis, and the Stemmer sign (inability of the examiner to grasp the skin at the base of the second digit of the foot or hand).\textsuperscript{20}

Examine the axillary or inguinal areas for scars, which may denote injury to the lymphatic system from radiation treatment. Further examination may reveal vascular malformations or cutaneous problems such as hyperkeratosis, lymphorrhea, and, in more severe cases, skin breakdown. If you suspect primary lymphedema, look for syndromic characteristics such as the following:

- An extra row of eyelashes, eyelid ptosis, yellow nails (lymphedema distichiasis syndrome)
- Sparse hair, cutaneous telangiectasias (hypotrichosis-lymphedema-telangiectasia syndrome)
- Generalized edema, visceral involvement, developmental delay, flat faces, hypertelorism (widely spaced eyes), and a broad nasal bridge (Hennekam syndrome)
- Short stature, webbed neck, and a broad chest (Turner syndrome).\textsuperscript{20}

Imaging and tests

Tissue biopsies and urine and blood tests are not required for the diagnosis of lymphedema but may help define underlying causes of the lower- or upper-extremity or abdominal edema.

Ultrasonography, computed tomography, magnetic resonance imaging. In most patients, lymphedema is diagnosed with a detailed history and physical examination, but many undergo ultrasonography to evaluate the venous system or computed tomography (CT) before their referral to a specialist. These
imaging tests are not recommended because they have low sensitivity for detection of lymphedema. Reportedly, signs of lymphedema on CT and magnetic resonance imaging (MRI) include thickening of the skin, a honeycombed pattern in the subcutaneous tissue, and the absence of edema within muscular compartments. MRI has greater specificity than lymphoscintigraphy for detecting delayed lymphatic drainage and greater sensitivity for delineating lymph vessels. CT and MRI may help rule out causes such as deep venous thrombosis, chronic venous insufficiency, or malignancy.

Near-infrared lymphography is a newer method for assessing lymphedema that uses indocyanine green fluorescent dye. It is used as an adjunctive tool in lymphatic microsurgery.

Radionuclide lymphoscintigraphy is now generally considered the gold standard for diagnosing lymphedema, but it is not widely available. It is an invasive procedure that requires injecting radiolabeled sulfur colloid subcutaneously into the interdigital region of the toes or fingers of the affected limb and using a gamma camera to assess the lymphatic vasculature and function. In patients with lymphedema, it shows absent or delayed radiotracer transport, backflow, or poorly visualized lymph nodes.

Other tests such as tonometry (which measures tissue’s resistance to compression) and perometry (which measures overall limb volume including muscle and fat) may help confirm the diagnosis and allow for better assessment of edema volume vs limb volume, but are not commonly used or available.

### TREATMENT FOR LYMPHEDEMA

Early diagnosis and treatment can help slow the progression of this disease. Patients should be referred to a lymphedema specialist to learn about evidence-based coping strategies. An approach to management is outlined in Table 3.

### Conservative treatment

Complete decongestive therapy is the primary treatment for lymphedema and helps reduce limb volume and fibrotic tissue. It encompasses manual lymph drainage, compression garments, exercise, skin care, and psychological support.

**Manual lymph drainage** involves massage of the affected limb. It enhances lymphatic contractility, redirects lymph flow through nonobstructed cutaneous lymphatics, and helps increase lymph flow and reduce limb volume. Manual lymph drainage sessions are done at least 3 times per week for no less than 4 weeks.

**Compression garments and bandaging** should be applied after manual lymph drainage. This includes multilayered (short-stretch) compression bandaging to prevent fluid from reaccumulating after the limb volume is reduced. A single-center, randomized, non-blinded study of compression therapy and education vs education alone showed that compression therapy resulted in a lower incidence of recurrent cellulitis in adults with chronic edema of the leg. However, most quality-of-life measures did not differ between groups.

Compression garments should be chosen with the help of a lymphedema professional, and they must be fitted properly. If improperly fitted or too tight, they can cause more swelling and limit blood flow, which may worsen lymphedema. In the evening, some patients may need short-stretch garments or intermittent pneumatic compression devices to obtain maximal benefit.

Garments can be circular or flat knit; the choice depends on the severity of lymphedema and limb shape. Circular compression garments are seamless, tube-shaped, and not as dense or stiff as flat-knit garments. They provide more compression at the ankle and less at the thigh. Circular compression garments are often employed in patients with mild swelling and normal-shaped legs. Flat-knit elastic compression garments are thicker and stiffer and, being custom-made, tend to be more expensive. They are better for patients with severe lymphedema. The stiff compression allows the garment to cross skin folds without cutting into the adjacent skin. Typical indications include significant differences in leg circumference, deep skin folds, and edema of the toes and forefoot.
Light exercise can help patients maintain or lose weight, promotes protein absorption via muscle contraction, and promotes lymph drainage. Examples are stretching, walking, aquatic therapy, aerobics, and other low-impact exercises.

Skin hygiene is key to preventing secondary infections (cellulitis). Instruct the patient to wash the affected limb daily, apply moisturizer, and use antifungal agents between the toes.

Psychological support should be provided to patients who may face loss of function, restriction of movement, or disfigurement with loss of body image and self-esteem.

Drug therapy
Benzopyrones historically have been used to treat lymphedema by limiting the amount of fluid that collects in subcutaneous tissue. They are believed to increase macrophage activity and hence lysis of tissue protein, leading to reabsorption of fluid and prevention of fibrosis. They can be taken orally or applied topically. However, owing to poor reporting and limited information in randomized controlled trials, a Cochrane meta-analysis could not conclude that they were effective in treating lymphedema.

Diuretics may be used with physical therapy in the initial phases of treatment, but because their benefits are minor, long-term use is not recommended. Diuretics may induce imbalances in fluid and electrolytes and increase the protein concentration in the lymphatic fluid, potentially increasing the risk of fibrosis due to protein accumulation. An interdisciplinary and shared decision-making approach is needed for patients with underlying cardiac or renal insufficiency.

Antibiotics are used if an underlying acute infection is suggested, especially if there are clinical signs or symptoms (erythema, high fever, pain), or if a complete blood count indicates leukocytosis or blood and skin cultures reveal a bacterial infection. Antibiotics should be discontinued once the white blood cell count has returned to normal to avoid excessive treatment.

Analgesics should be used to control pain. Prolonged use of nonsteroidal anti-inflammatory drugs should be avoided, however, to minimize cardiovascular, renal, and gastrointestinal toxicity and their side effect of causing swelling.

Other agents that can be considered include antifibrotic agents and anti-transforming growth factor beta-1 antibodies, which have been shown to be effective in regulating fibrosis and severity of lymphedema in mouse models and some clinical trials. These medications may not be readily accessible to all patients but may be available to participants in clinical trials; this may be a beneficial option and should be discussed with patients, if available.

Nonconservative and surgical therapies
Patients should be referred to a vascular or lymphedema specialist or clinical lymphologist, as well as a surgeon (plastic surgeon) knowledgeable in lymphedema surgery.

Low-level laser therapy is used to improve lymphatic motility and prevent tissue fibrosis. It uses a wavelength between 650 and 1,000 nm to deliver low-level doses to target tissue.

Extracorporeal shockwave therapy is noninvasive and activates vascular endothelial growth factor and fibroblasts. It may help reduce edema and skin fibrosis and has been proposed to be used with complete decongestive therapy.

Surgical therapies encompass physiologic procedures that attempt to restore or increase lymphatic clearance and ablation procedures that remove excess subcutaneous tissue to facilitate conservative procedures. Examples are removal of edematous tissue by an open technique or liposuction or lymphatic reconstruction including lymph vessel-to-vein anastomosis or lymph node-to-vein anastomosis.

Debulking involves resection of excess skin and expanded subcutaneous tissue down to the muscle fascia. It is being used in combination with other treatments in earlier stages of lymphedema to reduce the volume of the arms and legs and improve quality of life. It is also recommended in end-stage lymphedema in a multidisciplinary holistic approach to improve quality of life.

Suction-assisted protein lipectomy removes fatty deposits and lymphatic solids in patients with chronic lymphedema and functional problems in the limb. It is most often used in advanced stages of lymphedema, and patients must faithfully wear their compression garments afterward.

IS THIS LIPEDEMA?
Lipedema (adiposis dolorosa, or the painful fat syndrome) is a loose connective tissue disease. Its estimated prevalence is about 1 in 72,000 individuals (although this is likely a significant underestimate), and it has a marked female predominance, affecting an estimated 1 in 9 adult women.

The etiology and pathophysiology of lipedema are not well understood, but it is thought to be triggered
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by hormonal changes during puberty, childbirth, or menopause; stressful lifestyle changes; or alteration in tissue associated with surgery or trauma. Estrogen is theorized to play a role, as it regulates lipid and glucose metabolism and female-associated adipocyte distribution.³⁹ In addition, very few men are affected.⁴⁰,⁴¹

A cross-sectional study found the prevalence of lipedema increased with weight and body mass index,⁴² and obesity is believed to be an aggravating factor for lymphatic harm and edema leading to lymphatic overload.

Lipedema is characterized by increased palpable nodular and fibrotic adipose tissue deposits in the abdomen, buttocks, hips, and limbs. Hypermobility of the joints and sparing of the hands and feet (also known as the “cuff phenomenon”)³ are classically present. Lipedema is also characterized by a feeling of heaviness in the affected areas and a worsening of symptoms over the course of the day. Lipedema is bilaterally symmetrically distributed and is associated with pain and easy bruising. Increased perception of pain is possibly due to dysregulation of local-regional sensory nerve fibers resulting from inflammatory and hypoxic mechanisms.

Lipidema is thought to have a genetic predisposition, with autosomal-dominant inheritance and sex limitation.

Often confused with other disorders
Lipedema is often confused with obesity, lipodystrophy, lipohypertrophy, or lymphedema. Lipodystrophy is a disorder that causes abnormal fat distribution.⁴ It can include lipohypertrophy, a disorder characterized by lumps of fat or scar tissue under the skin caused by repeated injections or infusions in the same area.

Misdiagnosis can delay treatment for decades and increase the risk of complications such as recurrent infections, ulcers, or worsening of the lymphatic system.²¹,⁴³ Often, women with this condition are told that their symptoms are a result of their inability to control their diet or due to their sedentary lifestyle. This can result in increased fixation on weight, false accusations of poor compliance, and “fat shaming,” leading to psychosocial distress, anxiety, depression, eating disorders, and social isolation.

Diagnostic evaluation
A detailed history should consider family history of lipedema. This includes the onset of weight gain and disproportionate body fat distribution; pain, tenderness, or heaviness of the arms or legs; easy bruising or vascular fragility; difficulty in losing weight despite diet and exercise or bariatric surgery; and no reduction of pain or discomfort with limb elevation.

Comorbid conditions should also be assessed, eg, hypermobility of joints, loss of tissue elasticity, lymphedema, obesity, metabolic disease, and vascular disease.⁴³

In the physical examination, note any symmetric tissue enlargement; painful, palpable tissue nodules on the arms, abdomen, and legs; spared of the hands or feet (the cuff phenomenon); hypothermia of the skin; telangiectasias; and a negative Stemmer sign. Pitting edema is noted when there is underlying venous insufficiency or lymphedema. Nonpitting bilateral edema is often found in lipedema. It is characterized by swelling, usually in the limbs, that does not indent when pressure is applied. If nonpitting edema is suspected, thyroid tests should be done to rule out myxedema due to hypothyroidism.

Clinical criteria for the diagnosis of lipedema, proposed by Wold et al⁵ and amended by Herbst⁴⁴ and Kruppa et al,³ are as follows:

• Female patient (almost exclusively)
• Bilateral, symmetrical, disproportionate fatty tissue hypertrophy of the limbs and abdomen
• Sparing of the hands and feet (cuff phenomenon)
• Minimal pitting edema
• Negative Stemmer sign (ie, the examiner can pinch or tent the skin at the base of the second toe or finger, unlike in lymphedema, in which the Stemmer sign is positive and the examiner can’t pinch this area)
• Feeling of heaviness and tension in affected limbs
• Pain and tenderness on pressure or touch
• Easy bruising and a tendency to form hematomas
• Stable limb circumference despite weight reduction or caloric restriction
• Worsening of symptoms over the course of the day
• Telangiectasias and visible vascular markings around fat deposits
• Hypothermia
• Hypermobile joints.

Laboratory tests and imaging
There are currently no specific imaging criteria or biomarkers available to confirm the diagnosis of lipedema, but a combination of imaging tests is used to strengthen the diagnosis.⁴³

Laboratory tests should be obtained to exclude heart, kidney, liver, thyroid (hypothyroidism), hormonal, or edema-promoting disturbances such as secondary effects of medications (eg, calcium channel...
blockers, gabapentin, and oral corticosteroids). Serum selenium levels are often checked because selenium deficiency due to oxidative stress can lead to tissue injury by inflammation, apoptosis, or necroptosis.\(^4\)\(^5\)

Ma et al\(^4\)\(^6\) identified platelet factor 4 as a promising diagnostic marker of lymphatic malfunction that could help in diagnosing and clinically differentiating lymphedema, lipedema, and obesity. Furthermore, it was found at higher levels in women with lipedema even if they were not overweight or obese. Thus, elevated levels of platelet factor 4 may provide evidence of underlying lymphatic structural and functional vasculature dysfunction in the pathogenesis of lipedema. It is not routinely used in practice as a diagnostic marker, but research continues on this topic.

Imaging tests such as ultrasonography, CT, or MRI can be used to study the skin and subcutaneous tissue. Ultrasonography can show thinner skin and increased thickness and hypoechogenicity of subcutaneous fat toward the medial calf and distal extremities. CT can show fatty hypertrophy in the lower extremities, and MRI can show dilation of lymphatic vessels in the legs. Indirect lymphography, functional lymphatic scintigraphy, and fluorescence microlymphography can be used to evaluate the structure and function of the lymphatic system.\(^3\)

Dual-energy x-ray absorptiometry can be useful in assessing fat mass and lean body mass to rule out lipedema.

### Treatment for Lipedema

Patients should be referred to a specialist knowledgeable in the disorder to better assess the stage and to personalize treatment (Figure 3).\(^6\)\(^,\)\(^4\)\(^5\). They should be informed that a conservative approach may help relieve symptoms but will have minor effects on the appearance of the extremities. Studies have shown that conservative management results in only about a 5% to 10% volume reduction.\(^3\)

It is important to routinely measure body weight, body mass index, waist-to-hip ratio, waist-to-height ratio, and circumference and volume of the limbs to monitor response to treatment.

**Conservative treatment**

Conservative management consists of treating current underlying medical problems, plus the following:
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**Table 4**

**Lipidema: Clinical stages and compression recommendations**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Characteristics</th>
<th>Compression recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Smooth skin, homogenous increase in subcutaneous tissue, cool skin in certain areas Subdermal pebble-like feel due to underlying loose connective tissue fibrosis Small nodules Edema reverses with elevation Circadian rhythmicity</td>
<td>Micromassage compression garment 10–20 mm Hg as needed</td>
</tr>
<tr>
<td>2</td>
<td>Irregular or uneven skin surface (skin dimpling) Palpable nodules (may be walnut size) Nodular change of subcutaneous tissue Tissue begins to hang off the arm, wrist cuff sign Reversible or irreversible edema Moderate to severe fibrosis Circadian rhythmicity</td>
<td>Micromassage compression garment 20–40 mm Hg if pain, swelling, or heaviness is present</td>
</tr>
<tr>
<td>3</td>
<td>Tender subcutaneous nodules Pronounced increase in circumference with loose skin and tissue Bulging protrusion of fat mainly at inner and outer thighs and knees Marked sclerosis and fibrosis Often concomitant lymphedema with a positive Stemmer sign (lipolymphedema)</td>
<td>Micromassage compression garment 20–40 mm Hg as tolerated if pain, swelling, or heaviness is present May have to layer different garments</td>
</tr>
</tbody>
</table>

Based on information from references 4, 5, 43.

- **Anti-inflammatory diet**
- **Education** on self-management of diet and exercise
- **Physical exercise** or referral to physical or occupational therapy to help improve mobility, muscle strength, gait, and balance; exercise prescriptions should be tailored to the patient’s needs with the guidance of a physical therapist
- **Avoiding medications that increase fluid retention** such as nonsteroidal anti-inflammatory drugs and hormone replacement therapy
- **Manual lymph drainage**, sequential pneumatic compression pumps, or both should be considered to improve lipedema tissue and decrease pain[^43]
- **Compression garments** (either circular or flat knit). Flat knits are often used in patients with severe lipedema and should be prescribed with the help of a therapist familiar with lipedema (Table 4)[^4, 5, 43]
- **Weight management** with medications for weight loss (glucagon-like peptide-1 receptor agonists, phentermine, phentermine-topiramate, naltrexone-bupropion, or other appetite suppressants)
- **Metformin** is recommended for patients with metabolic complications, as it inhibits hypoxia-induced fibrosis in adipose tissue[^43]
Interventive or surgical treatment is becoming more widely available, but insurance often does not cover it. Patients are encouraged to see a specialist in vascular medicine, lipedema, or lymphedema to make informed decisions on interventive or surgical therapy, preferably before complications and disabilities develop.

Liposuction removes abnormal lipedema tissue while sparing blood and lymphatic vessels. It is useful when lipedema does not respond to conservative measures. It also improves symptoms, mobility, gait, and quality of life, and it is the only treatment that slows the progression of the disease.

Bariatric surgery should be considered in patients who have a body mass index of 40 kg/m² or more—or 35 or more if they have type 2 diabetes or other serious weight-related problems—and for whom a nonsurgical weight management approach has failed.

■ REFERENCES


■ CASE REVISITED

After visiting our lymphedema-lipedema clinic and undergoing an extensive physical evaluation that showed nonpitting edema, varicose veins, cuff sign at her wrist and ankles, hypermobile joints, and painful, palpable nodules involving her abdomen, arms, and legs, she was diagnosed with lipedema.

We discussed a personalized therapeutic plan in detail with the patient. As part of a multidisciplinary approach, a dietitian referral was placed to educate her about nutrition programs to aid with weight loss. She also saw an exercise physiologist to learn about a personalized exercise regimen that could help her overcome her physical limitations. Her endocrinologist started her on a glucagon-like peptide-1 receptor agonist to optimize her glycemic control and modify her cardiometabolic and renal risk factors. These steps helped her lose 50 pounds over the subsequent 6 months. Treatment of her lipedema included manual lymph drainage and compression garments, and within 6 months she underwent liposuction. The patient reported a reduction in her leg pain and size and an overall improvement in her quality of life.

■ DISCLOSURES

Dr. Makin has disclosed teaching and speaking for Bayer. Dr. Burguera has disclosed serving as an advisor or review panel participant and as a research principal investigator for Novo Nordisk, Inc. 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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Preventing herpes zoster in immunocompromised patients: Current concepts

ABSTRACT

Herpes zoster (HZ) incidence is much higher in immunocompromised individuals than in immunocompetent individuals. HZ also occurs at a younger age and is often more severe in immunocompromised persons. Preventive strategies center around the recombinant zoster vaccine (RZV), which is approved for immunocompromised adults age 19 and older. Identifying those at greatest risk is critical. For those considering vaccination, evidence gaps regarding vaccine efficacy, toxicity, length of protection, and potential effects on underlying conditions may complicate shared and informed decision-making. Recent data have filled some of these gaps, with several societies issuing recommendations regarding vaccination. Remaining gaps are currently addressed by expert opinion.

KEY POINTS

Patients who are immunocompromised are at increased risk for HZ and its complications.

The RZV is highly effective for preventing HZ. It is approved for immunocompromised patients age 19 and older.

The immunocompromised population is complex and heterogeneous. Hence, appraising individual risk and weighing the risks and benefits of the RZV can be challenging.

Filling knowledge gaps about HZ can help clinicians individualize shared and informed decision-making, leading to risk reduction.

Herpes zoster (HZ), also known as shingles, occurs due to reactivation of latent varicella-zoster virus (VZV) and generally presents as a painful cutaneous eruption. VZV is typically first acquired during a primary infection (chickenpox), but may also be acquired via live, attenuated virus vaccines (Varivax or ProQuad). HZ is common in the general population, with about 1 million cases reported annually in the United States. Incidence increases with age, especially after age 50.

HZ most often is a self-limiting disease, commonly accompanied by severe pain with loss of productivity, but in its most severe form can be life-threatening. Patients who are immunocompromised due to an underlying disease (eg, cancer, transplantation, primary or acquired immunodeficiency states, immune-mediated inflammatory diseases) or exposure to immunosuppressive drugs are at increased risk for uncomplicated HZ as well as HZ-related complications. This review discusses clinically important aspects of preventing HZ in immunocompromised patients, focusing primarily on vaccination: identifying at-risk populations, weighing the risks and benefits of a recombinant zoster vaccine (RZV), and using best practices for administering RZV and monitoring patients afterwards.
chickenpox result from dissemination of the virus during the viremic phase of the illness. As the infection resolves, cell-free virus is believed to infect sensory nerves in the skin, travel in a retrograde fashion, and establish lifelong latency in regional ganglia along the entire neural axis.4,5 Cell-mediated immunity appears to be central to maintaining viral latency. Disruption of cell-mediated immunity, most commonly observed as a function of aging and immunosenescence, increases the likelihood of viral reactivation.6 Once VZV is reactivated within sensory ganglia, it can spread neuronally in an antegrade fashion, often accompanied by inflammation and necrosis in a dermatomal distribution.

Immunocompromised individuals are more vulnerable to loss of viral control and development of HZ and its complications than those who are in generally good health. Complications of HZ include more severe local-regional tissue inflammation and destruction as well as widespread viral dissemination.4 Implicit in this pathogenic framework is the fact that immunocompromised patients often have far more severe deficits of immunologic function that may occur at any age. In contrast, healthy individuals’ major risk for loss of virologic control is immunosenescence.

### COMPLICATIONS MORE COMMON, SEVERE IN IMMUNOCOMPROMISED PATIENTS

HZ is a disease with significant morbidity that disproportionally affects immunocompromised patients.3 It most commonly manifests as an acute neuritic rash that is generally diagnosed clinically based on the presence of a unilateral, usually painful, vesicular eruption with a well-defined dermatomal distribution. In immunocompromised individuals, the appearance of the vesicles can be atypical, and unroofing and swabbing the vesicles may be necessary to make a diagnosis. In typical cases, new vesicles continue to form over 3 to 5 days, after which the rash progressively dries and scabs over, usually healing in 2 to 4 weeks.

Although HZ is self-limiting in most cases, its clinical severity should not be underestimated. It often has adverse effects on health-related quality of life, primarily loss of function and productivity.6 The pain associated with HZ is often severe and has been described by patients as feeling like a severe electric shock or a blowtorch.5

The complications of HZ can be serious (Table 1).1,2 Postherpetic neuralgia, the persistence of pain, often

### TABLE 1

**Complications of herpes zoster**

<table>
<thead>
<tr>
<th>Complications</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postherpetic neuralgia</td>
<td>Most common complication of herpes zoster</td>
</tr>
<tr>
<td></td>
<td>Manifests as persistent pain beyond 90 days of rash</td>
</tr>
<tr>
<td>Herpes zoster ophthalmicus</td>
<td>Vision-threatening complication from involvement of ophthalmic division of cranial nerve V</td>
</tr>
<tr>
<td></td>
<td>High risk of vision loss if antiviral therapy is not promptly initiated</td>
</tr>
<tr>
<td>Acute retinal necrosis</td>
<td>Necrotic infection of the retina that often leads to profound vision loss</td>
</tr>
<tr>
<td></td>
<td>Caused by herpes viruses, most often by herpes zoster or varicella</td>
</tr>
<tr>
<td>Ramsay Hunt syndrome (herpes zoster oticus)</td>
<td>Major otologic complication of herpes zoster from viral reactivation within the geniculate ganglion, with potential spread to cranial nerves V, VII, VIII, IX, and X</td>
</tr>
<tr>
<td></td>
<td>Often manifests as the triad of facial palsy, ear pain, and otic vesicular lesions</td>
</tr>
<tr>
<td>Miscellaneous neurologic complications</td>
<td>Stroke syndromes, motor neuropathy, myelitis, encephalitis, central nervous system vasculitis</td>
</tr>
<tr>
<td>Disseminated infection</td>
<td>Disseminated varicella infection with potential for visceral target organ involvement with possible widespread cutaneous involvement</td>
</tr>
</tbody>
</table>

Based on information from references 1 and 2.
severe, lasting beyond 3 months, is the most common. Postherpetic neuralgia occurs in about 10% to 15% of all HZ cases in the general population,\(^1,2\) and immunocompromised patients are at increased risk for this complication.\(^3\)

Other complications include zoster paresis with motor impairment of involved nerves, disseminated infection resulting in VZV meningitis, central nervous system vasculitis or vasculopathy,\(^7\) other end-organ involvement, and death.\(^1,3\) Ocular involvement may manifest as keratitis or acute retinal necrosis, which can lead to uveitis, retinal detachment, and blindness, particularly in immunocompromised individuals.\(^2,4,8\) In general, while all of these complications are observed in the general population, they are more common and more severe in the immunocompromised population.\(^3\)

Best practices for diagnosis and treatment of uncomplicated and complicated forms of HZ have been reviewed elsewhere.\(^1,2\)

### EPIDEMIOLOGY

#### General population

An estimated 1 million cases of HZ are reported in the United States each year.\(^9\) Over a lifetime, the cumulative risk of developing HZ is about 1 in 3, with rates increasing with age, a phenomenon generally ascribed to age-related weakening of the immune system.\(^1\) The incidence is higher in women and lower in Black adults.\(^1,4\) Between 1% and 6% of otherwise healthy individuals will experience a second episode of HZ over a lifetime.\(^3,10\) The risk for recurrent HZ is higher in immunocompromised patients.

#### Immunocompromised population

Given the importance of a well-functioning, integrated immune system in maintaining a state of lifelong viral latency, it is logical that patients who are immunocompromised are at increased risk of developing HZ, having a more severe episode, and having complications such as postherpetic neuralgia and a range of complex end-organ manifestations that could lead to severe disability and death.\(^3\) Recurrent HZ is also a concern in this patient population.

Unfortunately, determining who is immunocompromised, and to what degree, is complex. Estimates suggest that around 3% to 6% of the US general population are immunocompromised.\(^11\) However, these data likely do not adequately reflect the number of patients on immunosuppressive therapies, including the rapidly expanding class of biologic agents being employed for a growing list of indications.\(^2,13\)

The Centers for Disease Control and Prevention (CDC) has identified 7 groups as immunocompromised based on underlying conditions or use of immunosuppressive therapies (Table 2).\(^12\) The CDC notes that the list of immunocompromised groups is not limited to these discrete categories and that consultation between patient and clinician may be necessary.

A recent systematic review of HZ and its complications in patients with hematopoietic cell transplant, cancer, human immunodeficiency virus (HIV) infection, or solid-organ transplant revealed incidence rates 6 to 11 times higher than in the adult general population in the United States.\(^3\) Among the 16 immunocompromised groups examined, hematopoietic stem cell transplant recipients had the highest risk. Incident risk in other groups varied widely, but increased rates were noted, not surprisingly, in patients with solid tumors receiving chemotherapy and patients with solid-organ transplants.\(^3\) HIV infection traditionally has been associated with an increased risk of HZ. Although this risk has declined since antiretroviral therapy became available, HZ incidence remains greater in patients living with HIV than in the general population.\(^14\)

The data are less clear regarding the risks associated with immune-mediated conditions and their therapies and with primary immunodeficiency diseases, especially those with humoral immune deficiency states. In these populations, risk is highly influenced by the immunologic pathways affected and the severity of the defect. For those with immune-mediated diseases like rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis, and psoriasis, the risk for HZ is primarily related to the intensity and duration of the immunosuppressive regimens and the specific immunosuppressive therapy employed (eg, biologic agents,
kinase inhibitors, antimetabolites, glucocorticoids). These variables are discussed separately below.

PREVENTION FOCUSES ON VACCINATION

There are 2 strategies for preventing HZ in the immunocompromised population: vaccination and antiviral prophylaxis. By far the most comprehensive and effective modality is vaccination, which in the United States is currently limited to RZV, a subunit vaccine composed of a surface glycoprotein and a potent adjuvant.

RZV was introduced in 2017 as a 2-dose series administered 2 to 6 months apart to prevent HZ in adults age 50 or older, and was shown to be 90% effective at preventing HZ incidence over a 4-year period. RZV replaced a live, attenuated vaccine for HZ prevention first introduced in 2006 that is no longer available in the United States (but is available in other countries). In 2021 the Advisory Committee on Immunization Practices recommended RZV for adult patients age 19 and older who are or will be immunodefi cient or immunosuppressed because of disease or therapy.

Antiviral prophylaxis, generally with low-dose valacyclovir, may be considered in select immunocompromised patients who are not candidates for RZV or who have had recurrences despite full immunization.

RZV EFFICACY AND TOXICITY

RZV has proven to be highly effective and durable in the general population. In 2 large randomized controlled trials with a combined 7 years of follow-up, ZOE-50 (Zoster Efficacy Study in Adults 50 Years of Age or Older) and ZOE-70 (Zoster Efficacy Study in Adults 70 Years of Age or Older), a regimen of 2 vaccine doses administered at baseline and 2 to 6 months later had an efficacy against HZ incidence of 97.2% in adults age 50 and older and 91.3% in adults 70 and older. In these studies, RZV was also shown to be highly effective in preventing postherpetic neuralgia.

Evidence for the efficacy of RZV in immunocompromised patients remains limited, however. Data from 2 randomized controlled trials formed the basis of the recommendation for administering RZV in immunocompromised patients age 19 and older. These studies have recently been summarized. Bastidas et al evaluated the efficacy of RZV in patients who underwent autologous hematopoietic stem transplantation, and reported an efficacy of 68.2%. Dagnew et al evaluated RZV use in patients with hematologic malignancies receiving immunosuppressive therapy, and reported an efficacy of 87.2%.

Local and systemic reactogenicity are common in RZV recipients, with 1 in 10 reporting systemic reactogenicity that limits activity. The safety profile of RZV appears to be similar in the general and immunocompromised populations, with primarily reactogenicity-type responses like fever, myalgias, headache, and injection-site reactions and few serious adverse effects.

The biology, efficacy, and toxicity of RZV have been thoroughly reviewed elsewhere.

SPECIAL CONSIDERATIONS IN IMMUNOCOMPROMISED PATIENTS

A number of unique questions and challenges arise when considering strategies for preventing HZ in immunocompromised patients. These include concerns regarding vaccine administration, patient education, and patient selection. The responses to the following questions are based on varying levels of clinical evidence, including expert opinion (identified as such) in areas where there is particular uncertainty.

Recommendations for administering the RZV in immunocompromised groups are summarized in Table 3.

What are the risks of RZV in general and in terms of flaring an underlying immune-mediated disease? The adverse event profile of RZV, including reactogenicity, is similar in immunocompromised patients age 18 and older and those 50 and older who are not immunocompromised. Patients should be counseled accordingly, keeping in mind that there are no head-to-head clinical trials addressing this question.

A significant concern when using any adjuvanted vaccine in patients with immune-mediated diseases is the potential to flare the underlying disease. Several studies that examined the potential for disease flare in patients with autoimmune and inflammatory diseases have recently been reviewed. Rheumatologic disorders have been the most extensively evaluated, and it appears that flares after RZV vaccination are uncommon. When they do occur, they are mostly self-limited and do not require therapy.

There are currently no high-quality data on the risk of postvaccine flares in neurologic diseases like multiple sclerosis.

What is the potential for diminished efficacy of RZV? The efficacy of RZV in immunocompromised patients is based in part on data from Bastidas et al in the hematopoietic transplantation population. During the 21-month median follow-up, the reduction in incident
HZ was significant, with an incidence rate ratio of 0.32 (95% confidence interval 0.22–0.44, \(P < .001\)), equivalent to a vaccine efficacy of 68.2%. This study also showed reductions in the incidence of postherpetic neuralgia and overall HZ-related pain.\(^6,20\) Although this is well below the durable reduction in HZ demonstrated in the pooled analysis of the pivotal ZOE-50 and ZOE-70 trials,\(^16,17\) which showed RZV efficacy of 91.3% for HZ incidence and 88.8% for postherpetic neuralgia incidence,\(^19\) such reductions are still clinically meaningful.

The duration of protection in the immunocompromised population, while currently unknown, is likely less than that in the general population. Long-term, real-life studies are underway. Serial assessment of immune responses to RZV has shown good but diminished humoral responses to RZV in immunocompromised adults.\(^32\) The interpretation of such data is problematic, however, because there is no agreed-upon ex vivo correlate of protection.\(^33\) The results of ongoing studies on the duration of clinical effectiveness in a variety of immunocompromising conditions are eagerly awaited.
Do certain immunosuppressive drugs and regimens pose a higher risk for incident HZ?

Individuals with immune-mediated diseases being treated with immunosuppressive drugs (e.g., glucocorticoids, antimeabolites and related agents, biologics, targeted therapies such as kinase inhibitors) are the most rapidly expanding group of immunocompromised patients, spanning all ages. The attendant risks vary with the intensity of the immunosuppressive regimen, its duration, and, in particular, the use of agents known to increase HZ risk based on mechanism of action.

Glucocorticoids are the most commonly prescribed class of drugs with immunosuppressive potential. Doses greater than 20 mg per day of prednisone or equivalent are considered high-dose and are associated with an increased HZ risk compared with low-dose regimens. Risk for HZ is elevated, but modestly, with many biologic agents, including tumor necrosis factor inhibitors, interleukin-6 inhibitors, B-cell–depleting agents, and T-cell co-stimulatory inhibitors.

The most commonly used therapies associated with the highest risk of HZ are Janus kinase (JAK) inhibitors, which are now approved for numerous rheumatic, dermatologic, and inflammatory bowel indications, potentially affecting millions of patients. The toxicity of JAK inhibitors has recently been reviewed. Even within this class, the risk for HZ varies considerably for specific agents and with concomitant immunosuppressive therapies. In general, HZ risk appears to be increased with concomitant glucocorticoid therapy. Also, the risk of HZ in patients on JAK inhibitors does not diminish over time, and a previous history of HZ is a strong risk factor for a second episode. The risk for recurrent HZ is relatively low, however. Collectively, these observations should serve to make patients on JAK inhibitors a high priority for prevention.

The type 1 interferon inhibitor anifrolumab, approved for the treatment of systemic lupus, is also associated with a significant risk of HZ. This is not surprising given the centrality of type 1 interferon in antiviral defense. Unlike the risk of HZ associated with JAK inhibitors, the risk with anifrolumab appears greatest in the first year and diminishes sharply for those who continue taking it.

Awareness of the changing landscape of risks associated with immune-based therapy is critical to risk-mitigation strategies.

Should patients with humoral immunodeficiency states receive RZV?

The spectrum of primary immunodeficiency disorders is rapidly expanding, with 485 genetic disorders identified and approximately 1% of the global population affected. Primary humoral immunodeficiency accounts for more than half of these patients. Immunoglobulin replacement therapy is often indicated in patients with humoral deficiency, and while anti-VZV antibodies are present in pooled immunoglobulin, the quantity is not standardized or validated across formulations or lots. Furthermore, data on the incidence of HZ in patients with humoral immunodeficiency states are limited.

The CDC currently recommends RZV for patients age 19 or older with immunodeficiency conditions that increase the risk of VZV reactivation. Although humoral deficiency is not clearly defined in these recommendations, patients with such deficiencies may be candidates. There are currently no formal society guidelines regarding the use of RZV in this sizable subset of patients with primary immunodeficiency. We currently recommend RZV for such patients with a history of remote HZ. Decisions on the use of RZV in the remaining segment of this patient population are made on an individual basis. More data are needed to further define the epidemiology and risks of HZ in this highly heterogeneous group.

What are the recommendations for timing?

The spectrum of immunocompromise is broad among patients with cancer, immunodeficiency states, transplantation, and immune-mediated diseases. Hence the need for and timing of vaccine administration varies widely. In general, it is best to administer all vaccines at least 2 weeks before planned immunosuppression to allow time for optimal response. This is frequently not feasible, and therefore vaccination during active immunosuppression is still recommended.

Many studies show the safety and maintained effectiveness with co-administration of adult vaccines, with rare exceptions. The CDC and Advisory Committee on Immunization Practices advise that RZV can be co-administered with any other adult vaccine, provided the vaccines are given at different injection sites. Concomitant administration of vaccines is often recommended, and even encouraged, to improve vaccine uptake. Practically speaking, however, given the potential for reactogenicity with the RZV series, many experts opt to separate RZV from other vaccines if the patient is able and amenable to receiving vaccines on different days. If a patient receives more than 1 vaccine at the same time and has an adverse event or significant reactogenicity, how can you determine which vaccine is the culprit? This experience may dissuade the patient from getting vaccines in the future.
Regardless of whether patients receive RZV alone or with other vaccines, reactogenicity counseling is key.

**Is antiviral prophylaxis warranted as a strategy to prevent HZ?**

RZV is the primary strategy to prevent HZ and its complications in immunocompromised patients. However, vaccination is not always possible or, more commonly, is not effective, with some patients experiencing vaccine breakthrough. Data for the efficacy of antiviral prophylaxis in most settings are limited. It is recommended, however, in patients who have undergone hematopoietic transplantation; in these patients, efficacy has been demonstrated for up to 2 years, with the incidence of HZ increasing when prophylaxis is discontinued.42

More common is the scenario of HZ breakthrough in patients fully vaccinated with RZV but facing treatments likely to induce either extreme immunosuppression or that include drugs linked to incident HZ described above. Recommendations in this scenario are mostly limited to expert opinion. We currently offer antiviral prophylaxis to such patients.

**What changes in practice can enhance HZ prevention in immunocompromised patients?**

Vaccination with RZV is essential to HZ prevention efforts. Reaching out to immunocompromised patients in a process of shared and informed decision-making, especially regarding RZV, is equally important. Offering and administering all appropriate vaccines to immunocompromised patients is complex, as the Infectious Diseases Society of America showed in their practice guideline more than a decade ago.43 While new vaccines have emerged since this publication, the principles of collaboration between patients, their primary care physician, and the specialist who cares for the condition that contributes to their state of immunocompromise remain at the core of this process. All too often patients are caught in the middle of well-meaning clinicians struggling to figure out who will take the lead to approach them regarding the increasingly complex landscape of old and new vaccines. Unfortunately, the guidance document provided annually by the CDC18 has become increasingly complex and ponderous, leaving many clinicians uncertain themselves regarding which patients are eligible candidates and when to administer the increasing array of available vaccines. Helping immunocompromised patients understand their increased risks of developing HZ, the significant burden of symptoms they may incur, the increased risk of complications, and the risks and benefits of RZV (including how to prepare for the strong likelihood of reactogenicity balanced by the extremely low incidence of serious adverse events) are key to this discussion.

**CONCLUSION AND FUTURE DIRECTIONS**

HZ is a serious illness in the general population, and more so in the immunocompromised population. Effective prevention through administration of RZV to vulnerable patients age 19 and older is currently recommended. The vaccine has been demonstrated to be both safe and effective in this group. Numerous questions remain, however, regarding how to identify immunocompromised patients and what the long-term efficacy of RZV in the immunocompromised will be. For now, sufficient data exist to aggressively engage vulnerable patients in a process of shared and informed decision-making regarding vaccination.

**DISCLOSURES**

Dr. Cassandra Calabrese has disclosed consulting with Astra Zeneca, Lilly, and Pfizer, and consulting, teaching, and speaking for Sanofi-Reproducer. Dr. Kirchner has disclosed consulting with Janssen Pharmaceutica, Lilly, and Pfizer; teaching and speaking for RhaPP; and acting as an advisor or review panel participant for Boehringer Ingelheim, Horizon Pharma, and UCB. Dr. Fernandez has disclosed teaching and speaking for Baxalta. Dr. Leonard Calabrese has disclosed consulting for Abbvie Pharmaceuticals, GSK, Genentech-Roche, Janssen, Novartis, Sanofi Aventis, and UCB; teaching and speaking for Astra Zeneca, Genentech-Roche, Janssen, and UCB; and acting as an advisor or review panel participant for Genentech-Roche.


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