VOLUME 93 • NUMBER 2 • FEBRUARY 2026 • www.ccjm.org

CME MOC

Cleveland Clinic Journal of Medicine

A new direction in pain management?

Profound xanthomas in a young man

Xanthomas: A clue to undiagnosed lipid disorders

PCABs vs PPIs in severe esophagitis

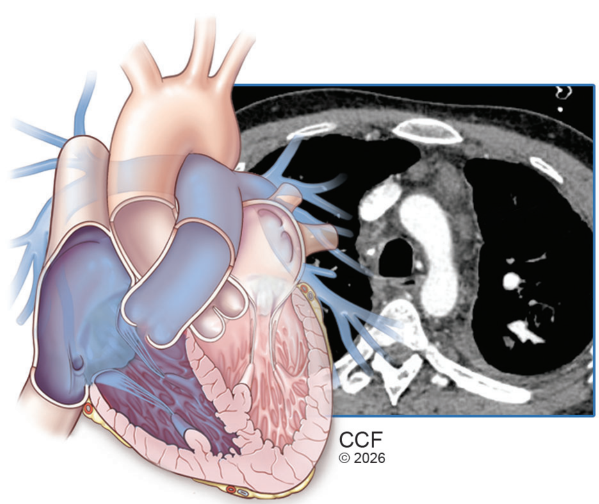
Screening for liver disease in patients who drink heavily

Suzetrigine: A novel nonopioid systemic analgesic

Rapidly progressive kidney failure in an 82-year-old man

Artificial intelligence in medicine: How it works, how it fails

Right ventricular failure in a young man



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Cleveland Clinic Journal of Medicine [ISSN 0891-1150 (print), ISSN 1939-2869 (online)] is published monthly by Cleveland Clinic at 9500 Euclid Avenue, JJ44, Cleveland, OH 44195.

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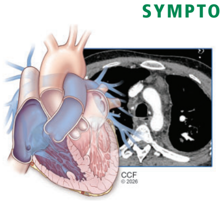

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A new direction in pain management?

While we all have our individual biases and practice preferences when working with patients with acute and chronic pain, complying with professional society, governmental, and institutional guidelines and social trends has been a roller-coaster ride. In "shared decision-making" with individual patients, I frequently find our decisions in disagreement with some or all of the above regulatory guidance. The frustration points are many, but our limited therapeutic armamentarium is a significant one.

In January 2025, suzetrigine was approved by the US Food and Drug Administration (FDA) for treatment of moderate to severe acute pain.[1] As discussed by Divito et al[2] in this issue of the *Journal*, suzetrigine is a novel orally active nonopioid selective inhibitor targeting a specific sodium channel predominantly expressed on peripheral nociceptive (pain-sensing) neurons. In part because the initial regulatory approval studies were in the perioperative setting of abdominoplasty and bunionectomy,[3] there has been as yet little fanfare about the drug in the general medicine literature. Also, considering how sensitized the medical community and the pharmaceutical industry are to issues surrounding the marketing of pain medications based on prior experiences, this is no surprise. And it is by no means clear that this drug will provide a panacea for the many dilemmas we face in treating our patients who are coping with acute and, particularly, chronic pain.

As a result of increased awareness about suboptimal pain control in many patients with cancer or chronic conditions and during end-of-life care, the Veterans Health Administration in 1999 supported initiatives by the American Pain Society and designated "pain" as the fifth vital sign (joining heart rate, blood pressure, respiratory rate, and temperature). In the same time frame, new opioid compounds were marketed and the Joint Commission on the Accreditation of Healthcare Organizations mandated that pain must be addressed in all patients in accredited healthcare settings by 2001 in order for institutions to receive federal financial support. As discussed by Tompkins et al,[4] there was also a loosening of concerns about physicians prescribing greater amounts of opioids and reduced potential for negative regulatory actions taken against physicians who were "overprescribing" them. These well-intentioned efforts to improve management of patients' chronic pain were not uniformly successful[5] and may well have contributed to the wider prescription of opioids that is now defined as a problem that needs to be constrained.

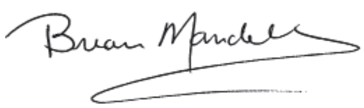
Nonetheless, the need to treat patients with both acute and chronic pain remains an ongoing challenge. Despite the regulatory scrutiny and bureaucratic red tape associated with prescribing opioids as well as some other medications, patients still seek our help. Perhaps creating some expectation for some patients that their pain can be totally relieved, and that pain medications may be escalated to deal with every pain, our medical assistants, as they bring patients back to their room in clinic, ask each of them, "Are you currently experiencing any pain?" and, if the response is yes, then ask them to rate its severity from 0 to 10. It would be nice to have another treatment option for pain that is less limited by metabolic or organ-targeted side effects, cognitive dysfunction, addiction potential, and red tape.

Suzetrigine is an oral, twice-daily tablet that selectively targets the $Na_V1.8$ sodium transport channel that is expressed mainly in peripheral nociceptive nerve fibers. These channels are not expressed in the brain, and preclinical studies did not demonstrate behavioral changes or addictive

doi:10.3949/ccjm.93b.02026

potential in rodents and monkeys.[1,6] Other less subtype-specific sodium channel blockers like lidocaine have cardiac and central nervous system side effects when given systemically. Currently, suzetrigine is approved by the FDA for short-term use in patients with acute pain. Results from fairly small phase 3 trials demonstrated efficacy greater than placebo and comparable but not superior to hydrocodone 5 mg and acetaminophen 325 mg over 48 hours following abdominoplasty or bunionectomy. Studies predominantly included White women. In these and other short-term studies, suzetrigine was well tolerated, with a few patients experiencing muscle spasms, rash, or reversible elevations in creatine kinase. There is little information regarding postoperative opioid-sparing effects. Whether there will be wide acceptance of this new drug in the perioperative setting remains to be seen. For example, celecoxib, which unlike other nonsteroidal anti-inflammatory drugs does not adversely impact platelet function, decreased postoperative pain and opioid use in clinical trials,[7] but has not apparently achieved widespread use for control of postoperative pain.

Given the many challenges of treating patients with chronic pain, undoubtedly suzetrigine will be tried off-label in those patients whose pain has not adequately responded to medications like gabapentin, duloxetine, nonsteroidal anti-inflammatory drugs, and so on. Very preliminary studies suggest that suzetrigine may have some efficacy in treating the pain of diabetic neuropathy, but had no greater effect than placebo in treating the pain associated with chronic radiculopathy.[1] Although other sodium channel blockers have not shown significant efficacy in treating fibromyalgia, I'm sure suzetrigine will also be tried in patients with this condition. Given that this is currently felt to be a syndrome associated with central sensitization and pain escalation,[8] demonstration of efficacy of a peripherally acting neural channel antagonist could contribute to a better understanding of fibromyalgia. But at $15 per pill,[2] results of individual patients' anecdotal experiences with suzetrigine may not rapidly accrue.



Brian F. Mandell, MD, PhD
Editor in Chief

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FEBRUARY

MULTIDISCIPLINARY COLORECTAL ONCOLOGY COURSE
February 6
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February 13
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MARCH

CULTIVATING JOY AND PURPOSE IN HEALTHCARE
March 7
Cleveland, OH, and Live stream

COMPREHENSIVE NEUROTOXIN COURSE FOR NEUROLOGICAL CONDITIONS
March 14–18
Dallas, TX

APRIL

HEALTHCARE PROFESSIONAL COACH TRAINING
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Live stream

SEVA PROGRAM
April 16–18
Cleveland, OH

CLEVELAND CITYWIDE COPD SUMMIT
April 17
Beachwood, OH

INNOVATIONS IN NEUROSCIENCE
April 24
Cleveland, OH, and Live stream

WELLNESS AND PREVENTIVE MEDICINE ANNUAL CONFERENCE
April 24
Beachwood, OH, and Live stream

HEALTHCARE PROFESSIONAL COACH TRAINING
April 29–30
Live stream

NEPHROLOGY UPDATE
April 29–May 1
Cleveland, OH

MAY

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May 2
Mayfield Heights, OH

DIABETES DAY
May 7
Cleveland, OH, and Live stream

POCUS360: INTEGRATING ULTRASOUND INTO OUTPATIENT AND INPATIENT CARE
May 7–9
Cleveland, OH

OBESITY SUMMIT
May 8–9
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MEDICAL DERMATOLOGY THERAPY UPDATE
May 14–16
Cleveland, OH

CARING FOR YOUNG ADULTS WITH HEART DISEASE
May 15–16
Chicago, IL

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June 6
Cleveland, OH

HEART OF THE CITY CARDIOVASCULAR SYMPOSIUM
June 6
Fort Lauderdale, FL

INTENSIVE REVIEW OF INTERNAL MEDICINE
June 8–12
Live stream

INNOVATIONS IN CEREBROVASCULAR CARE
June 10–11
Cleveland, OH

CLEVELAND HEART FAILURE SUMMIT
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Cleveland, OH, and Live stream

UPDATE IN MULTIPLE SCLEROSIS
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Cleveland, OH

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September 10–12
Cleveland, OH

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September 18–19
Cleveland, OH, and Live stream

GLOBAL EP SUMMIT
September 18–19
Cleveland, OH

UPDATES IN PRIMARY IMMUNODEFICIENCY
September 18–19
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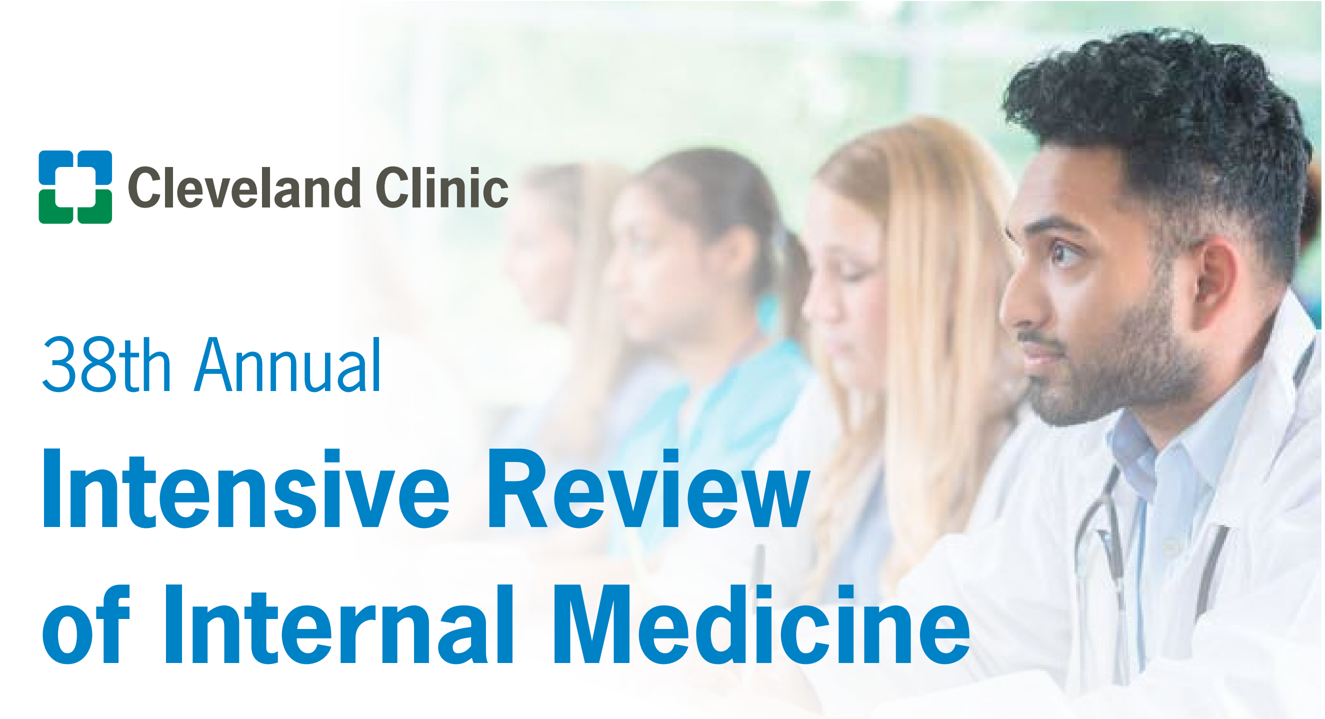

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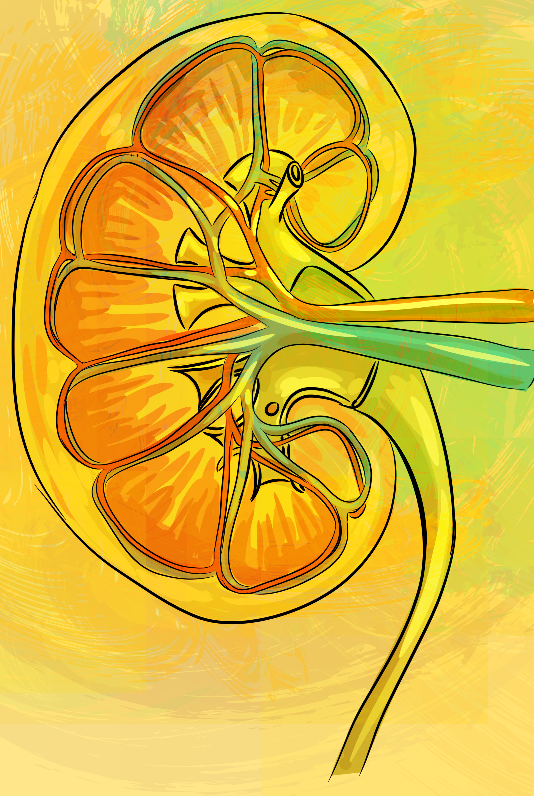

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Profound xanthomas in a young man

A 33-year-old man with a medical history of obesity (body mass index 31 kg/m^2), uncontrolled type 2 diabetes mellitus, severe hypertriglyceridemia, and hypercholesterolemia was hospitalized due to acute abdominal pain secondary to recurrent acute hypertriglyceridemia-induced pancreatitis. In the previous year, he had been admitted to the hospital multiple times due to acute hypertriglyceridemia-induced pancreatitis. Because he had a suboptimal response to insulin therapy during his second hospital admission earlier in the year, the patient required initiation of plasma exchange, which was also required during each of his subsequent admissions.

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Nine years earlier, the patient was diagnosed with hypertriglyceridemia, hypercholesterolemia, and type 2 diabetes mellitus with a fasting serum triglyceride level of 9,000 mg/dL, hemoglobin A1c 10.8%, and total cholesterol 550 mg/dL. Initial management included fenofibrate 48 mg daily, niacin, fish oil supplements, metformin 1,000 mg twice daily, and insulin glargine and lispro combination. The patient reported intolerance to statin therapy (myalgias and fatigue) after a short trial. His course was complicated by dietary and medical nonadherence. Six years after being diagnosed with type 2 diabetes, he required treatment for osteomyelitis of the right great toe but did not complete recommended routine diabetes screenings.

At the time he was initially diagnosed with metabolic syndrome, the patient reported development of diffuse keloid-like xanthomas. On current presentation, he reported marked progression of the skin lesions over the previous 9 years. On current physical examination, he was found to have clusters of pronounced raised, pink, tendinous xanthomas with scattered yellow cholesterol deposits surrounded by keloid hypertrophic scars involving the face, the lower and upper extremities (**Figure 1**), and a majority of the trunk

doi:10.3949/ccjm.93a.24093

Figure 1. (A) Clusters of keloid-like eruptive xanthomas and cholesterol deposits throughout the dorsum of the right hand and wrist. (B) Profound constellation of eruptive xanthomas involving a majority of the posterior right elbow with extension into the distal upper arm. (C) An organized collection of raised eruptive xanthomas involving the posterior left arm with multiple foci of cholesterol deposits scattered throughout.

(**Figure 2**). Based on their distinct appearance and clinical presentation, the skin lesions were believed to be secondary to profound lipid derangement, due in part to chylomicronemia syndrome, augmented by uncontrolled diabetes and dietary noncompliance. The prominent fibroproliferative (keloid) scarring was believed to be induced by severe eruptive xanthoma and the inflammatory effect of clustered xanthomas.

Chylomicronemia syndrome was considered based on the patient's clinical presentation; however, the patient denied a family history of hypertriglyceridemia and declined genetic testing. Medication review and additional laboratory testing (comprehensive metabolic panel, thyroid-stimulating hormone, urinalysis,

Figure 2. Scattered xanthomatous cholesterol deposits involving a majority of the posterior trunk.

vitamin B_{12}, serum toxicology screen, human immunodeficiency virus testing) were unremarkable.

Over the course of the next year, the patient's lipid profile improved with escalation of medical therapies, including rosuvastatin 10 mg nightly (a repeat trial of statin therapy without recurrent side effects), fenofibrate 145 mg daily, icosapent ethyl 2 g twice daily, and a multimodal diabetes regimen. His adherence to the diabetes regimen improved but remained intermittent. The xanthomatous skin findings remained unchanged. Plasma exchange therapy resulted in resolution of acute pancreatitis and reduced his fasting triglyceride level to 540 mg/dL.

LINKED TO LIPID DISORDERS

Xanthomas, localized fatty deposits in the skin, can vary immensely in clinical presentation, ranging from subtle reddish-yellow papules over extensor surfaces to more severe tendinous xanthomas with a keloid-type appearance, as seen in our patient. Cutaneous xanthomas are commonly associated with lipid derangements, including severe hypertriglyceridemia, hyperlipidemia, and poorly controlled type 2 diabetes, with varying reported prevalence.[1]

The differential diagnosis includes both Langerhans histiocytosis and non-Langerhans histiocytosis, disseminated granuloma annulare, and generalized eruptive histiocytoma. In patients without profound lipid abnormalities, targeted biopsy is often required to establish a diagnosis.[2]

Treatment of xanthomatous skin findings involves aggressive correction of underlying triglyceride derangements with medical therapies, low-fat diet, alcohol avoidance, and improved glycemic control. Apolipoprotein C-III and angiopoietin-like 3 inhibitors are emerging therapies with early success, and should be considered in patients with severe hypertriglyceridemia that does not respond to medical therapy.[3,4] Local xanthoma-directed therapies such as laser removal and surgical resection can be considered for cosmetic or symptomatic purposes, but are limited in patients with multiple skin lesions.[5]

Early detection of lipid disorders and initiation of appropriate therapies can decrease risk of premature cardiovascular disease and multiple downstream complications of metabolic syndrome. In patients who decline genetic testing and have clinical features of familial chylomicronemia syndrome, the use of well-validated scoring calculators to quantify the likelihood of familial chylomicronemia syndrome is recommended.[6]

Patients with hypertriglyceridemia-induced pancreatitis are often younger than patients with pancreatitis due to other causes but have higher risk of morbidity and mortality, emphasizing the importance of early recognition and intervention.[7] When evaluating a patient with cutaneous xanthoma of any degree, it is crucial to obtain appropriate screening lipid profiles and treat metabolic derangements aggressively to avoid life-threatening complications. ■

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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EDITORIAL

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Xanthomas: A clue to undiagnosed lipid disorders

Xanthomas (lipid deposits) and their associated histologic findings were described as early as 1904.[1] Xanthomas are classically associated with disorders of lipid metabolism. However, not all persons with lipid disorders have xanthomas, and not all with xanthomas have lipid disorders.[2] Still, xanthomas identified during a clinical examination may provide a unique opportunity to recognize the presence of severe dyslipidemias.

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In this issue of the *Cleveland Clinic Journal of Medicine*, Leonhardt and Maroz[3] describe a case in which a 33-year-old man with severe (perhaps extreme) hypertriglyceridemia—a fasting serum triglyceride level of 9,000 mg/dL—along with poorly controlled diabetes mellitus, obesity, and hypercholesterolemia presented with a variety of striking eruptive xanthomas. This presentation was functionally felt to be consistent with chylomicronemia syndrome, specifically familial chylomicronemia syndrome, although the patient declined genetic testing.

XANTHOMAS AND FAMILIAL LIPID DISORDERS

Familial chylomicronemia syndrome is a rare autosomal recessive genetic disorder that typically involves impaired activity of the lipoprotein lipase enzyme.[4] It dramatically increases the risk of recurrent hypertriglyceridemia-induced acute pancreatitis. Accurate and timely recognition of familial chylomicronemia syndrome is crucial as it allows the clinician to start treatment to lower triglyceride levels, decreasing the risk of acute pancreatitis, and to recommend cascade screening to look for the disorder in close family members. In the present case,[3] the patient's history of obesity and uncontrolled diabetes mellitus may have contributed to their hypertriglyceridemia, but the extreme nature of triglyceride elevation coupled with a history of acute pancreatitis makes familial chylomicronemia syndrome a strong consideration. This patient received multiple therapies to lower their triglycerides, ultimately undergoing plasmapheresis to reduce triglyceride levels and resolve their acute pancreatitis.

Familial chylomicronemia syndrome is not the only condition associated with xanthomas. Familial hypercholesterolemia is an autosomal dominant genetic condition characterized by very high plasma levels of low-density lipoprotein cholesterol and a risk of atherosclerotic cardiovascular disease up to 20 times higher than that of the general population.[5,6] The heterozygous form of familial hypercholesterolemia (HeFH), in which an individual carries a pathogenic mutation in 1 allele, may be present in about 1 in 250 individuals in the United States, yet may be underdiagnosed in 90% or more cases in many countries.[7] Tendon xanthomas, particularly in the Achilles tendons, are strongly associated with familial hypercholesterolemia and are part of the Dutch Lipid Clinic Network criteria used to diagnose this condition.

A rarer condition associated with xanthomas is cerebrotendinous xanthomatosis, a lipid storage disease that is associated with progressive neurologic issues.[1]

XANTHOMAS—STILL A VALUABLE CLINICAL FINDING

Whether a working knowledge of xanthomas still matters for trainees and clinicians in the modern era of widely available direct-to-consumer laboratory testing is a reasonable question. Also, at a time when statin therapy is widely used for primary prevention, xanthomas may not be common even in those with an underlying lipid disorder. In the CASCADE-FH (Cascade Screening for Awareness and Detection of Familial Hypercholesterolemia) registry, only 19% of those with HeFH had tendon xanthomas.[8]

doi:10.3949/ccjm.93a.25116

When present, however, xanthomas are sometimes nearly pathognomonic for the presence of lipid disorders, which are underdiagnosed at the population level, and thus finding xanthomas during an examination offers an opportunity to identify these disorders early. At a routine primary care visit, urgent care visit, or emergency department visit, the astute clinician who notes the presence of cutaneous xanthomas in a young patient may be prompted to undertake a dedicated evaluation for genetic disorders of lipid metabolism, which should generally include both a fasting lipid panel that evaluates total cholesterol, low-density lipoprotein cholesterol, triglycerides, and high-density lipoprotein cholesterol and a targeted family history focused on hyperlipidemia, cardiovascular disease, and pancreatitis.

For families with previously undiagnosed HeFH or familial hypercholesterolemia syndrome, an index diagnosis of one of these genetically inherited diseases, triggered by the presence of cutaneous xanthomas, can encourage genetic testing to identify affected relatives at early ages, and potentially allow early treatment and modification of the natural history of these conditions and their associated morbidity and mortality risks. The possibility of early treatment is particularly salient, given the availability in modern practice of multiple therapies for lowering low-density lipoprotein cholesterol and triglycerides levels. For example, olezarsen (an antisense oligonucleotide) and plozasiran (a small interfering RNA therapy) target apolipoprotein C-III and were recently approved by the US Food and Drug Administration for reducing triglyceride levels in individuals with familial chylomicronemia syndrome.[9,10]

It remains of value for general clinicians to be familiar with xanthomas and what they may represent: a potential window into an individual's disease, genetics, and future morbidity and mortality risks. ■

DISCLOSURES

Dr. Sarraju reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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ONE MINUTE CONSULT

BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should potassium-competitive acid blockers replace proton pump inhibitors as first-line therapy for patients with severe (Los Angeles grade C or D) esophagitis?

My patient with severe heartburn is newly diagnosed with Los Angeles grade C/D esophagitis and is not on any medical therapy. Should I start a potassium-competitive acid blocker (PCAB) like vonoprazan as first-line treatment?

A: Proton pump inhibitors (PPIs) remain first-line treatment for esophagitis, while PCABs are reserved for patients intolerant of or unresponsive to PPIs, particularly if erosive esophagitis persists. PCABs have not been shown to provide a statistically significant difference in inducing and maintaining healing in patients with Los Angeles grade C or D esophagitis when compared with dose-optimized PPIs.

WHAT IS ESOPHAGITIS, AND HOW IS IT GRADED?

Esophagitis is inflammation of the esophagus, commonly caused by gastroesophageal reflux disease, allergies (eosinophilic esophagitis), infections, or drug-induced injury. Symptoms include heartburn, dysphagia, regurgitation, and chest or abdominal pain.[1]

Reflux esophagitis is classified as nonerosive (symptoms without visible mucosal damage on endoscopy) or erosive (visible mucosal breaks on endoscopy). Erosive esophagitis, more common in men, is graded by using the Los Angeles classification[2]:

doi:10.3949/ccjm.93a.25044

- Grade A: mucosal break 5 mm or less, not extending between folds
- Grade B: mucosal break greater than 5 mm, not extending between folds
- Grade C: continuous mucosal break less than 75% of the esophageal circumference
- Grade D: mucosal break 75% or more of the esophageal circumference.

Patients with higher grades (C and D) have a greater risk of stricture formation, Barrett esophagus, esophageal carcinoma, and significant gastrointestinal bleeding.

HOW IS ESOPHAGITIS TREATED?

Treating esophagitis includes controlling symptoms, recommending lifestyle modifications, and confirming that healing has occurred with endoscopy. The American Gastroenterological Association[3] recommends a once-daily PPI for at least 8 weeks as first-line therapy for patients with mild nonerosive esophagitis (grade A or B), increasing to a twice-daily dose if patients do not respond. In patients with C or D esophagitis, the American College of Gastroenterology[1] recommends endoscopy after an initial 8-week course of once-daily PPI treatment to evaluate healing and to screen for Barrett esophagus, with the lowest-dose PPI therapy continued indefinitely to prevent recurrence.

HOW DO PPIs WORK, AND WHAT ARE THE DRAWBACKS OF USING THEM TO TREAT ESOPHAGITIS?

PPIs are prodrugs that irreversibly bind to inactive hydrogen-potassium adenosine triphosphate (the proton pump) in the stomach. The acidic environment in the stomach converts the PPI into its active form, thereby reducing acid production.

Omeprazole equivalent, a measure of how effectively PPIs sustain elevation of gastric pH, is used to compare their relative potency.[4] Dexlansoprazole and rabeprazole are among the most potent PPIs, while lansoprazole and pantoprazole are the least potent (**Table 1**).[4,5] Twice-daily dosing increases drug levels and sustains gastric pH. High-grade (C or D) esophagitis is often treated with PPIs once or twice daily for 8 weeks and adjusted based on healing response.[4–6]

Although PPIs are highly effective, treatment failure can occur. Up to 30% of patients with high-grade esophagitis do not heal after a full course of PPI therapy, and 20% to 30% relapse within a year, especially those with severe disease.[7]

Additionally, observational data have linked long-term use of PPIs to various possible adverse effects. Potential risks include the following[8]:

- Vitamin B_{12} and calcium deficiencies leading to osteoporosis
- Small intestinal bacterial overgrowth
- *Clostridioides difficile* infection
- Kidney disease (interstitial nephritis with rare progression to chronic kidney disease).

These concerns have fueled interest in alternative treatments like PCABs.

WHAT ARE PCABs?

PCABs, including vonoprazan, tegoprazan, and fexuprazan, are a newer alternative to PPIs. They reversibly inhibit both active and inactive hydrogen-potassium adenosine triphosphate pumps, thus providing faster onset and longer acid suppression.[9]

Vonoprazan, first approved in Japan in 2014, is the only PCAB approved by the US Food and Drug Administration to treat *Helicobacter pylori* infection (in 2022), erosive esophagitis (in 2023), and nonerosive gastroesophageal reflux disease (in 2024). It is the most extensively studied PCAB, so it has the data available to compare with PPIs.

An integrated safety analysis of 14 clinical trials that evaluated up to 5 years of vonoprazan use, as well as 9 years of postmarketing surveillance data, did not show an increased risk of serious complications.[10] Side effects included constipation, diarrhea, indigestion, and abdominal pain. Serious adverse events were rare and were similar to PPIs; the most common was hypergastrinemia. Other rare adverse events reported were elevated levels of alanine aminotransferase, aspartate aminotransferase, or both; tubulointerstitial nephritis; and gastric cancer.

As PCABs are relatively new, longer-term use is needed to clarify their full side-effect profile.

TABLE 1
Relative omeprazole equivalent doses of proton pump inhibitors when compared with omeprazole 20 mg

Drug and dose	Omeprazole equivalent
Dexlansoprazole 30 mg	50–60 mg
Rabeprazole 20 mg	36 mg
Esomeprazole 20 mg	32 mg
Omeprazole 20 mg	20 mg
Lansoprazole 15 mg	13.5 mg
Pantoprazole 20 mg	4.5 mg

Drugs are listed in order of most to least potent.

Based on information from references 4 and 5.

DO PCABs OUTPERFORM PPIs FOR HIGH-GRADE ESOPHAGITIS?

Using PCABs as a potential alternative to PPIs has been explored, particularly for erosive esophagitis. Most initial randomized controlled trials were noninferiority studies that were designed to show treatment is not worse than standard care. These trials set a predefined margin that determines the acceptable loss of efficacy—typically requiring at least 50% preservation of the minimal treatment effect—based on previous studies. While PCABs were shown to be as effective as PPIs, none has shown superiority over PPIs optimized for dose and potency.

Efficacy and Safety of Oral Once-Daily Vonoprazan (TAK-438) in Participants With Erosive Esophagitis, a phase 3 randomized, double-blind, multicenter trial conducted across 56 sites from 2015 to 2017, compared esophagitis healing rates between vonoprazan 20 mg and lansoprazole 30 mg in 481 Asian patients with endoscopically confirmed erosive esophagitis.[11] Participants received daily treatment for 8 weeks, and underwent an endoscopy at weeks 2, 4, and 8 to evaluate healing. The study confirmed vonoprazan's noninferiority, with a −10% margin. While healing rates were higher with

TABLE 2
Efficacy of vonoprazan and proton pump inhibitors for mucosal healing failure in initial and maintenance treatment of grade C and D esophagitis

	Risk ratio of treatment failure (95% credible interval)[a]	SUCRA score
Initial treatment		
Compared with vonoprazan 20 mg once daily	1.0	0.89
Keverprazan 20 mg	0.86 (0.14–4.32)	0.87
Dexlansoprazole 60 mg	2.23 (0.97–6.71)	0.66
Esomeprazole 40 mg	1.92 (0.84–5.61)	0.61
Rabeprazole extended release 50 mg	1.75 (0.64–6.28)	0.48
Pantoprazole 40 mg	2.97 (0.94–11.16)	0.29
Lansoprazole 30 mg	**2.97 (1.64–6.71)**	0.26
Esomeprazole 20 mg	2.99 (0.93–12.33)	0.29
Omeprazole 20 mg	**3.5 (1.31–11.79)**	0.15
Maintenance treatment		
Compared with vonoprazan 20 mg once daily	1.0	0.87
Lansoprazole 30 mg	1.54 (0.24–11.81)	0.73
Vonoprazan 10 mg	3.05 (0.35–36.35)	0.50
Tegoprazan 20 mg	3.44 (0.12–111.46)	0.49
Esomeprazole 20 mg	4.00 (0.23–107.25)	0.44
Lansoprazole 15 mg	6.04 (0.88–63.38)	0.24
Pantoprazole 20 mg	7.38 (0.21–393.95)	0.22

[a]Bold indicates significant differences in treatment failure for lansoprazole 30 mg and omeprazole 20 mg compared with vonoprazan 20 mg in the healing phase; a significant difference in efficacy was not found between vonoprazan and the other proton pump inhibitors.

SUCRA = surface under the cumulative ranking

Adapted with permission from the American College of Gastroenterology. Zhuang Q, Chen S, Zhou X, et al. Comparative efficacy of P-CAB vs proton pump inhibitors for grade C/D esophagitis: a systematic review and network meta-analysis. Am J Gastroenterol 2024; 119(5):803–813. doi:10.14309/ajg.0000000000002714; journals.lww.com/ajg/pages/default.aspx.

vonoprazan in patients with grade C or D esophagitis, these differences were not statistically significant. Symptom relief also did not significantly differ.

Given that differences in diet and cytochrome P450 metabolism between Asian and Western patients can potentially affect PPI efficacy, another phase 3 randomized, double-blind, multicenter trial, Efficacy and Safety of Vonoprazan Compared to Lansoprazole in Participants With Erosive Esophagitis, evaluated vonoprazan for inducing and maintaining healing of erosive esophagitis.[9] The study included 1,027 adults (34.1% had grade C or D esophagitis) across 111 sites in the United States and Europe.

Patients received vonoprazan 20 mg or lansoprazole 30 mg daily for 8 weeks (healing phase), and were assessed with endoscopy at weeks 2 and 8. Those who achieved healing were rerandomized to vonoprazan 20 or 10 mg or lansoprazole 15 mg for 24 weeks (maintenance phase). Results showed that vonoprazan was noninferior to lansoprazole for inducing and maintaining esophagitis healing and superior for severe esophagitis based on predefined exploratory and secondary end-point analyses, while symptom relief did not differ significantly.

However, clinical applicability of higher healing rates must consider the chosen PPI comparator. Once-daily dosing with lansoprazole 30 mg, a PPI with a lower omeprazole equivalent, had the lowest esophagitis healing rate when compared with double-dose PPI drug therapies.[12] Similarly, lansoprazole 15 mg was shown to have a sustained healing rate of less than 75%, while higher-dose and -potency PPI regimens have demonstrated healing rates of more than 90%.

To further evaluate vonoprazan's efficacy in patients with grade C or D esophagitis, a systematic review and network meta-analysis compared the efficacy of PCABs with that of various PPIs.[7] The analysis included 24 randomized trials covering 9,267 patients in treatment phases and 1,834 patients in maintenance phases. The analysis revealed that, while vonoprazan was superior to lansoprazole in direct comparisons, this finding was not supported when vonoprazan was compared with PPIs of higher dose and potency. The relative risk of initial treatment failure was higher with lansoprazole 30 mg (risk ratio 2.97, 95% credible interval 1.64–6.71) and omeprazole 20 mg (risk ratio 3.5, 95% credible interval 1.31–11.79) compared with vonoprazan 20 mg (**Table 2**).[7] (Credible intervals are presented because they are a direct statement of probability that the true value is within the interval by using the Bayesian approach of combining previous knowledge with new data, whereas confidence intervals interpret probability over the long term.) However, when compared with more potent PPIs such as esomeprazole 40 mg, dexlansoprazole 60 mg, and rabeprazole 50 mg, there were no significant differences in treatment failure.

Surface under the cumulative ranking (SUCRA), a probability ranking metric used in network meta-analyses, was also used to assess vonoprazan's efficacy. Vonoprazan 20 mg ranked highest for both the initial healing and maintenance phases, followed by, in the initial healing phase, dexlansoprazole 60 mg and esomeprazole 40 mg.[7] For maintenance of healing, however, vonoprazan only demonstrated superiority over lansoprazole 15 mg in direct comparisons.

While SUCRA offers a convenient means of synthesizing complex data into an accessible ranking system, it does not incorporate critical factors such as effect size, safety profiles, or cost. Thus, high SUCRA scores should be interpreted cautiously, as they may overstate the clinical value of treatment when not contextualized within the broader evidence.

WHEN SHOULD WE USE A PCAB?

PCABs, while an alternative to PPIs, have not been shown to have superior efficacy and are significantly more expensive. Their use should be limited to patients who cannot tolerate PPIs, do not respond to treatment, or require an alternative therapy; however, they are not currently recommended as a first-line treatment.

THE BOTTOM LINE

PPIs remain the gold standard for treating erosive esophagitis, despite concerns over long-term efficacy and safety. Although PCABs are an alternative, most existing trials show only noninferiority to PPIs, and data showing superiority in severe esophagitis are based on low-dose, low-potency comparators. While PCABs are a novel pharmacologic mechanism that offer exciting promise, more research is needed to define their role in clinical practice.

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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COMMENTARY

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Preventing cirrhosis: Why primary care clinicians should screen for liver disease in patients who drink heavily

The American College of Gastroenterology (ACG)[1] recommends screening individuals with heavy alcohol use for liver disease. Universal screening for alcohol use is most applicable in the primary care setting because it is where patients with heavy alcohol use and alcohol-related liver disease may be identified before they develop advanced liver damage. Once these patients present to a gastroenterology clinic, their liver disease is often significantly progressed or even irreversible.[2] However, liver disease screening in individuals with heavy alcohol use is currently not standard in primary care, in part because no major primary care organizations have followed the ACG in endorsing this practice.

In this commentary, we make the case that screening patients with heavy alcohol use for liver disease is a valuable tool for primary care clinicians to consider. To this end, we review the existing literature on screening methods, outline ongoing research that will inform this topic in the future, and propose a simple screening pathway for primary care.

PREVALENCE OF ALCOHOL-RELATED LIVER DISEASE IS INCREASING

Approximately 2.6% of Americans, or 5.7 million people, have cirrhosis,[3] and it is estimated that 45% of cirrhosis diagnoses are related to alcohol use.[4] The prevalence of cirrhosis has doubled over the past decade, and once patients progress to end-stage liver disease (also known as *decompensated cirrhosis*), their prognosis is grim.[5] Median survival for patients with decompensated cirrhosis is comparable to, if not worse than, many advanced cancers. Unlike most cancers, though, cirrhosis can be prevented if those at risk are identified early.

Alcohol use is a modifiable risk factor, and it accounts for a large share of cirrhosis cases and mortality. Indeed, age-adjusted mortality rates from alcohol-related liver disease doubled between 1999 and 2022.[6] According to the ACG,[1] patients who engage in heavy drinking are at risk of alcohol-related liver disease. The National Institute on Alcohol Abuse and Alcoholism[7] defines heavy drinking as follows:

- For men: consuming 5 or more drinks on any day or 15 or more drinks per week
- For women: consuming 4 or more drinks on any day or 8 or more drinks per week.

Over 16 million Americans engage in heavy drinking.[8] Many of these patients may not meet the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*,[9] criteria for alcohol use disorder, so the health consequences of their heavy alcohol use are discussed largely in primary care settings rather than in specialty psychiatric or addiction medicine clinics.

EVIDENCE SHOWS EARLY INTERVENTION CAN BENEFIT PATIENTS

Targeted liver disease screening in primary care for those who drink heavily could result in improved population health outcomes.

Existing health inequities are deepened by the disproportionate and worsening burden of alcohol-related liver disease among working-class Americans. Between 1992 and 2021, among Americans without a college degree, mortality from alcohol increased approximately 81% (from 21 per 100,000 people in 1992 to 38 in 2021) but increased minimally among

doi:10.3949/ccjm.93a.25045

TABLE 1
Pharmacotherapy for alcohol use disorder

Medication	Efficacy	Typical dosage	Notes
Naltrexone	Number needed to treat of 11 to prevent return to heavy drinking Number needed to treat of 18 to prevent return to any drinking	Oral: 50–100 mg daily Subcutaneous: 380 mg monthly	Generally first-line treatment given ease of dosing Contraindicated in concurrent opioid use or acute hepatitis Discuss risks and benefits in decompensated cirrhosis
Acamprosate	Number needed to treat of 11 to prevent return to any drinking[a]	Oral: 666 mg 3 times daily	Safe in liver disease Contraindicated in severe kidney impairment
Disulfiram	Limited data suggest only effective when given under supervision	Oral: 250–500 mg daily	Contraindicated if any alcohol was used in preceding 12–48 hours Can cause severe reaction if alcohol is consumed up to 14 days after ingestion
Topiramate[b]	Reduced percentage of drinking days and heavy drinking days	Oral: maximum 100–150 mg twice daily	More significant side-effect profile Requires slow dose escalation Use with caution in decompensated cirrhosis
Gabapentin[b]	Limited data suggest may reduce drinking in patients with protracted withdrawal symptoms	Oral: up to 1,800 mg daily in 2 or 3 divided doses	More significant side-effect profile Risk of misuse, especially with other substance use disorders
Baclofen[b]	Variable efficacy seen in trials, likely more effective in patients already abstinent	Oral: 10–25 mg 3 times daily	Safe in hepatic impairment
Glucagon-like peptide 1 agonists (eg, semaglutide)[b]	Emerging evidence of reduced alcohol intake	Subcutaneous: weekly	Multiple ongoing trials evaluating benefit and safety Can target comorbid metabolic dysfunction–associated liver disease

[a]Benefit only found in European trials where abstinent patients were recruited from treatment centers. Benefit not demonstrated in US trials with a more general population.
[b]Off-label use.

Based on information from references 12–15.

those with a college degree (from 11 per 100,000 people in 1992 to 13 in 2021).[10] A similar education gap emerged in deaths from liver cancer, which nearly doubled among those without a college degree but changed minimally among degree holders.[10]

Effective alcohol use disorder treatment and counseling can prevent alcohol-related liver disease. Indeed, pharmacologic treatment of alcohol use disorder decreases incidence and prevalence of alcohol-related liver disease.[11] Furthermore, in patients with heavy alcohol use, liver disease screening can inform both diagnosis and treatment of alcohol use disorder. Patients who continue to drink despite known liver damage may meet diagnostic criteria for alcohol use

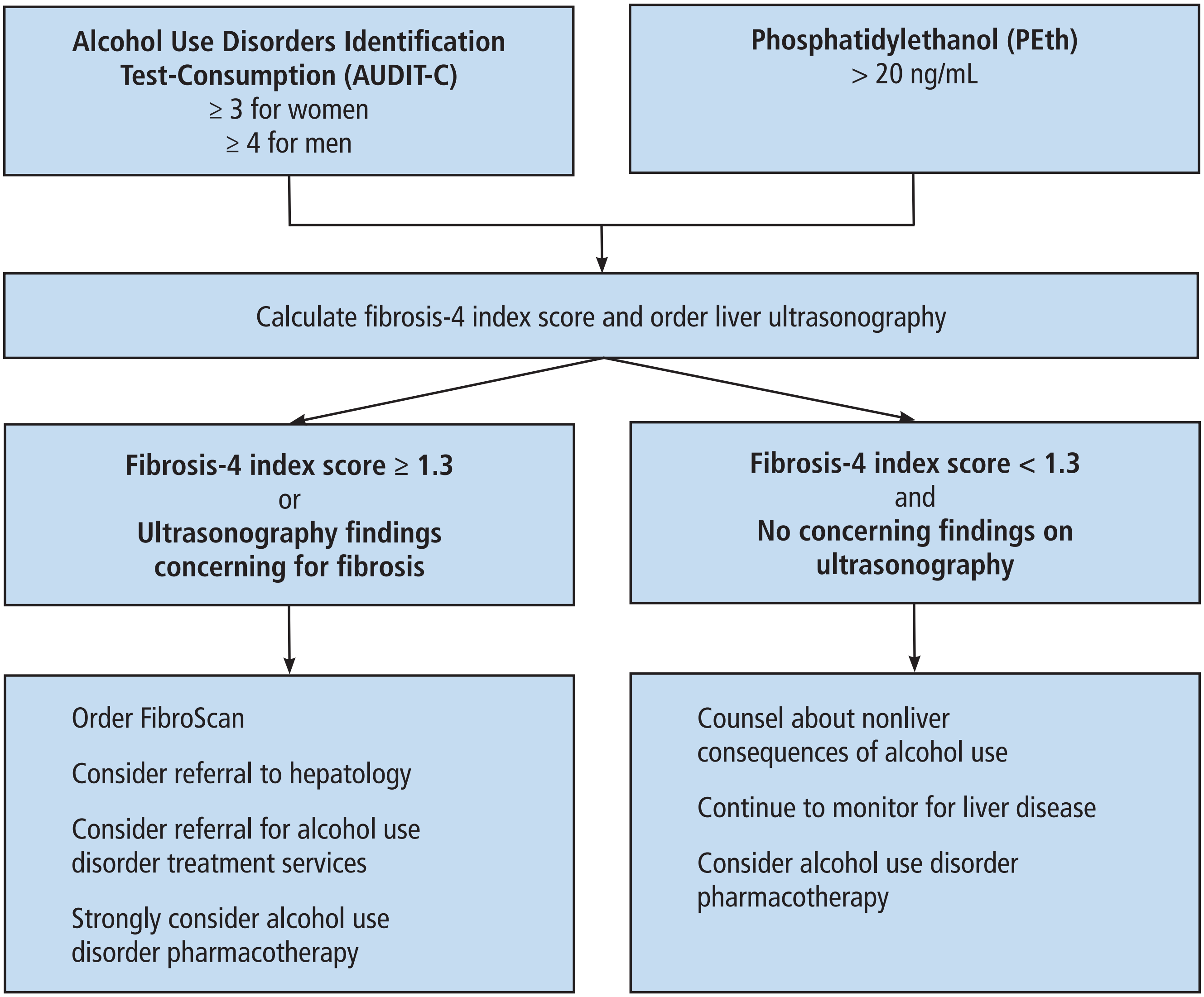

Figure 1. Proposed algorithm for liver disease screening in the primary care setting.

disorder,[9] which should prompt more intensive interventions, including consideration of pharmacotherapy for alcohol use disorder (**Table 1**)[12–15]—a highly effective but remarkably underused tool.[16]

Liver disease screening has also been shown to change behavior. For one, patients with heavy alcohol use are interested in learning about the effects of alcohol on their liver.[17] A few studies have investigated how screening with transient elastography, an ultrasonography-based technology that assesses liver stiffness, affects care. In a prospective cohort study of 86 patients in the United Kingdom who were screened with transient elastography, alcohol consumption decreased meaningfully in patients not only with elevated liver stiffness but also with normal findings.[18]

A randomized controlled trial by the same research group showed that incorporating liver transient elastography into alcohol addiction treatment clinics was feasible.[19] Furthermore, patients randomized to transient elastography had higher engagement in care and greater decreases in alcohol consumption than patients in the control group. Similar findings were demonstrated in an inpatient setting, where hepatology evaluation of patients with alcohol use disorder increased both prescriptions for alcohol use disorder medication and receipt of important preventive hepatology care.[20]

In our primary care practices, we have found that discussing liver disease screening with patients engaging in heavy alcohol use, regardless of the result of the

TABLE 2
Alcohol Use Disorders Identification Test-Consumption

Question	Score: 0 points	1 point	2 points	3 points	4 points
How often did you have a drink containing alcohol in the past year?	Never	Monthly or less	2–4 times per month	2–3 times per week	4 or more times per week
How many drinks did you have on a typical day if you were drinking in the past year?	1–2	3–4	5–6	7–9	10 or more
How often did you have more than 6 drinks on 1 occasion in the past year?	Never	Less than monthly	Monthly	Weekly	Daily or almost daily

A score of 3 or higher in women or 4 or higher in men is considered positive for heavy drinking.

Adapted from reference 23.

screening, can lead to fruitful discussions about the health risks of their drinking.

A SIMPLE WAY TO INTEGRATE SCREENING INTO PRIMARY CARE

Primary care guidelines from the US Preventive Services Task Force[21] recommend screening patients for heavy alcohol use but leave subsequent counseling and management up to clinicians. Among all of the major primary care, psychiatry, and addiction medicine professional organizations, including the US Preventive Services Task Force, American Academy of Family Physicians, US Department of Veterans Affairs, American Society of Addiction Medicine, and National Institute on Alcohol Abuse and Alcoholism, only the American Psychiatric Association mentions liver disease screening in their guidelines.[22]

Therefore, we propose the following pathway to screen for heavy alcohol use and liver disease (**Figure 1**), which can be integrated into existing primary care workflows around alcohol use.

Identify heavy alcohol use

The Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) tool can be used to identify patients who drink heavily. AUDIT-C is a 3-question screening tool that can be easily implemented into primary care team workflows (**Table 2**).[23] A score of 3 or higher in women or 4 or higher in men is positive for heavy drinking.

A phosphatidylethanol blood test, where available, can quantify alcohol use over the previous month and has demonstrated great promise as an objective measure of alcohol consumption.[13] Values are typically divided into the following 3 categories[24]:

- Less than 20 ng/mL indicates abstinence or very light alcohol use
- 20 to 199 ng/mL indicates moderate to significant alcohol use
- Greater than 200 ng/mL indicates heavy alcohol use.

Then screen for liver disease

Based on assessment results, at-risk patients should be screened for liver disease with the **fibrosis-4 index** (a fibrosis risk index derived from basic laboratory tests) and **liver ultrasonography**. We recommend both because the complementary roles of these diagnostic tests increase the sensitivity of this screening strategy: a normal fibrosis-4 index result makes advanced liver fibrosis highly unlikely,[1] and liver ultrasonography can detect hepatic steatosis.[25] Combined, these 2 tests can determine the presence and severity of alcohol-related liver disease.

The fibrosis-4 index was initially developed for patients with viral hepatitis and human immunodeficiency virus coinfection, and low scores (< 1.3 in patients 65 years or younger) are associated with a low likelihood of liver-related outcomes.[26] For this reason, expert consensus recommends that the fibrosis-4 index be used to risk stratify patients with alcohol-related liver disease.[27]

Patients with possible liver fibrosis should undergo evaluation with **FibroScan**, a noninvasive ultrasound-based test that uses vibrations to measure liver scarring or fibrosis, to confirm the diagnosis of cirrhosis and receive more intensive consideration of pharmacotherapy for alcohol use, referral to an addiction medicine specialist, and consultation with hepatology. Patients without concerning liver findings should still be counseled about the adverse effects of alcohol on other organ systems and offered pharmacotherapy for alcohol use, and should continue to be monitored because they could develop liver disease in the future.

POSSIBLE IMPLEMENTATION CHALLENGES

The recommendation to screen for liver disease in primary care has limitations. First, there is limited evidence that liver disease screening improves patient outcomes. While some randomized data exist, the impact of screening on mortality, the gold-standard outcome for screening trials, has not been evaluated. The European LIVERAIM consortium (liveraim.eu) will address this gap by investigating how liver fibrosis screening affects hospitalization and mortality in a randomized controlled trial of 100,000 participants. This is an important first-of-its-kind study that extends from 2024 to 2030. We are in the early days of evaluating liver disease screening, but evidence from other diseases (eg, lung cancer) shows that screening impacts health behaviors favorably.[28]

Another limitation to our recommendation is primary care capacity. Primary care clinicians already have many competing priorities and limited time with patients. The clear screening workflow we provide in **Figure 1** aims to make incorporating liver disease screening into practice more feasible, and creative uses of technology could potentially streamline workflows. For example, a clinical decision-making support tool in the electronic medical record could automatically calculate a fibrosis-4 index score with existing data in patients with a positive AUDIT-C result. A pilot of this approach would be a reasonable first step to evaluate feasibility.

It is worth noting that even if uptake of liver disease screening increased in primary care, there are many patients with heavy alcohol use or alcohol use disorder who do not consistently receive primary care. Patients with low socioeconomic status are less likely to receive liver disease screening and treatment[29] and management of alcohol use disorder,[14] so efforts targeted to this population are crucial.

Finally, the economics of liver disease screening in primary care remain uncertain. Widespread use of liver ultrasonography in patients who drink heavily would likely incur significant costs, and, importantly, the patient may bear the cost of this testing if it is not covered by medical insurance. Furthermore, advanced diagnostic devices, like FibroScan, are not yet universally available. On the other hand, a cost-effectiveness study found that alcohol-related liver fibrosis screening, regardless of the method used, may increase quality-adjusted life years at a relatively low cost.[30] This finding suggests that the benefits of screening in primary care could justify the expense by improving patient outcomes.

OUR CLOSING ARGUMENT

Despite the challenges of screening, primary care clinicians remain on the front line of healthcare and are uniquely positioned to diagnose liver disease in its early stages. Screening for liver disease in appropriate patients may address the rising prevalence of cirrhosis and liver-related mortality by informing discussions with patients about heavy drinking, alcohol use disorder, and the risk of liver disease progression. While we await gold-standard evidence from randomized controlled trials, the data we already have suggest that screening for liver disease may be a helpful tool for primary care clinicians to consider when addressing heavy alcohol use with their patients.

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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Suzetrigine: A novel nonopioid systemic analgesic

Opioids have been the mainstay of postoperative analgesia for decades. However, their side effects and potential complications, such as respiratory depression, postoperative nausea, vomiting, and ileus, have fueled the search for alternative ways to control pain. Thus, the concept of multimodal analgesia was born—a technique using a combination of different analgesic modalities, including acetaminophen, nonsteroidal anti-inflammatories, N-methyl-D-aspartate receptor antagonists, intravenous lidocaine infusion, local anesthetic infiltration, regional anesthesia, and peripheral nerve blocks, that can result in maximal pain relief with the minimum necessary dose of opioids to lessen their side effects. This strategy has coincided with the adoption of enhanced recovery after surgery protocols that have helped promote multimodal analgesia to minimize opioid use while permitting a more expedient recovery.[1]

Recently, suzetrigine, a voltage-gated sodium channel 1.8 ($Na_V1.8$) blocker, was approved by the US Food and Drug Administration (FDA), leading to interest in possibly adding this nonopioid analgesic to the multimodal analgesic regimen.

THE FIRST SYSTEMIC SODIUM CHANNEL BLOCKER ORAL ANALGESIC

Sodium channels have long been a known target for analgesia. Local anesthetics, in particular, inhibit nerve conduction via the intracellular blockade of sodium channels. However, systemic administration of local anesthetic agents has remained limited and considered off-label use. Systemic lidocaine administration has been studied for acute postsurgical pain, but side effects stemming from nonselective inhibition of sodium channels in the heart and central nervous system, as well as a lack of evidence that it is effective beyond 24 hours postoperatively, have limited its use.[2,3]

Suzetrigine is the first systemic sodium channel blocker that has been approved by the FDA for the indication of treating moderate to severe postoperative pain. If suzetrigine proves over time to be effective enough to reduce or even supplant opioids, the current workhorse, it would be a significant advancement in pain management.

PHARMACODYNAMICS AND PHARMACOKINETICS

Suzetrigine is a highly selective sodium channel blocker that primarily targets the $Na_V1.8$ voltage-gated sodium channel.[4] Its chemical name is 4-[(2R,3S,4S,5R)-3-(3,4-difluoro-2-methoxyphenyl)-4,5-dimethyl-4-(trifluoromethyl)oxolane-2-amido]pyridine-2-carboxamide, and in clinical trials it was referred to as VX-548.[4] The $Na_V1.8$ voltage-gated sodium channel appears to be highly expressed in the dorsal root ganglia of peripheral sensory neurons but not significantly expressed in the central nervous system or the heart.[5–7] Because $Na_V1.8$ channels are only found in peripheral sensory neurons, there is optimism that a peripherally mediated therapeutic effect can be achieved without a significant risk of central nervous system–mediated side effects, arrhythmogenesis, or high potential for abuse and addiction.[8,9]

Suzetrigine has a peak plasma time to maximum concentration of 3 hours in fasting conditions and a half-life of 23.6 hours; 49.9% is eliminated in feces and 44% in urine.[10] There seems to be no clinically significant pharmacokinetic differences based on age, sex, body weight, race, or renal impairment.

Suzetrigine is primarily metabolized by the liver into the active metabolite M6-SUZ, which is a weaker $Na_V1.8$ inhibitor.[11] Because this process is mediated

doi:10.3949/ccjm.93a.25087

through the cytochrome P450 3A (CYP3A) enzyme, suzetrigine should be used cautiously in those taking moderate to strong CYP3A inhibitors, as well as in patients with hepatic impairment as increased levels of the drug and its active metabolite have been seen. In those with moderate hepatic impairment (Child-Pugh class B), the area under the plasma concentration-time curve from time 0 to 12 hours for suzetrigine increased by 1.5-fold and the maximum concentration increased by 1.3-fold.[10] Therefore, lower doses should be used in patients with hepatic impairment classified as Child-Pugh class B and should be avoided in patients with Child-Pugh class C cirrhosis.[11]

FDA APPROVAL PROCESS FOR NEW PAIN MEDICATIONS

For a new medication to earn FDA approval as a non-opioid analgesic indicated for acute pain, supporting clinical trials must meet rigorous design and evidentiary standards. Investigational drugs may pursue either a general indication for acute pain by demonstrating efficacy across varied pain models or a specific indication for acute pain, eg, postoperative pain. A general indication requires at least 2 well-controlled trials in different pain populations, while novel mechanisms of action may necessitate broader testing.[12]

Trials must be randomized, double-blind superiority studies, with the treatment duration reflecting the pain model and lasting at least 24 hours for multidose regimens.[13] The primary end point should be a patient-reported measure of pain intensity, using a numerical rating scale assessed at regular intervals. The sum of pain-intensity difference is often used to evaluate cumulative pain relief over time.

The trial design must also account for rescue medication use, ensuring it does not mask the investigational drug's effect. Additional secondary end points, such as time to onset of pain relief and need for rescue medication use, also help characterize the drug's efficacy profile.

PAIN MANAGEMENT EFFECTIVENESS

Acute postsurgical pain

The FDA approved suzetrigine based on 2 phase 3 randomized controlled trials that evaluated pain-control response in adults age 18 to 80 years undergoing abdominoplasty or bunionectomy who were expected to experience moderate to severe postoperative pain (verbal numerical pain score ≥ 4 of 10).[14] Patients with any sensory abnormalities and those with painful physical conditions that might interfere with their ability to assess postoperative pain were not eligible. The trials also excluded patients with a history of long-term opioid or nonsteroidal anti-inflammatory use.

Patients in the abdominoplasty trial were given fentanyl for postoperative analgesia until they were lucid enough for oral medication, at which point they were randomized in a 2:2:1 fashion 15 minutes after last analgesic administration to either suzetrigine, hydrocodone bitrate and acetaminophen, or placebo.[14] Patients in the bunionectomy trial had their pain initially controlled with a popliteal nerve block, so randomization occurred once the block had worn off completely. Ibuprofen 400 mg every 6 hours was allowed as rescue medication for breakthrough pain, but all other pain medications, including opioids, were restricted. The total amount of rescue medication use was recorded, and prerescue pain scores were carried over for 6 hours to ensure the integrity of the pain assessment. The primary end point was a time-weighted sum of pain-intensity difference from baseline over 48 hours. The secondary end point was the time needed to achieve a 2-point or greater reduction in pain compared with hydrocodone bitrate 5 mg and acetaminophen 325 mg.

Suzetrigine showed statistically significant superiority over placebo in reducing pain intensity over 48 hours in both the abdominoplasty (least squares mean difference 48.4, $P < .0001$) and bunionectomy (least squares mean difference 29.3, $P = .0002$) trials.[14] However, suzetrigine did not meet the secondary end point of superiority over hydrocodone bitrate and acetaminophen, as no significant difference in pain scores after abdominoplasty and inferior results after bunionectomy were seen. Suzetrigine provided faster onset of clinically meaningful pain relief (≥ 2-point numeric pain rating scale reduction), with median times of 119 minutes after abdominoplasty and 240 minutes after bunionectomy, compared with placebo.

Post hoc analyses confirmed more rapid relief, especially in patients in the bunionectomy trial who had higher baseline pain. Suzetrigine also showed faster time to perceptible pain relief (≥ 1-point reduction); greater responder rates at 12, 24, and 48 hours; and higher patient global assessment scores vs placebo. Additionally, suzetrigine was associated with significantly lower rates of nausea and vomiting than hydrocodone bitrate and acetaminophen, and patients required less rescue medication after abdominoplasty, though rescue medication use was the same after bunionectomy (ibuprofen 800 mg in both groups). The results of the sum of the pain-intensity difference over 24 hours supported the primary findings, confirming suzetrigine's efficacy in acute postsurgical pain management.[14]

Acute nonsurgical pain

Suzetrigine is currently only available in an oral formulation, which severely limits its perioperative use to postsurgical pain after patients resume oral intake but creates an opportunity to potentially use it for acute nonsurgical pain.

A single-arm, open-label, phase 3 study evaluated suzetrigine's efficacy for both surgical and nonsurgical acute pain.[15] Investigators included patients who presented with new acute pain (onset < 48 hours) in addition to the acute postsurgical pain populations seen in prior studies. A wider variety of surgical populations were enrolled, including otorhinolaryngology and general surgery. The modestly sized nonsurgical group (n = 34) included patients with back, extremity, and facial pain. The dosing regimen was consistent with the previous phase 3 trials: 100 mg for the first dose and subsequent doses of 50 mg every 12 hours for 14 days or until pain resolved.

Good to excellent pain relief, the secondary outcome in this study, was experienced by 91.2% of the nonsurgical population compared with 82% of the surgical population.[15] This is a strong signal that suzetrigine might have a role in managing acute nonsurgical pain, but more robust, placebo-controlled studies are required for FDA approval in this population.

SIDE EFFECTS

In the study that evaluated suzetrigine's efficacy for nonsurgical pain, the primary end point was adverse events, which were seen in 36.7% of participants, but were mostly mild (27.7%) and included side effects like headache (7%), nausea (3.1%), and constipation (3.5%).[15] Five patients had significant adverse events that required discontinuation, and these included accidental overdose, exacerbation of preexisting arrhythmia, nausea, rash, and somnolence. These incidents were not covered in detail, but it was noted that the patients did not experience poor outcomes.

Although long-term carcinogenic potential has not been studied, animal studies of suzetrigine have shown no effect on mutagenesis or fertility.[11] Dependence and addiction are not expected due to the lack of central nervous system receptors, but further studies will be needed. Tolerance development and effects on bowel motility are also highly relevant primary end points for future safety studies.

All trials thus far have also been limited to short follow-up periods of only a few weeks, so phase 4 studies will show what side effects may occur with chronic use.

FDA LABELING REQUIREMENTS

The FDA does not support vague labeling claims like "opioid sparing" because such wording lacks clarity. However, it does provide labeling guidance for more specific benefits like reducing or eliminating opioid use.[12,13] A nonopioid drug must meet 3 qualifications to merit label inclusion of these claims:

- Eliminates the need for opioids in a pain setting where they are typically required
- Allows patients to be discharged without opioid prescriptions when opioids are usually needed after discharge
- Reduces opioid use in conjunction with a direct clinical benefit, such as faster functional recovery or fewer opioid-related side effects (eg, less nausea or sedation).

A drug may qualify for these labels if they are supported by data from at least 2 adequate, well-controlled trials and if the nonopioid medication provides analgesia comparable to that of opioids.[13] Simply reducing opioid dose or duration is not sufficient without demonstrating a clear, meaningful benefit to the patient.

In clinical trials, suzetrigine was unable to establish superiority when compared with the comparator opioid medication, suggesting that it may be unable to eliminate opioid use in most patients.[14] Additionally, over 80% of participants still required rescue ibuprofen, and opioid rescue was not assessed. Furthermore, no data were reported on discharge without opioids or long-term functional outcomes. While suzetrigine was associated with reductions in nausea and vomiting compared with the comparator opioid hydrocodone bitrate and acetaminophen, these findings were not clearly linked to reduced opioid exposure.

OPPORTUNITIES AND LIMITATIONS

As previously mentioned, suzetrigine is only available as an oral formulation, which imposes challenges but offers opportunities at the same time. The oral formulation limits its use to the postoperative period after oral intake is resumed. An intravenous formulation might be more useful during the perioperative period, expanding its use to the intraoperative and immediate postoperative periods, and may prove to be more effective than the current formulation. On the other hand, the oral formulation makes it useful for postoperative pain management after discharge by potentially reducing or replacing opioid therapy, as well as enabling it to treat different acute and perhaps chronic nonsurgical pain indications, such as back pain, renal colic, biliary pain, and so on.

TABLE 1
Suzetrigine prescribing and cost information

Indication	Approved by US Food and Drug Administration to treat acute postoperative pain for 14 days
Dose	Loading: 100 mg Maintenance: 50 mg every 12 hours
Duration	Half-life of 23.6 hours
Cost	$15.50 per pill[18] (typical course is 2 weeks)
Common side effects	Nausea and vomiting, pruritis, rash, muscle spasms, increased serum creatine phosphokinase level
Contraindications	Hormonal contraceptives: may impair efficacy Cirrhosis: reduce dose for Child-Pugh class B; do not use in Child-Pugh class C CYP3A substrates: inhibitors may cause accumulation of drug and metabolites; inducers may reduce effect

Based on information from reference 11.

As suzetrigine becomes more widely available, off-label use by physicians seems likely to increase. Current off-label use includes treatment of acute and chronic pain as well as combining it with analgesic treatment modalities to decrease the side effects of opioids by lowering their dose. Although efforts to limit perioperative opioid use are clinically valuable, current evidence indicates that inadequate postoperative pain control and preoperative opioid exposure are among the most significant predictors of both prolonged opioid use and the development of opioid use disorder.[16,17]

Finally, while suzetrigine is not extremely expensive (wholesale cost is $15.50 per pill or approximately $434.00 for a 2-week supply), cost-effectiveness is yet to be established.[18] In addition, coverage by Medicare, Medicaid, and private insurance is highly variable and depends on the formularies they use.

Suzetrigine prescribing and cost information is listed in **Table 1**.[11,18]

CONCLUSION

Although suzetrigine is a promising novel agent in the analgesic landscape, current clinical trials have not yet demonstrated its superiority over opioids in managing acute postoperative pain. Furthermore, suzetrigine's efficacy in patients with chronic opioid use—particularly in reducing the daily dose of opioids required or improving pain outcomes—as well as the possibility of dependence remain unstudied. Suzetrigine has certainly shown it is an effective analgesic for acute pain and may have an important role as another option for multimodal postoperative analgesia regimens and for managing acute nonsurgical pain.

DISCLOSURES

Dr. Abdelmalak has disclosed teaching and speaking for Medtronic and Mindray North America. 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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Rapidly progressive kidney failure in an 82-year-old man with respiratory symptoms

An 82-year-old man presented to the emergency department for evaluation of worsening dry cough, lower-extremity edema, and fatigue. His symptoms began about 2 weeks earlier, which prompted him to come to the emergency department. At that time, a presumptive diagnosis of congestive heart failure exacerbation was made, and he was admitted for intravenous diuresis with furosemide. He was discharged to his home after his lower-extremity edema partially improved. However, he worsened clinically and returned to the hospital 1 week after discharge.

His past medical history was significant for the following:

- Rheumatoid arthritis, diagnosed about 5 years earlier and treated with methotrexate since diagnosis
- Stage 2 chronic kidney disease, diagnosed about 2 years earlier, with no documented proteinuria or hematuria and no structural kidney abnormalities found on computed tomography of the abdomen and pelvis around the time of diagnosis
- Diffuse large B-cell lymphoma, diagnosed about 3.5 years earlier and treated with 6 cycles of chemotherapy (rituximab, cyclophosphamide, hydroxydaunorubicin [or doxorubicin], vincristine, and prednisone); posttreatment positron emission tomography showed complete remission with no recurrence noted on follow-up imaging
- Heart failure with preserved ejection fraction
- Hypertension.

The patient had no known family history of solid or hematologic malignancy. His home medications included methotrexate, amlodipine, carvedilol, allopurinol, aspirin, and simvastatin.

doi:10.3949/ccjm.93a.25037

INITIAL EVALUATION

The patient's blood pressure was 151/60 mm Hg, heart rate was 69 beats per minute, and he had a new oxygen requirement of 2 L/min to maintain 95% saturation. On physical examination, he was not in acute distress. Cardiovascular examination revealed normal heart sounds without jugular venous distension or murmurs. Respiratory examination was remarkable for bilateral coarse breath sounds. Skin examination revealed 2+ pitting edema on the bilateral lower extremities with no rash or ulcers. Neither lymphadenopathy or hepatosplenomegaly was appreciated.

Blood test results

Remarkable results from complete blood cell count and other blood tests included the following:

- Hemoglobin 10.6 g/dL (reference range 13.5–17.5)
- Mean corpuscular volume 97.3 fL (80–100)
- White blood cell count 5.55×10^9/L (4.0–11.0)
- Neutrophils 3.12×10^9/L (1.5–8.0)
- Lymphocytes 0.5×10^9/L (1.0–3.0)
- Monocytes 1.61×10^9/L (0.2–1.0)
- Immature granulocytes 0.22×10^9/L (< 0.1)
- Platelet count 147×10^9/L (150–450)
- Serum creatinine 1.8 mg/dL (0.74–1.35; this represented a rise from his baseline of 1.0–1.2)
- Albumin 3.8 g/dL (3.5–5.0)
- B-type natriuretic peptide 3,476 pg/mL (< 92).

Urinalysis

A urine dipstick test showed 3+ blood (none), 1+ protein (none), and 2+ leukocyte esterase (none). A fresh urine sediment test revealed more than 20 red blood cells per high-power field, more than 20 white blood cells per high-power field, and abundant hyaline casts

(> 10/low-power field). Although no red cell casts, white cell casts, or dysmorphic erythrocytes were identified, delayed transport to the laboratory may have contributed to degradation of any cellular casts (an important consideration when interpreting results).

Imaging studies

Chest radiograph was concerning for pulmonary edema. Kidney and bladder ultrasonography was negative for hydronephrosis or structural abnormalities. Echocardiography showed preserved ejection fraction (56%), normal right ventricular size and function, left ventricular hypertrophy, and grade 1 diastolic dysfunction.

■ INITIAL MANAGEMENT

Due to concerns for recurrent exacerbation of heart failure with preserved ejection fraction, intravenous furosemide was started. Despite adequate diuresis, his serum creatinine increased to 2.7 mg/dL. Given the patient's persistent kidney dysfunction, a nephrology team was consulted to investigate the etiology of acute kidney injury on chronic kidney disease (stage 2).

■ DIFFERENTIAL DIAGNOSIS

1 Which is the most likely etiology of this patient's acute kidney injury?

☐ Cardiorenal syndrome
☐ Prerenal azotemia due to overdiuresis
☐ Acute interstitial nephritis
☐ Intrinsic kidney pathologies

Cardiorenal syndrome involves a complex and bidirectional relationship between the heart and the kidneys, in which dysfunction in 1 organ causes or worsens dysfunction in the other.[1] Cardiac insufficiency causes elevated central venous pressure, leading to venous congestion in the kidneys, ultimately resulting in decreased glomerular filtration rate.[1,2] This activates the renin-angiotensin-aldosterone system and sympathetic nervous system, leading to sodium and water retention, further impairing kidney function.[3] Eventually, this phenomenon creates a cycle in which both heart and kidney failure are exacerbated.

Although the patient had new edema and significantly elevated brain natriuretic peptide levels, the absence of jugular venous distension, lack of gallop, and failure of creatinine to improve despite adequate diuresis argued against heart failure exacerbation as the primary cause. His respiratory symptoms improved partially with diuresis, suggesting a multifactorial process. The presence of proteinuria and hematuria shifted suspicion toward an intrinsic glomerular process. While immune complex–mediated glomerulonephritis often produces red blood cell casts, only abundant hyaline casts were identified; the absence of red blood cell casts may have reflected sampling limitations and degeneration of cellular casts during transport.

In **prerenal azotemia due to overdiuresis**, a decrease in kidney perfusion leads to an increase in nitrogenous waste products in the blood, particularly creatinine and urea. Overdiuresis occurs when aggressive diuretic therapy reduces effective circulating volume, causing decreased kidney perfusion and a subsequent rise in serum creatinine without intrinsic kidney damage.[4] Urinalysis reveals concentrated urine with elevated specific gravity and occasionally shows hyaline casts. Notably, creatinine levels usually improve after discontinuation of the diuretics. Although our patient's urinalysis revealed hyaline casts, the presence of hematuria and proteinuria suggested an intrinsic kidney disease.

Acute interstitial nephritis involves an immunologic reaction in which the offending drug or its metabolites act as antigens that trigger the recruitment of inflammatory cells. This inflammatory infiltrate, comprising lymphocytes, eosinophils, and occasionally plasma cells, results in interstitial edema and tubular damage. It is often triggered by medications such as penicillins, cephalosporins, and nonsteroidal anti-inflammatory drugs. The classic clinical presentation includes fever, rash, and eosinophilia, but most patients do not present with all 3.[5] A presumptive diagnosis is usually based on recent exposure to a culprit drug, sterile pyuria with a negative urine culture, and the presence of white blood cell casts, with biopsy providing confirmation. Even though our patient was taking methotrexate, which can cause acute interstitial nephritis at high doses used in chemotherapy,[6,7] he had no supportive urinary findings, and the combination of hematuria and proteinuria favored a glomerular process over an interstitial one.

Intrinsic kidney pathologies include the following:

- Acute tubular necrosis, the most common cause of acute kidney injury in hospitalized patients, is typically characterized by muddy brown granular casts on urine microscopy and occurs due to ischemia or nephrotoxins
- Glomerular diseases, in contrast, present with features of either nephrotic syndrome (marked proteinuria and edema) or nephritic syndrome (hematuria, hypertension, red cell casts, and impaired kidney function)

- Infiltrative diseases, such as amyloidosis or lymphomatous invasion of the kidney, can lead to progressive proteinuria and chronic kidney dysfunction, often with bland urinary sediment and minimal hematuria.[8]

In our patient, rapidly worsening kidney function with 3+ hematuria, 1+ proteinuria, more than 20 red blood cells per high-power field, and the absence of muddy brown casts favored an active glomerular inflammatory process instead of acute tubular necrosis or a slowly progressive deposition disorder.

Furthermore, as noted, our patient had an approximately 2-year history of stage 2 chronic kidney disease with a stable creatinine level between 1.0 and 1.2 mg/dL and glomerular filtration rate between 60 and 80 mL/min/1.73 m^3. Mild fluctuation in creatinine is common in chronic kidney disease, especially during illness or diuresis, which occasionally leads to diagnostic inertia. However, a high index of suspicion for an acute kidney pathology is necessary when creatinine continues to worsen, particularly in the presence of new urinary findings. This patient's rapidly deteriorating kidney function, as well as new-onset hematuria and proteinuria, prompted an aggressive workup to find the cause of the acute kidney injury.

CASE CONTINUED: ADDITIONAL URINE AND SERUM TESTING

A 24-hour urine protein measurement revealed proteinuria of 0.68 g/day (< 0.15 g/day), and the urine protein-to-creatinine ratio was elevated at 0.45 mg/mg (< 0.15 mg/mg).

Serum complement levels were also measured to check for potential immune-mediated glomerular disease. The C4 level was markedly low at less than 2 mg/dL (15–45), while C3 was normal at 109 mg/dL (88–201). Serum cryoglobulins were positive. Rheumatoid factor was markedly elevated at more than 650 U/mL from a baseline level of 313 U/mL measured 3 years earlier.

Due to the patient's history of hematologic malignancy, serum protein electrophoresis was performed to evaluate for monoclonal gammopathy, which revealed a monoclonal spike of 0.1 g/dL (0) in the gamma region. Immunofixation electrophoresis confirmed the presence of a monoclonal immunoglobulin (Ig) M lambda light chain. Quantitative immunoglobulin analysis showed an IgG level of 219 mg/dL (600–1,600), IgM 552 mg/dL (40–230), and IgA 4 mg/dL (70–400).

HOW CAN THESE TEST RESULTS BE INTERPRETED?

Notably, this patient had a chronically elevated baseline rheumatoid factor because of his rheumatoid arthritis. However, the recent significantly increased rheumatoid factor level in the absence of signs or symptoms of rheumatoid arthritis flare, and in the setting of monoclonal IgM spike, low C4, and cryoglobulins, suggested that the rheumatoid factor activity was mediated by the monoclonal IgM itself, as seen in type II cryoglobulinemia. In this condition, monoclonal IgM often serves as a rheumatoid factor directed against polyclonal IgG, forming immune complexes that drive complement consumption and vascular injury.[9] These findings, along with hematuria and proteinuria, further raised suspicion for an underlying glomerular process.

CASE CONTINUED: KIDNEY BIOPSY

A decision was made to pursue a kidney biopsy. The immunofluorescence pattern on kidney biopsy revealed granular mesangial and segmental capillary loop deposits staining for IgM (2+ to 3+), kappa (trace), and lambda (1+ to 2+). Further staining on formalin-fixed paraffin-embedded tissue after pronase digestion revealed mesangial and segmental capillary loop staining for IgG (3+ to 4+), IgM (2+ to 3+), IgA (equivocal), C3 (1+), kappa (trace to 1+), and lambda (3+ to 4+) and cryoglobulin plugs staining for IgG, IgM, kappa, and lambda. On electron microscopy, subendothelial electron-dense deposits were present.

2 Combining the biopsy findings with the other clinical and laboratory data, what is the most likely diagnosis?

☐ Infection-related glomerulonephritis
☐ IgA nephropathy
☐ Cryoglobulinemic glomerulonephritis
☐ Anti–glomerular basement membrane disease

Infection-related glomerulonephritis typically presents with low complement levels (C3 more commonly than C4) and is associated with a history of recent infection, particularly a streptococcal infection. The kidney biopsy usually shows subepithelial humps on electron microscopy.[10] None of these features were present in our patient.

IgA nephropathy is characterized by mesangial deposition of IgA, and often presents with episodic hematuria after an upper respiratory infection. Its presentation can vary, including gross hematuria, microscopic hematuria with or without proteinuria, nephrotic syndrome, or rapidly progressive glomerulonephritis. IgA nephropathy does not typically present with low C4 levels or monoclonal protein on immunofixation electrophoresis.[11]

Cryoglobulinemic glomerulonephritis typically presents with low C4 levels, monoclonal protein on immunofixation electrophoresis, and proliferative glomerulonephritis with pseudothrombi on kidney biopsy. While a monoclonal protein can support the diagnosis, cryoglobulinemic glomerulonephritis may occur without it.[12] These findings align with our patient's presentation, especially in the context of a monoclonal gammopathy. Specifically, kidney biopsy demonstrated proliferative glomerulonephritis with numerous intracapillary pseudothrombi, consistent with cryoglobulinemic glomerulonephritis. The immunofluorescence staining pattern indicated a mixed type rather than type I cryoglobulinemia. The patient's serum cryoglobulins, consisting of a mixture of monoclonal IgM with rheumatoid factor activity and polyclonal IgG, also suggested type II or mixed cryoglobulinemia.

Anti–glomerular basement membrane disease is characterized by rapidly progressive glomerulonephritis. It can also present with pulmonary manifestations such as alveolar hemorrhage. The pathognomonic finding on a kidney biopsy is immunofluorescence showing linear IgG staining along the glomerular basement membrane, and light microscopy usually shows crescentic glomerulonephritis, which is not consistent with our patient's kidney biopsy findings.[13] It does not typically present with low complement levels or monoclonal protein on immunofixation electrophoresis.

CASE CONTINUED: BONE MARROW BIOPSY AND DIAGNOSIS

In addition to findings that suggested mixed type cryoglobulinemic glomerulonephritis, the serum monoclonal IgM lambda spike was concerning for a B-cell lymphoproliferative disorder. Therefore, a bone marrow biopsy was performed, which showed a small abnormal population of CD19+ B cells, along with a subset of monoclonal plasma cells expressing lambda light chains, consistent with Waldenström macroglobulinemia.

Overall, the presence of monoclonal IgM lambda and cryoglobulins, along with bone marrow findings and proliferative glomerulonephritis with pseudothrombi observed on kidney biopsy, supported the diagnosis of Waldenström macroglobulinemia–associated cryoglobulinemic glomerulonephritis.

CRYOGLOBULINEMIC GLOMERULONEPHRITIS

Cryoglobulinemic glomerulonephritis is a form of kidney inflammation characterized by the deposition of cryoglobulins (ie, abnormal proteins usually consisting of immunoglobulins and complement components) within the small blood vessels of the glomeruli. Cryoglobulins precipitate from serum or plasma at temperatures below 37°C (98.6°F), causing obstruction and triggering immune-mediated injury of the kidney tissue. Patients often present with proteinuria, hematuria, and varying degrees of kidney impairment.[14]

There are 3 types of cryoglobulinemia: I, II, and III (**Table 1**).[15] Types II and III are commonly referred to as mixed cryoglobulinemia. Chronic hepatitis C virus infection is often associated with mixed cryoglobulinemia. Other potential causes include infections (hepatitis B or human immunodeficiency virus), autoimmune diseases (Sjögren disease, lupus, rheumatoid arthritis), or lymphoproliferative disorders. In our patient, serologic testing for hepatitis C virus, hepatitis B virus, human immunodeficiency virus, and autoimmune disease was negative. The Meltzer triad, which consists of palpable purpura, arthralgia, and weakness, can be occur in patients with mixed cryoglobulinemia,[16] but our patient did not have any of these signs or symptoms.

Waldenström macroglobulinemia–associated cryoglobulinemic glomerulonephritis

A monoclonal IgM lambda spike, markedly elevated serum IgM, and bone marrow involvement by a lymphoplasmacytic process supported Waldenström macroglobulinemia as the underlying driver of the cryoglobulinemia in this patient, rather than rheumatoid arthritis. It is also important to note that our patient's presentation met criteria for monoclonal gammopathy of renal significance, while cryoglobulinemic glomerulonephritis is a specific type of monoclonal gammopathy of renal significance.[17] The cryoglobulinemia was attributed to the monoclonal immunoglobulins produced by the clonal plasma cells in the bone marrow, which were directly responsible for the kidney injury, even without other classic systemic features of cryoglobulinemia.

The characteristic biopsy pattern of cryoglobulinemic glomerulonephritis involves the presence of endocapillary proliferation and intracapillary infiltration of monocytes, along with either glomerular pseudothrombi or deposition of cryoglobulin substructures noted under electron microscopy. Direct immunofluorescence reveals positive staining of

TABLE 1
Types of cryoglobulinemia with associated disorders and clinical manifestations

Type	Characteristic features	Associated disorders	Common clinical manifestations
I	Involves monoclonal immunoglobulins, particularly immunoglobulin (Ig) M and rarely IgG or IgA	Plasma cell dyscrasia or B-cell malignancies (multiple myeloma, Waldenström macroglobulinemia, monoclonal gammopathy of unknown significance, and chronic lymphocytic leukemia)	Purpura, arthralgia, peripheral neuropathy, glomerulonephritis, vasculitis, and skin ulcers Hyperviscosity syndrome Raynaud phenomenon No involvement of central nervous system, heart, lungs, or gastrointestinal tract
II	Includes monoclonal IgM with rheumatoid factor activity and polyclonal IgG	Mainly associated with infections (hepatitis C virus, hepatitis B virus, human immunodeficiency virus) and autoimmune disorders (rheumatoid arthritis, systemic lupus erythematosus, Sjögren disease) Lymphoproliferative disorders (Waldenström macroglobulinemia, chronic lymphocytic leukemia, and non-Hodgkin lymphoma)	Palpable purpura, arthralgia, weakness, peripheral neuropathy, glomerulonephritis, and cutaneous ulcers Involvement of central nervous system, heart, lungs, or gastrointestinal tract is rare but can occur
III	Mixture of polyclonal IgG and IgM with rheumatoid factor activity	Mainly associated with infections (hepatitis C virus, hepatitis B virus, human immunodeficiency virus) and autoimmune disorders (rheumatoid arthritis, systemic lupus erythematosus, Sjögren disease)	Similar to type II

Based on information from reference 15.

monoclonal IgM with specificity for lambda or kappa light chains in the walls of glomerular capillaries or mesangium or glomerular pseudothrombi.[9,18–22]

3 What is the next best step in this patient's treatment?

- ☐ High-dose steroids and treatment of underlying malignancy
- ☐ Low-dose corticosteroids and nonsteroidal anti-inflammatory drugs
- ☐ Anti-CD38 therapy
- ☐ Plasma exchange alone

High-dose steroids and treatment of the underlying malignancy are the recommended management strategies for Waldenström macroglobulinemia–associated cryoglobulinemic glomerulonephritis. Pulsed doses of steroids (1,000 mg daily for 3 days), followed by a steroid taper, prevent immune-complex formation. The preferred first-line treatment for symptomatic Waldenström macroglobulinemia includes a combination of either bendamustine (an alkylating agent) and rituximab (a monoclonal anti-CD20 antibody) or ibrutinib (a tyrosine kinase inhibitor) with or without rituximab. Rituximab is avoided as a first therapy because it can cause IgM flare, resulting in hyperviscosity. It is typically incorporated into the treatment regimen after a first response is achieved.[9,17,23]

Low-dose corticosteroids and nonsteroidal anti-inflammatory drugs are insufficient for managing severe cryoglobulinemic vasculitis with kidney involvement. Although corticosteroids can help control inflammation, they are typically used in higher doses and in combination with other therapies to treat the underlying condition.[24]

Anti-CD38 therapy, daratumumab, is reserved for treating the underlying malignancy in refractory cases.[25] Additionally, an immunosuppressive agent is first warranted to reduce kidney inflammation.

Plasma exchange is typically necessary in patients with life-threatening vasculitis, marked hyperviscosity, or refractory kidney failure not improving with immunosuppressive therapy. Our patient did not present with hyperviscosity or catastrophic vasculitic complications (pulmonary hemorrhage or extensive skin necrosis) requiring immediate plasmapheresis to remove circulating cryoglobulins.[26]

In our patient, a multidisciplinary approach was used to address both the kidney and hematologic aspects of his disease. The patient was started on high-dose methylprednisolone and a bendamustine-based chemotherapy regimen. Additionally, rituximab was planned to be added cautiously in subsequent cycles to minimize the risk of an IgM flare.

WALDENSTRÖM MACROGLOBULINEMIA

Waldenström macroglobulinemia is a subtype of lymphoplasmacytic lymphoma, a rare B-cell lymphoproliferative disorder accounting for 1% to 2% of hematologic malignancies.[27] It is characterized by infiltration of the bone marrow with lymphoplasmacytic cells and elevated levels of monoclonal IgM in the serum.[28,29] The incidence of Waldenström macroglobulinemia is higher in White individuals and males (55%–70%), with a median age at diagnosis between 63 and 68 years.[28]

Risk factors for Waldenström macroglobulinemia include preexisting IgM monoclonal gammopathy of undetermined significance, autoimmune disorders (eg, rheumatoid arthritis, Sjögren disease, and Crohn disease), and infections (including hepatitis and human immunodeficiency virus).[30,31] More specifically, rheumatoid arthritis is a well-known risk factor for B-cell lymphomas, particularly diffuse large B-cell lymphoma, likely due to chronic immune stimulation and dysregulated immune surveillance. In addition, long-term methotrexate therapy has been linked to methotrexate-associated lymphoproliferative disorders, though these are most often Epstein-Barr virus–positive and may regress after withdrawal of the drug.[32,33]

In our patient, the occurrence of Waldenström macroglobulinemia years after treatment for diffuse large B-cell lymphoma represented a second primary B-cell malignancy rather than transformation, as reverse progression from diffuse large B-cell lymphoma to Waldenström macroglobulinemia is exceptionally rare. In contrast, Waldenström macroglobulinemia transforms into diffuse large B-cell lymphoma in up to 10% of cases.[34] Survivors of aggressive lymphomas such as diffuse large B-cell lymphoma remain at elevated risk for secondary hematologic malignancies, including multiple myeloma and Waldenström macroglobulinemia.[35] This patient's combination of underlying autoimmune disease, prolonged immunomodulatory therapy, and prior lymphoma likely contributed to his cumulative risk of developing Waldenström macroglobulinemia.

Symptoms related to Waldenström macroglobulinemia result from elevated serum IgM levels and clonal plasma cell infiltration of the bone marrow and extramedullary sites. Bone marrow infiltration leads to cytopenias, especially anemia, resulting in excessive fatigue. Elevated serum IgM levels can also cause hyperviscosity and cryoglobulinemia.[28,34] Kidney involvement is rare in Waldenström macroglobulinemia (< 8%), with cryoglobulinemic glomerulonephritis as one of the most common kidney manifestations.[30,36]

CONCLUSION

This is an interesting case of Waldenström macroglobulinemia with rapidly progressive kidney failure due to cryoglobulinemic glomerulonephritis as the presenting manifestation. The association between Waldenström macroglobulinemia and cryoglobulinemic glomerulonephritis is well-documented; however, de novo presentation of Waldenström macroglobulinemia with cryoglobulinemic glomerulonephritis is less common. This case highlights the significance of a systematic diagnostic approach and underscores that seemingly common presentations, such as glomerulonephritis, can have uncommon and serious underlying causes.

TAKE-HOME POINTS

- Unexplained kidney dysfunction, particularly with proteinuria and hematuria, warrants a thorough investigation, including consideration of hematologic malignancies.
- A kidney biopsy enables the precise identification of the underlying pathology, guiding treatment decisions.
- Cryoglobulinemic glomerulonephritis can be the presenting manifestation of Waldenström macroglobulinemia.

DISCLOSURES

Dr. Anwer has disclosed consulting, teaching and speaking, and acting as a research principal and co-principal investigator for Bristol-Meyers Squibb Co., and consulting for Caribou Bio. 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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Right ventricular failure in a young man

A 31-YEAR-OLD MAN presented to the hospital for dyspnea that had progressively worsened over the previous 2 years. Initially, his dyspnea was present only on exertion, but during the past 2 months it had progressed to shortness of breath at rest. He also noted an intermittent dry cough. He reported no fevers, chills, chest pain, dizziness, syncopal episodes, hemoptysis, wheezing, or unintentional weight loss.

The patient's past medical history included a reported but undetermined fungal infection 12 years earlier that had been treated with itraconazole. He had no significant surgical or family history and did not take any medications on a regular basis. He did not smoke cigarettes, drink alcohol, or use illicit drugs.

Physical examination revealed 2+ pitting edema in the bilateral lower extremities and crackles throughout bilateral lung fields. The cardiac examination was notable for a prominent second pulmonary heart sound, right ventricular heave, grade 3 of 6 holosystolic murmur most evident at the left sternal border, jugular venous distention, and hepatojugular reflux.

Initial laboratory values included elevated levels of troponin and B-type natriuretic peptide. Serum creatinine, lactate, and complete blood cell count were within normal range (**Table 1**). The patient's initial chest radiograph is shown in **Figure 1**.

FURTHER STUDIES: ECHOCARDIOGRAM AND RIGHT HEART CATHETERIZATION

The initial transthoracic echocardiogram demonstrated a diffusely hypokinetic left ventricle with an ejection fraction of 45%, dilated inferior vena cava of 3.3 cm (reference range 1.5–2.5) with abnormal collapse of less than 50% consistent with volume overload, and flattening of the interventricular septum. Right-sided measurements of the heart revealed a severely dilated right ventricle of 7.4 cm (2–4.1), severely depressed right ventricular function, moderately dilated right atrium of 30.3 cm^2 (10–18), moderate tricuspid valve regurgitation, and elevated pulmonary artery systolic pressure of 58 mm Hg (< 30) (**Figure 2**).

Given his severe right ventricular dysfunction, the patient underwent a right heart catheterization during which the following measurements were obtained:

- Mean right atrial pressure: 28 mm Hg (0–8)
- Right ventricular pressure: 118/10 mm Hg (systolic 15–25, diastolic 0–10)
- Pulmonary artery pressure: 137/31 mm Hg; mean 77 mm Hg (systolic 15–25, diastolic 4–12, mean < 25)
- Pulmonary capillary wedge pressure: 8 mm Hg (4–14)
- Cardiac output: 5.76 L/min using the thermodilution method (4–8)
- Cardiac index: 2.56 L/min/m^2 (2.5–4)
- Pulmonary vascular resistance: 12 Wood units (< 2).

The findings indicated the presence of severe precapillary pulmonary hypertension. The right ventricular stroke work index ([mean pulmonary artery pressure − mean right atrial pressure] × stroke volume index), a measure of how much energy the right ventricle expends to pump blood into the pulmonary circulation, was severely elevated at 17.39 g/m/beat/m^2, indicating a high ventricular workload. The pulmonary artery pulsatility index ([pulmonary artery systolic pressure − pulmonary artery diastolic pressure]/right atrial pressure), a measure of how strongly the right ventricle is pumping, was elevated at 3.78. Both calculations, derived from right heart catheterization measurements, indicate that the right ventricle was functioning under extreme pressure and volume overload, with concern for imminent right ventricle failure.

doi:10.3949/ccjm.93a.25048

TABLE 1
The patient's initial laboratory results

Test	Result[a]	Reference range
Sodium	139 mmol/L	135–146
Potassium	3.8 mmol/L	3.5–5.3
Chloride	99 mmol/L	98–110
Bicarbonate	32 mmol/L	20–32
Anion gap	**8 mEq/L**	10–20
Blood urea nitrogen	12.2 mg/dL	7–25
Creatinine	1.2 mg/dL	0.60–1.26
Calcium	9.5 mg/dL	8.6–10.3
White blood cell count	9.15×10^9/L	4–11
Hemoglobin	13.9 g/dL	13–17
Platelet count	281×10^9/L	150–450
B-type natriuretic peptide	**2,257 pg/mL**	< 100
Troponin I	**0.10 ng/mL**	< 0.04
Lactate	1.9 mmol/L	0.5–2.2

[a]Out-of-range results are shown in bold.

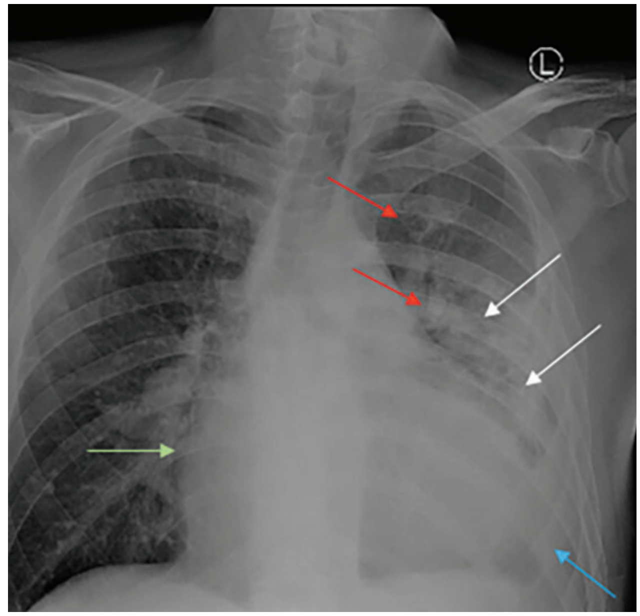

Figure 1. Chest radiograph obtained at admission was notable for consolidations in the left lower and middle lung field concerning for alveolar edema (white arrows); blunting of the left costophrenic angle, likely reflecting a small left pleural effusion (blue arrow); and scattered rounded lesions in the left lung field (red arrows). The cardiac silhouette appears enlarged, with a prominent, bulging right heart border (green arrow), suggesting possible right atrial enlargement and volume overload. The right lung field appears clear.

FINDING THE CAUSE OF PULMONARY HYPERTENSION

1 Which of these diagnostic tests is indicated to identify the etiology of this patient's pulmonary hypertension?

- ☐ Computed tomography (CT) of the chest
- ☐ Ventilation-perfusion scan
- ☐ Autoimmune serologies
- ☐ All of these

Right heart catheterization is the gold standard for diagnosing pulmonary hypertension, defined as a mean pulmonary arterial pressure of 20 mm Hg or higher.[1–3] Pulmonary hypertension is classified into 5 subgroups (**Table 2**).[3] Patients are grouped based on hemodynamic measurements on right heart catheterization.

Precapillary pulmonary hypertension (groups 1, 3, 4, and 5) is defined by mean pulmonary arterial pressure greater than 20 mm Hg, pulmonary capillary wedge pressure 15 mm Hg or less, and pulmonary vascular resistance 2 Wood units or higher.

Postcapillary pulmonary hypertension (groups 2 and 5) is defined by mean pulmonary arterial pressure greater than 20 mm Hg, pulmonary capillary wedge pressure greater than 15 mm Hg, and pulmonary vascular resistance less than 3 Wood units.

Combined pre- and postcapillary pulmonary hypertension is defined by a mean pulmonary arterial pressure greater than 20 mm Hg, pulmonary capillary wedge pressure greater than 15 mm Hg, and pulmonary vascular resistance 2 Wood units or higher.[1,3,4]

Further diagnostic evaluation is critical for classifying patients into the correct group and has significant implications for guiding treatment.

Patients with isolated precapillary pulmonary hypertension or combined pre- and postcapillary pulmonary hypertension require further workup with chest CT, autoimmune serologies, and ventilation-perfusion scan. This workup is especially important in patients who have left heart disease insufficient to explain the degree of pulmonary hypertension.

CT of the chest permits thorough evaluation of the lung parenchyma and pulmonary vasculature, helping clinicians determine whether a patient's pulmonary hypertension is due to parenchymal lung disease.[5] Additionally, chest CT may help identify occult systemic diseases such as scleroderma if characteristic findings (eg, esophageal dilation) are seen.[6,7]

Autoimmune serologies, including but not limited to antinuclear antibodies, rheumatoid factor, double-stranded DNA antibodies, and scleroderma-70 antibodies, should be requested because there is an association between various connective tissue diseases and group 1 pulmonary hypertension, particularly in women.[8,9] Among all connective tissue diseases, systemic sclerosis places patients at the highest risk of developing pulmonary arterial hypertension, with an 8% to 12% lifetime risk.[8] However, serologies are nondiagnostic and can only support a diagnosis of connective tissue disease in the appropriate clinical context. Careful physical examination to identify rashes, skin thickening, joint pain, and other autoimmune stigmata are critical in making the diagnosis.

Ventilation-perfusion scan, necessary to evaluate for chronic thromboembolic hypertension and group 4 pulmonary hypertension, has a diagnostic sensitivity of 97.4%.[10,11] Ventilation-perfusion scan measures both airflow and blood flow through the lungs using radioactive tracers. If mismatched perfusion defects are indicative of chronic thromboembolic hypertension, patients should be evaluated for pulmonary thromboendarterectomy as definitive treatment.[12] False-positive results on ventilation-perfusion scan can be seen with conditions that can lead to extrinsic compression of the pulmonary artery and reduced distal flow such as mediastinal lymphadenopathy or fibrosis.[13,14]

CASE CONTINUED: FURTHER EVALUATION

The patient underwent CT of the chest, which showed extensive mediastinal soft tissue infiltration (**Figure 3**). He also had calcified lymph nodes, severe enlargement of the pulmonary artery, and narrowing of the bilateral pulmonary arteries. The lung parenchyma appeared normal. The findings were consistent with a diagnosis of fibrosing mediastinitis.

Ventilation-perfusion scan showed 90% perfusion going to the right lung and 10% going to left lung, with severe parenchymal pulmonary disease involving the entire left lung and right upper lung.

Serology tests for antinuclear antibodies, double-stranded DNA antibodies, rheumatoid factor, and scleroderma-70 antibodies were negative. Fungal serologies were notable for the following:

- *Histoplasma* antigen: negative
- *Histoplasma* mycelial antibody: 1:16 (> 1:8 = antibody detected)
- *Coccidioides* immunoglobulin (Ig) G: negative

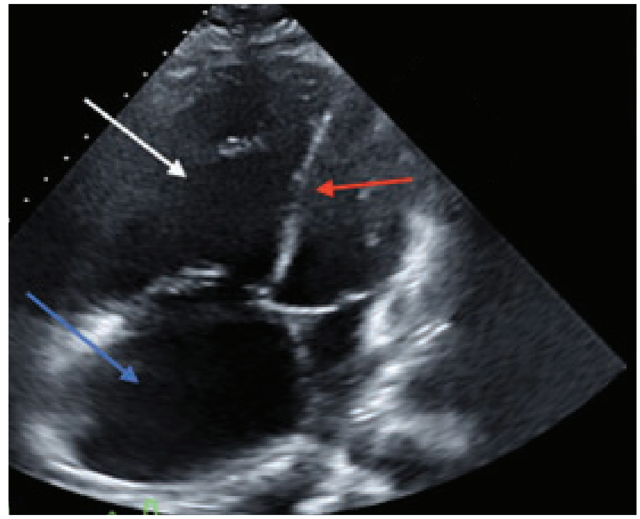

Figure 2. Transthoracic echocardiography apical 4-chamber view showed severe right ventricular dilation (white arrow), dilated right atrium (blue arrow), and flattening of the intraventricular septum (red arrow) consistent with right ventricular pressure and volume overload.

- *Coccidioides* IgM: negative
- Galactomannan: negative
- Respiratory culture and acid-fast bacilli smear: negative for bacteria.

FINDING THE CAUSE OF FIBROSING MEDIASTINITIS

2 What is the most likely etiology of this patient's fibrosing mediastinitis?

☐ Histoplasmosis
☐ Sarcoidosis
☐ IgG4 disease

Fibrosing mediastinitis, also known as mediastinal fibrosis or sclerosing mediastinitis, is a rare cause of group 5 pulmonary hypertension characterized by abnormal proliferation of fibrous tissue within the mediastinum.[15] With continued proliferation, fibrous tissue can encase, invade, and compress mediastinal structures, resulting in obstruction of airways, cardiac vessels, and the esophagus.

Fibrosing mediastinitis affects individuals ages 13 to 65 years and has a strong predilection for affecting young women.[16] Radiographic abnormalities confirm its presence. A chest radiograph most commonly shows mediastinal widening and lymphadenopathy in the subcarinal, paratracheal, and hilar regions. Calcifications

TABLE 2
Clinical classification of pulmonary hypertension

Group	Description	Considerations
1	Pulmonary arterial hypertension	Idiopathic; associated with genetic conditions, drugs and toxins, connective tissue disease, human immunodeficiency virus infection, portal pulmonary hypertension, schistosomiasis, and congenital heart disease; pulmonary arterial hypertension with features of venous or capillary involvement; persistent pulmonary arterial hypertension of the newborn
2	Pulmonary hypertension secondary to left heart disease	Associated with heart failure with preserved or reduced ejection fraction, valvular heart diseases, or cardiovascular conditions leading to postcapillary pulmonary hypertension
3	Pulmonary hypertension secondary to lung disease	Associated with chronic obstructive pulmonary disease, emphysema, or both; interstitial lung disease; combined pulmonary fibrosis and emphysema; other parenchymal lung diseases; nonparenchymal restrictive diseases; hypoxia without lung disease; developmental lung diseases
4	Pulmonary hypertension associated with pulmonary artery obstruction	Related to chronic thromboembolic disease and other pulmonary artery obstructions
5	Pulmonary hypertension with unclear or multifactorial mechanisms	Related to hematologic disorders, systemic disorders (sarcoidosis, pulmonary Langerhans cell histiocytosis and neurofibromatosis type 1), metabolic disorders, chronic renal failure with or without hemodialysis, pulmonary tumor thrombotic microangiopathy, fibrosing mediastinitis, complex congenital heart disease

Based on information from reference 3.

of the mediastinal lymph nodes may also be present and can suggest a fungal etiology. Contrast-enhanced CT of the chest can show mediastinal enhancement, calcified lymph nodes, and complications of fibrosing mediastinitis, including pulmonary vascular stenosis, bronchial stenosis, postobstructive pneumonias, and superior vena cava compression.[17]

Fibrosing mediastinitis has 2 major subtypes: granulomatous and nongranulomatous. The granulomatous form is more common and typically is associated with tuberculosis and fungal infections such as blastomycosis, aspergillosis, and histoplasmosis.[16]

Histoplasmosis. In the United States, fibrosing mediastinitis is most commonly associated with *Histoplasma capsulatum* infection; the reported prevalence of *H capsulatum* infection–related fibrosing mediastinitis is 3 in 100,000 individuals.[15]

Diagnostic association of fibrosing mediastinitis with fungal infection can be made via serologic assays and fungal staining from lymph node biopsies.[18] However, fungal stains have a reported sensitivity of 32% and do not help differentiate between active and prior *H capsulatum* infection.[19] Assays that detect antibodies against the H and M antigens specific to *H capsulatum* demonstrate a sensitivity of 64% to 95% in acute, subacute, chronic, and prior infection.[20] A negative antigen test can support a previous infection as the cause of a positive antibody test, though the sensitivity of each assay and clinical context must be considered.

Sarcoidosis, characterized by formation of granulomas in various organs, is a rare cause of granulomatous fibrosing mediastinitis. Its diagnosis is confirmed with a tissue biopsy of the organ involved, which reveals noncaseating granulomas.[21]

IgG4 disease, a fibroinflammatory condition in which IgG4-positive plasma cells infiltrate various organs, is a rare cause of nongranulomatous fibrosing mediastinitis. Diagnostic evaluation of IgG4 disease begins with serum protein electrophoresis and investigation of IgG subclasses to assess for elevated IgG4 levels. A biopsy is required to confirm the diagnosis; it reveals dense polyclonal, lymphoplasmacytic infiltrate with IgG4-positive plasma cells.[22,23] Rare cases of nongranulomatous fibrosing mediastinitis have been reported in patients with radiation exposure and those with a diagnosis of primary sclerosing cholangitis.[24]

If fibrosing mediastinitis is identified on imaging, fungal serologies may help establish evidence of prior

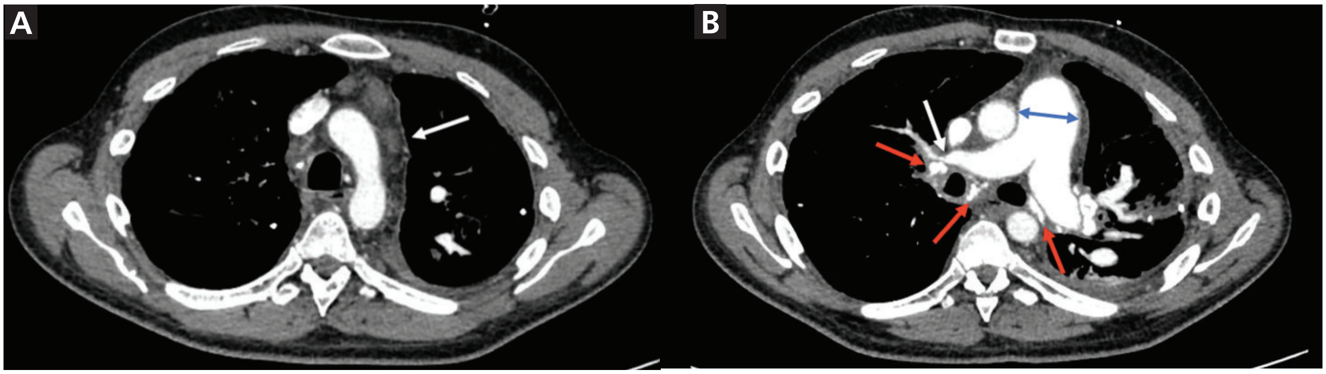

Figure 3. (A) Chest computed tomography with contrast demonstrated extensive mediastinal soft tissue infiltration (white arrow). (B) Calcified lymph nodes (red arrows), severe pulmonary artery enlargement with a diameter of 39.4 mm (blue double-head arrow), and narrowing of the bilateral pulmonary arteries (white arrow shows narrowing of the right pulmonary artery) were noted.

infection. In our patient, a positive histoplasmosis antibody test combined with a negative histoplasmosis antigen test suggested the diagnosis of fibrosing mediastinitis secondary to prior histoplasmosis infection. If noninvasive diagnostics are inconclusive, a bronchoscopy with bronchoalveolar lavage, lymph node biopsy, or mediastinal biopsy may be required.

CASE CONTINUED: MANAGEMENT OF PULMONARY HYPERTENSION

After the patient was diagnosed with fibrosing mediastinitis secondary to prior histoplasmosis, he was transferred to the intensive care unit for further management of his severe pulmonary hypertension and right ventricular failure. He received inotropic support with dobutamine and diuresis with furosemide and metolazone.

A cautious trial of pulmonary hypertension therapy with inhaled treprostinil was initiated to reduce right ventricular afterload, which was due in part to the marked elevation in pulmonary vascular resistance. A Swan-Ganz catheter was placed to monitor changes in cardiac output, cardiac index, pulmonary artery pressures, and central venous pressures. Despite multiple days of inotropic support, pulmonary hypertension–directed therapy, and diuresis, the patient developed worsening cardiogenic shock due to refractory ventricular failure with the following right heart catheterization measurements:

- Mean right atrial pressure: 21 mm Hg
- Right ventricular pressure: 109/6 mm Hg
- Pulmonary artery pressure: 116/29 mm Hg; mean 48 mm Hg
- Pulmonary capillary wedge pressure: not measured
- Cardiac output: 4.32 L/min using the thermodilution method
- Cardiac index: 1.92 L/min/m^2.

TREATMENT DECISIONS

3 What is the best treatment modality for this patient?

☐ Antifungal therapy
☐ Mediastinal tissue resection
☐ Endovascular stenting of the pulmonary arteries
☐ Combined heart and bilateral lung transplantation

Antifungal and anti-inflammatory therapies are ineffective for the treatment of fibrosing mediastinitis. The most recent guidelines from the Infectious Diseases Society of America[25] recommend against routine antifungal treatment as fibrosing mediastinitis is a late complication of fungal infections; further, antifungal therapy has minimal utility in the setting of irreversible, fibrotic changes.[18] As for medical management of fibrosing mediastinitis–associated pulmonary hypertension, no robust data exist on the use of pulmonary hypertension–specific therapy.

Mediastinal tissue resection. Minimally invasive techniques and surgical options should be considered to alleviate the mechanical burden of disease. The type of intervention depends on which structures are affected. Mediastinal debulking surgeries are unfavorable due to the high risk of bleeding and intraoperative complications. Surgical case series have reported an operative mortality as high as 20%.[15,26,27]

Endovascular stenting of the pulmonary arteries has been evaluated in small case series and is associated with a lower acute mortality and improved symptom relief. However, patients often require additional procedures for stent restenosis, stent migration, hemoptysis, and other graft-related complications.[15,28]

Combined heart and lung transplantation provides definitive management of fibrosing mediastinitis complicated by severe pulmonary hypertension and right ventricular failure. Typically, bilateral lung transplantation alone is curative for severe pulmonary hypertension.[29] However, with dense adhesions and extensive fibrous tissue within the mediastinum, a combined en bloc heart-lung transplant in which the heart and lungs are removed as one may be technically more feasible, with a lower intraoperative bleeding risk.[30] There are no standardized criteria for heart-lung transplant, although common indications include right ventricular failure with extensive right ventricular fibrosis, pulmonary arterial hypertension with severe cardiomyopathy, and interstitial lung disease with associated right ventricular dysfunction.[31] All surgical approaches must be considered in relation to the experience and expertise of a particular center. A multidisciplinary evaluation may help weigh the risks and benefits of each approach.

CASE CONCLUSION

Our patient's case was reviewed in a multidisciplinary conference that included clinicians in cardiology, transplant pulmonology, lung transplant surgery, cardiac surgery, and thoracic surgery. The group considered multiple surgical approaches and the risks and benefits of each. Given our patient's severe right ventricular failure and extensive mediastinal fibrosis, the panel made the decision to proceed with combined heart-lung transplantation, determined to be the lowest-risk surgical procedure for definitive management of right ventricular failure secondary to fibrosing mediastinitis.

The patient tolerated the surgery with minimal postoperative complications and was discharged from the hospital with outpatient transplant follow-up. He has retained excellent cardiac and pulmonary function during routine clinical follow-up.

TAKE-HOME POINTS

- A thorough diagnostic evaluation is required for patients newly diagnosed with pulmonary hypertension; the workup should include chest CT, ventilation-perfusion scan, autoimmune serologies, human immunodeficiency virus testing, and schistosomiasis antibody testing in endemic areas.[32]
- Fungal infections are the most common cause of fibrosing mediastinitis, with histoplasmosis the most common cause in the United States.[16]
- Antifungal and anti-inflammatory treatments are ineffective in treating fibrosing mediastinitis due to the irreversibility of fibrotic changes.[18,25]
- We recommend a multidisciplinary evaluation to determine the best surgical or catheter-directed approach for the management of fibrosing mediastinitis, with possible need for lung or heart-lung transplantation.[26,28,29]

DISCLOSURES

Dr. Matusov has disclosed being a research principal investigator for Aerovate, BioAegis Therapeutics, Mallinckrodt Inc., Penumbra Inc., and Tenax Therapeutics and being an advisor or review panel participant for Jupiter Endovascular. Dr. Sankar reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Artificial intelligence in medicine: How it works, how it fails

ABSTRACT

Artificial intelligence (AI) is transforming healthcare, with large language models emerging as important tools for clinical practice, education, and research. To use it safely and effectively, healthcare professionals need to understand how it works, and how it fails. Using practical clinical examples, the authors explain the subset of AI called large language models, highlighting their capabilities and their limitations.

KEY POINTS

AI is trained on vast amounts of data, which can itself be biased, leading to biased results.

AI essentially predicts the most probable sequence of words to complete a sentence. If the training data are ambiguous or incomplete, or if the query is outside the model's core knowledge, it might guess or infer information based on weak statistical signals, leading it to create plausible but untrue statements (hallucinations).

The way a question or prompt is phrased can significantly affect the response. Clinicians should thus triangulate answers by asking the same clinical question in 2 different ways to see if the model's reasoning remains consistent.

While large language models can enhance efficiency and clinical decision-making, they must be integrated with a human in the loop to ensure safe, ethical practice.

doi:10.3949/ccjm.93a.25089

Artificial intelligence (AI) is increasingly being integrated into education, clinical practice, and research. Clinicians today may encounter it through general-purpose tools like ChatGPT, automated documentation assistants like Ambience, or clinical decision support tools like Open Evidence.

We believe that AI can help us in our jobs as doctors—but with important caveats. We don't all have to be computer scientists, but we do need to know a little bit about AI to effectively and safely integrate it into practice, discerning when to rely on what it says, when to be skeptical, and when to strategically leverage its capabilities.[1]

Here, we try to explain AI, how it has evolved, how it works,[2] what it is good for, and critically, the specific risks, such as hallucination and bias, that can lead to clinical errors. We will use some clinical examples, such as cases of community-acquired pneumonia, to ground our discussion.

HOW ARTIFICIAL INTELLIGENCE HAS EVOLVED

Over the years, AI has progressed from rule-based systems, to machine learning, to deep learning, to large language models (**Figure 1**). Let's consider how each of these systems might help a clinician choose the best antibiotic for a patient with community-acquired pneumonia.

Rule-based systems are like very detailed flowcharts. We would program the computer with specific "if-then" instructions based on established clinical guidelines and local resistance patterns. For example, the system might

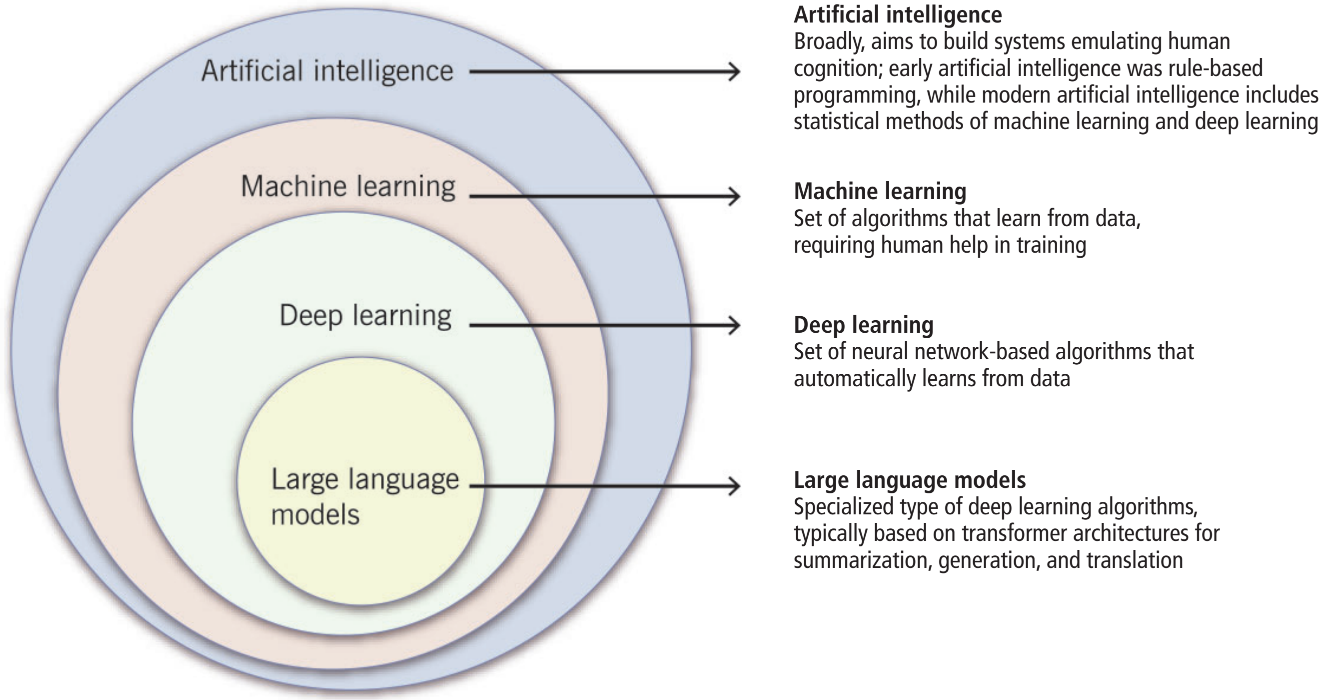


Figure 1. Different types of artificial intelligence.

be told: "IF the patient is over 65 AND has kidney problems, THEN suggest antibiotic X."

The major downside of these systems is their inflexibility: they can only handle situations they've been explicitly programmed for. If a new guideline comes out, or a patient presents with a slightly different set of symptoms not covered by a rule, or new antibiotics or bacterial resistance patterns emerge, then manual reprogramming is required.

Traditional machine learning systems came next.[3] Instead of being given rigid rules, these systems learn by analyzing vast amounts of past patient data.

To continue with our example, it's like showing the computer thousands of charts from patients with community-acquired pneumonia, with expert-selected variables that might influence the choice of correct antibiotics. We'd feed it data such as patient age, specific symptoms, and other health conditions, along with the successful antibiotic prescribed. The computer then finds its own patterns in that data to develop a model that provides antibiotic recommendations, learning which combinations of these factors tend to lead to a good outcome. This process of humans selecting the input or predictor variables to build a model is called *feature engineering*.

The advantage here is that the system can uncover connections that might not be obvious to humans and can continue to update itself over time.[4] However, the drawback is that feature engineering is labor-intensive and susceptible to "unknown unknowns." If a rare condition (eg, a specific genetic contraindication) was not included as a feature during training, the model will not account for it in future predictions.

Deep learning systems are the most advanced, often thought of as having a more brain-like structure.[5] What makes them powerful is their ability to learn directly from raw, messy data without the need for feature engineering. For our community-acquired pneumonia example, a deep learning system could analyze entire patient files, including the actual chest radiography images,[6] the free-text notes written by doctors and nurses,[7] and all the laboratory numbers and then figure out *on its own* which parts of this information are most important.

The huge advantage of deep learning systems is their ability to find complex and subtle patterns in vast and varied datasets, leading to highly accurate suggestions.[8] However, their primary drawbacks are that they require enormous amounts of data and processing power to learn effectively, and sometimes they act like a "black box"—it can be hard to understand exactly *why* they made a particular recommendation, which can be a concern in critical healthcare decisions. Large language models are a specialized subset of deep learning.

FEATURES IN, LABELS OUT

Note that when discussing AI we use the words "features" and "labels" in unconventional ways.

Features (input or predictive or independent variables) are like all the pieces of clinical information one gathers about a patient that help you choose an antibiotic. For a patient with suspected community-acquired pneumonia, these would be things like their age, their comorbidities or allergies, and their severity of illness.

The label (outcome or dependent variable) is the outcome you're trying to predict for that patient. It's the diagnosis or the most effective treatment that was determined for similar past patients, and what you want the AI model to learn to identify. So, for our community-acquired pneumonia example, the label for a past patient might be "antibiotic X was the most effective treatment for this specific case." The AI model learns from thousands of these features and their corresponding labels to predict the right label for a new patient.

Critical caveat: labels often reflect historical clinician behavior rather than objective truth. If the training data reflect that physicians historically prescribed antibiotic X most frequently, even if it wasn't the optimal evidence-based choice, the AI system will learn to mimic this habit rather than the best clinical practice.

MACHINE LEARNING: SUPERVISED, UNSUPERVISED, AND REINFORCED

Supervised learning trains the model on a dataset that provides both features and labels, eg, past cases of community-acquired pneumonia for which the correct antibiotic choice is known.[9] This model can then be used to predict the best antibiotic for future patients.

Unsupervised learning provides the model with features but not the labels. The model attempts to find patterns or groupings in the data, such as identifying clusters of infection types without knowing the correct antibiotic. This could reveal previously unrecognized subgroups of patients with community-acquired pneumonia that respond similarly or uniquely to certain interventions, potentially guiding new ways to categorize and treat patients more precisely.

Reinforcement learning trains an AI model to make decisions by learning from trial and error and continuous feedback on past actions, much like suggesting a series of moves in a game of chess as opposed to just the first move. For instance, in treating pneumonia, the AI model might suggest antibiotics in a simulated setting, then receive feedback on success or adverse events. This allows it to learn a dynamic strategy, providing evolving guidance throughout a patient's illness to optimize long-term outcomes, not just an initial recommendation.

Each learning type offers unique strengths, with supervised learning being widely used in clinical prediction, unsupervised learning helping discover unknown patterns, and reinforcement learning holding promise for adaptive decision-making in dynamic clinical environments.

NEURAL NETWORKS: THE ARCHITECTURES OF DEEP LEARNING

Each machine learning approach or learning framework uses layers of artificial neural networks arranged in specific designs and organizations, termed *architectures*, that mimic aspects of human learning. *Transformers* are one such architecture, and large language models are based on them. **Table 1** lists common machine learning architectures and their applications in healthcare; while most of these architectures are beyond the scope of this article, it is important for clinicians to be familiar with the breadth of AI applications in healthcare.

Transformers and attention

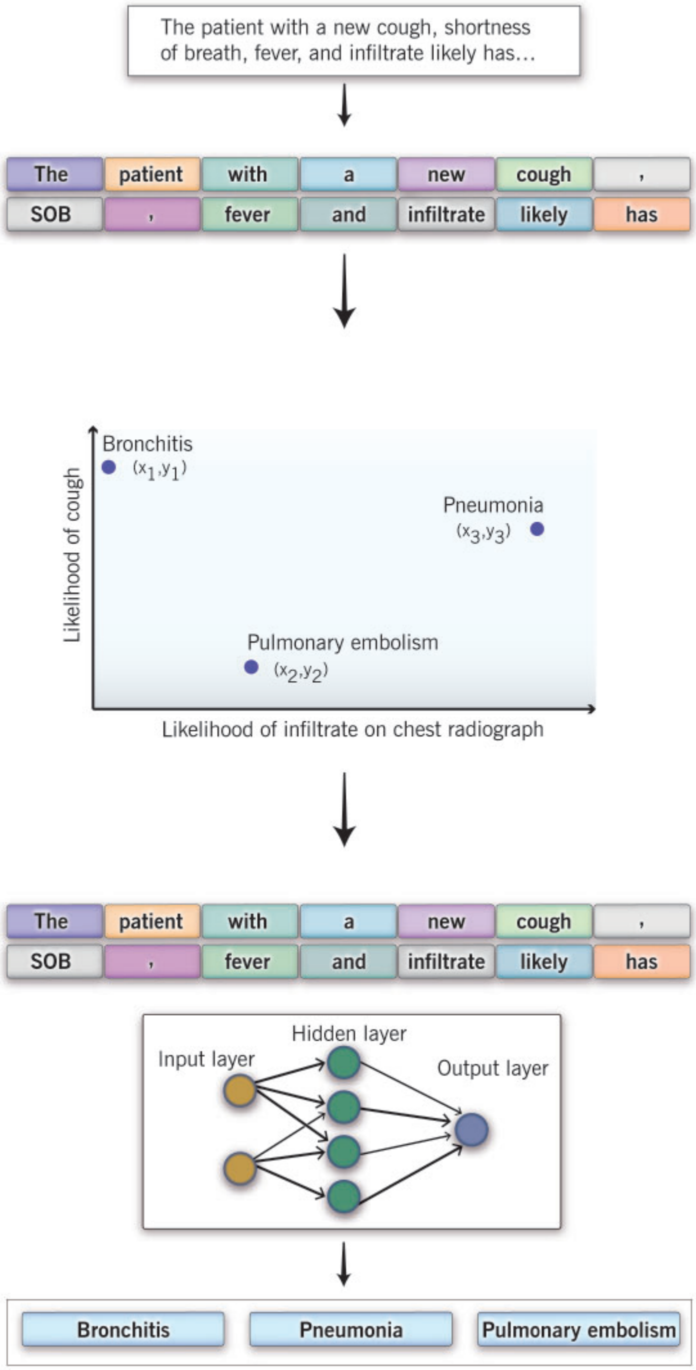
Transformers are designed to understand information that comes in a sequence, like words in a sentence or events over time.[2] They do this by figuring out how important each part of the input is to every other part—called the "attention mechanism"—allowing them to grasp the full meaning, even when pieces of information are far apart. The process goes through several steps—tokens, embedding, transformers, and feedback (**Figure 2**).

Imagine an expert clinician listening to a medical student presenting a new admission to the hospital. As they listen, they can identify and prioritize the key features that will help determine the diagnosis. This ability to weigh the importance of different pieces of information and focus on the most relevant parts of the input is like the attention mechanism of the transformer architecture.[10]

For example, when a large language model processes a sentence like, "The patient presented with cough and new infiltrate on chest x-ray, suggesting possible community-acquired pneumonia that may require antibiotic treatment," the attention mechanisms in transformers allow it to weigh the importance of each word. It recognizes that "new infiltrate on chest x-ray" is highly relevant to "cough" in the context of potential community-acquired pneumonia and establishes connections across the sentence to generate clinically appropriate interpretations.

TABLE 1
Architectures of neural networks in machine learning: What can they do?

Architectures	Uses and limitations in healthcare
Supervised	
Feedforward neural networks or multilayer perceptrons Data move in 1 direction through layers of "neurons," each fully connected to the next; the network learns by adjusting the strength of connections	Can be trained on structured patient data (eg, age, comorbidities, vaccination status) to predict a patient's individual risk of developing community-acquired pneumonia or experiencing a severe outcome, guiding preventive measures or early intervention While powerful, are less specialized for image or sequence data than other architectures
Convolutional neural networks Use filters that scan across the image to detect features like edges, shapes, and textures, the way your eye recognizes parts of a picture	Can be trained to quickly spot signs of pneumonia on a chest radiograph or computed tomography image, determine the extent of lung involvement, or even help assess the severity of the infection by identifying specific patterns, aiding in faster diagnosis and treatment planning Excellent at finding patterns in data that look like a grid, such as images Training data need to include normal studies and other thoracic conditions that mimic pneumonia so that the system can learn to distinguish pneumonia from look-alike abnormalities
Recurrent neural networks Designed to understand sequences of information where order matters Have a memory that allows them to consider past events when processing current information, making them ideal for data that unfold over time	Can monitor a patient's vital signs (eg, heart rate, respiratory rate), laboratory values, and symptom progression over hours or days Can learn patterns that predict worsening community-acquired pneumonia, like an increasing risk of sepsis or the need for intensive care, enabling earlier intervention
Transformers Excel at understanding complex relationships within long sequences of data (like text), even when important pieces of information are far apart Can process entire sequences at once, efficiently grasping the context and significance of each part	Can read and understand lengthy, unstructured physician's notes, nursing observations, and discharge summaries related to community-acquired pneumonia and then summarize key findings, extract all comorbidities, or identify subtle mentions of medication side effects, providing a comprehensive patient overview or flagging relevant clinical details for review
Unsupervised	
Autoencoders or variational autoencoders Learn to compress complex data into a simplified, meaningful "code" and then reconstruct similar data from that code Are particularly good at finding and representing underlying patterns in data; are often used for data compression, anomaly detection, and generating new data with learned characteristics	Can analyze vast clinical datasets (symptoms, laboratory results, demographics, treatment responses) for patients with community-acquired pneumonia without prior labels Could uncover hidden patient groups (eg, those with a specific inflammatory response that predicts poorer outcomes) that might benefit from targeted therapies, guiding personalized medicine approaches
Generative adversarial networks Composed of 2 competing artificial intelligence networks, one that creates new, realistic data (the "generator") and another that tries to tell whether the data are real or fake (the "discriminator"); through this competition, they learn to generate highly convincing, novel data	Can create realistic but entirely synthetic computed tomography images showing various stages of pneumonia, which can be invaluable for training other artificial intelligence models when real patient data are scarce or for creating diverse educational materials without compromising patient privacy Could also generate anonymized patient records for research
Supervised or unsupervised	
Graph neural networks Designed to understand and learn from data that are structured as a network or graph, where elements (nodes) are connected by relationships (edges); can analyze how information flows and interacts within these complex connections	Could model patient flow within a hospital, identifying high-risk infection transmission pathways for community-acquired pneumonia More broadly, can analyze complex networks of patient conditions, medications, and clinical events, helping to understand how different comorbidities influence community-acquired pneumonia outcomes or how specific antibiotics interact within a patient's overall drug regimen



Tokens are individual words, syllables, or punctuations that a body of text gets split into so a computer can work with it.

Embedding turns tokens into numbers that capture their meaning so that a computer can compare and work with them. Here, the words *bronchitis*, *pulmonary embolism*, and *pneumonia* might hypothetically be assigned numbers.

A transformer learns to pay attention to the important parts of a sentence so that it can understand and generate language. Here, the model may generate 3 words (with different probabilities) that best fit for completing the sentence. With feedback, it would be trained to suggest that *pneumonia* has the highest probability as the next word in the sentence.

Figure 2. How artificial intelligence chooses the next word—and makes a diagnosis.

Caveat. While transformers are excellent at understanding relationships within text, they can sometimes struggle with nuanced language, especially negation. For instance, if a physician asks a large language model about a patient's presentation, saying, "The patient has a cough, but denies fever or shortness of breath," a transformer-based model might focus strongly on "cough" and the general context of "pneumonia symptoms." It could then incorrectly suggest a higher likelihood of community-acquired pneumonia by failing to adequately process the denial of fever and shortness of breath. This occurs because the model's attention mechanism primarily learns statistical connections between words, rather than a human-like logical comprehension of the denial.

Transformers learn statistical correlations rather than symbolic logic. If a prompt says, "The patient is on high-dose corticosteroids and has a cough but no fever," a human knows steroids suppress fever. However, unless the model was explicitly trained on many examples linking steroids to afebrile infection, it might statistically associate infection with fever. It could then incorrectly lower the probability of pneumonia because the word "fever" is absent, failing to account for the physiologic effect of the drug.

HOW MACHINES LEARN

Pretraining

Large language models are initially trained on massive datasets of digital information from the Internet. This process, called *pretraining*, is analogous to a medical student going through years of medical school, reading textbooks, research papers, and clinical notes to acquire general medical knowledge before seeing patients.[11]

A large language model pretrained on a large corpus of medical literature will learn about various diseases, common symptoms, and treatments.[12] It learns that pneumonia often presents with cough, fever, and shortness of breath, and that antibiotics are a common treatment. It would learn about typical organisms causing community-acquired pneumonia and their clinical presentations.

But it can make mistakes. Pretraining exposes large language models to a wide range of medical information, but the data are not exhaustive. As a result, large language models may struggle with diseases that are newly emergent, rare, or have an atypical presentation.

For example, a large language model that is pretrained on data up to late 2024 may not know about cases of avian influenza in the United States. When asked about the differential diagnosis of a dairy farmer in California with influenza-like illness, it would not suggest an H5N1 infection.

For another example, *Chlamydia psittaci* pneumonia can present with a headache and rash and without classic features of community-acquired pneumonia. If the pretraining dataset has very few cases of this condition, the model may not learn robust associations for this. Unless the user specifically mentions exposure to a sick parrot, the model would likely not suggest *Chlamydia psittaci* as a differential for this presentation.

Applying weights and biases

During pretraining, the model adjusts internal numerical parameters called weights and biases, which determine the strength of connections between words and concepts.

For example, if a large language model is trained on many reports in which hypertension is associated with increased risk of stroke, the weight connecting these 2 concepts increases. The values of these weights and biases are crucial for the large language model's accuracy.[13] If the training data are biased or incomplete, the weights and biases may be adjusted in a way that leads to incorrect or suboptimal responses.

But the weights may be wrong. Consider a large language model trained to predict the likelihood that a patient has a pulmonary embolism based on various clinical factors. If the training data come primarily from tertiary care hospitals, the model might be biased toward severe diagnoses. For example, if "calf pain" in the training data is almost always associated with pulmonary embolism rather than muscle strain, the model might aggressively suggest pulmonary embolism even for a young, active patient with a clear history of strain. Here, the model's parameters have been skewed by the prevalence of a particular association in the training data, resulting in an erroneous prediction in a different clinical context.

Fine-tuning

After pretraining, large language models can be further trained on specific datasets to improve their performance on particular tasks. *Fine-tuning* adapts a general-purpose large language model to perform better in specific domains. It is analogous to a medical resident trained on all of internal medicine joining a cardiology fellowship and focusing on heart-related conditions.

Fine-tuning improves accuracy. For instance, a general large language model pretrained on a broad range of Internet text might be asked, "What is the most common cause of elevated troponin in a patient without chest pain?" The large language model might generate a list of common causes of elevated troponin, such as myocardial infarction, but may not rank them in the correct order of probability for a patient without chest pain. It might overemphasize myocardial infarction because, in general, that's a very common cause of troponin elevation.

The large language model could be fine-tuned on a large dataset of electronic health records from patients presenting with elevated troponin but without chest pain. This dataset would include cases of myocarditis, pulmonary embolism, renal failure, and other less common causes in this specific patient population. After fine-tuning, the large language model learns the subtle differences in troponin elevation in the absence of chest pain. It adjusts the weights and biases in its neural network to prioritize conditions like myocarditis and pulmonary embolism in this specific clinical context. When asked the same question, the fine-tuned large language model provides a more accurate, clinically relevant answer, prioritizing causes appropriately for the patient's presentation.

Retrieval augmented generation

Retrieval augmented generation enhances the foundational large language models by enabling access to external knowledge sources.[14] When a user asks a question, the large language model first retrieves relevant information from a database or knowledge base and then uses this information to generate more accurate, informed responses. This process is analogous to a clinician consulting a resource such as a textbook or guideline before making a clinical decision.

For example, a physician asks a large language model, "What is the best treatment for a patient with heart failure with reduced ejection fraction?" The large language model uses retrieval augmented generation to search a database of clinical guidelines, retrieves the latest recommendations, and then provides a response based on that information, rather than relying solely on pretrained knowledge.

Risks and limitations. While the retrieval augmented generation model uses appropriate resources such as clinical guidelines, it still must interpret the information, which is where it may make errors. Thus, in a patient with a history of "mild penicillin allergy" in the electronic health record, the guideline would suggest using a medication such as levofloxacin. The large language model may misinterpret "mild" or the "low" risk of cross-reactivity with another beta-lactam antibiotic and suggest using a cephalosporin with azithromycin. This is an issue of the large language model using statistical inference rather than prioritizing patient safety.

For another example, a patient developed bromism after consulting ChatGPT and following its medical advice to take bromide supplements.[15] This highlights the risk of relying on large language models for medical decisions and requires careful clinical evaluation of unusual symptoms. While large language models can enhance efficiency and clinical decision-making, they must be integrated with a human in the loop to ensure safe, ethical practice.[16]

POTENTIAL PITFALLS OF ARTIFICIAL INTELLIGENCE

Hallucinations: When AI makes stuff up

Large language models can generate information that is not present in the training data or any external knowledge source. This is often called *hallucination*.[17]

When a large language model generates a response, it is essentially predicting the most probable sequence of words to complete a sentence. If the training data are ambiguous or incomplete, or if the query is outside its core knowledge, the model might "guess" or infer information based on weak statistical signals, leading it to create plausible but untrue statements.[17]

For example, a clinician asks a large language model to list the common side effects of a new antibiotic to treat community-acquired pneumonia. The large language model provides a list that includes side effects not reported in any clinical trials or postmarketing surveillance.

It is thus necessary to double-check primary evidence before applying a large language model–generated response to clinical care. Explicitly prompting the model with, "*Answer using only information from professional society guidelines. If you do not know, state that you do not know. Do not fabricate references.*" can help reduce hallucinations but not completely eliminate them.

Prompt sensitivity: What you ask is what you get

The way a question or prompt is phrased can significantly affect the response.[18] Large language models learn statistical patterns from vast amounts of text data. They don't possess genuine understanding[19] or conscious reasoning. When you change a prompt, even slightly, it shifts the statistical probabilities that the large language model uses to generate its next words. This can nudge the model down a different path in its vast learned knowledge space, leading it to emphasize different information, omit crucial details, or even present a different conclusion.

For example, the following 2 prompts might give different responses.

- "What are the recommended empiric antibiotics for outpatient community-acquired pneumonia in an adult without comorbidities?"
- "What are the recommended empiric antibiotics for outpatient community-acquired pneumonia in an adult without comorbidities? *Please specifically address optimal choices, given the prevalence of macrolide resistance in many regions.*"

The second prompt might elicit a different response that deemphasizes azithromycin as empiric treatment. Clinicians should thus triangulate answers by asking the same clinical question in 2 different ways to see if the model's reasoning remains consistent.

WHAT ARE AGENTS?

Unlike large language models that give a single answer to a question or prompt, an *agent* can autonomously perceive its environment, reason about its observations, formulate plans, take actions (often by using various digital tools and resources), and continuously evaluate its progress toward a defined goal.[20]

Agents are very useful for complex tasks that might be run multiple times.[21] For example, take a patient with multiple complex problems including renal impairment, on multiple medications, admitted with community-acquired pneumonia. The agent would look up the clinical guideline for the most appropriate medication, then check the medical records for renal function and the medication list, then check an online drug-interaction checker, and then recommend a medication that is dosed appropriately for the patient's renal function.

EMPOWERING HEALTHCARE PROFESSIONALS

In this article, we have tried to use a clinical lens to demystify AI, particularly large language models, by illustrating their core mechanisms, learning paradigms, and pivotal concepts like attention, pretraining, weights and biases, and retrieval-augmented generation in the context of practical clinical examples. We also illuminated potential pitfalls such as hallucinations and prompt sensitivity that clinicians must carefully consider.

Armed with this understanding, we hope clinicians will be empowered to critically evaluate AI-generated information, judiciously integrate these powerful tools into their practice, and ultimately deliver care that is not only safer and more efficient but also more effective, truly augmenting human expertise for the benefit of patients.

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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