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Anchors away

A reticular eruption on the thighs

Is the *MTHFR* gene mutation associated with thrombosis?

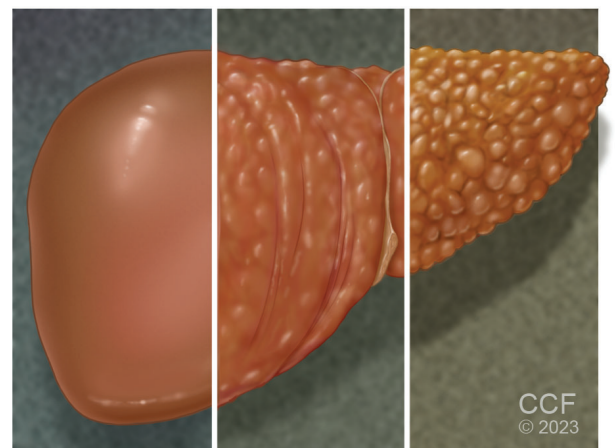
What is the role for terlipressin in hepatorenal syndrome?

Elevated aminotransferases in a 62-year-old woman

COVID-19: A management update

The new GFR equations: How will eliminating the race coefficient affect Black patients?

Cirrhosis: Primary care approaches to screening, immunization, and lifestyle modifications



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Cleveland Clinic Journal of Medicine [ISSN 0891-1150 (print), ISSN
1939-2869 (online)] is published monthly by Cleveland Clinic at
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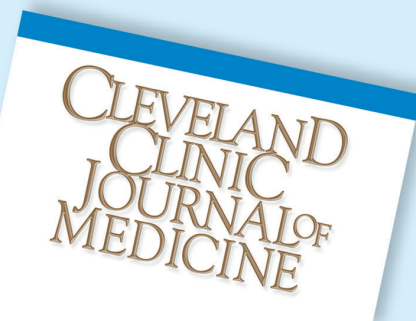
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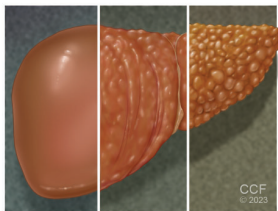
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Anchors away

Before you read this, please read the article by Prakash et al,¹ part of our Symptoms to Diagnosis series.

The *Journal* has published reviews and commentaries on the nuanced interpretation of laboratory tests. In the article by Prakash et al, challenges that arose while pursuing the diagnosis highlight limitations in how we interpret some of our most-ordered tests, as well as those we order more selectively. As you follow the authors' clinical reasoning behind the management of the 62-year-old patient, it is easy to see how results of nonspecific tests can be interpreted to support a diagnosis that is ultimately incorrect. Using results of less-specific tests to support a specific diagnosis without actively recognizing the limitations of the tests can lead to premature closure ("anchoring"), one of the deadly sins of clinical reasoning.

Three points in Prakash's teaching exercise struck me. The first is one that I have written about and have perseverated about with scores of medical residents. "Liver function tests" are definitely not as the name implies. They have little to do with liver function and, most importantly, when elevated, they do not unequivocally indicate a hepatic source. We must resist following the implicit implications in using the term liver function test. Aspartate aminotransferase and alanine aminotransferase are present in many cells, including myocytes.

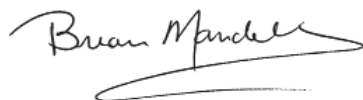
Liver disease is far more common than muscle disorders as a cause of aminotransferase elevation, so elevated aspartate and alanine aminotransferase levels will indeed most likely reflect hepatic injury. Symptoms of chronic liver and muscle disease that patients report are frequently similar, ie, fatigue and weakness. Unless we push to understand what "weakness" means to the specific patient (eg, general listlessness vs difficulty getting up from the toilet or from a low chair), it is easy to see how chronic myositis could be diagnosed as hepatitis. While this can usually be sorted out by checking the creatine kinase level, it takes clinical suspicion followed by an active decision to order this test. That suspicion usually arises from hearing an appropriately detailed history from the patient or the patient's family, or by the physical examination. Alternatively, the decision to order a creatine kinase test can (should?) be algorithmically made in all patients with elevated aminotransferases who do not have more direct evidence for hepatic pathology—eg, elevated gamma-glutamyl transferase, elevated hepatic alkaline phosphatase, or abnormal liver imaging.

The second point is our need to recognize and accept that notes in the medical record that a patient has been "asymptomatic" with a "normal physical examination" may not tell the whole story. Particularly, as clinicians are pressed for time during visits, and many of us wind up entering or completing our notes after the end of our clinic day is done, shortcuts like the use of visit-note templates pose challenges. Few of us have time to complete a full physical examination and obtain a detailed review of systems at every visit. We complete a more directed examination based on symptoms and prior history, and the review of symptoms is likely to be based on an obliquely worded, patient-completed questionnaire. So if there was no reason to seriously consider a myopathy, how likely was a truly focused evaluation of a patient's strength performed? Was the patient asked specifically about muscle fatigue with brushing the hair or difficulty walking up steps? Did we examine strength in the office—eg, how many seconds does it take the patient to sit and arise 10 times from a chair without using the arms to push off? I have found, especially when note templates have been used, that there are discrepancies in physical examination findings. Was the patient discussed by Prakash et al truly without any previous muscle symptoms or findings that might have provided a hint as to the nonhepatic source of the "liver tests"?

doi:10.3949/cjim.90b.11023

The third learning point relates to the limited utility of autoimmune serologies, the most frequently ordered test being the antinuclear antibody (ANA). ANA is not a specific test. It is positive in almost all patients with systemic lupus and scleroderma, and in many patients with rheumatoid arthritis, autoimmune thyroid disease, myositis, and Sjögren syndrome. Importantly, it can be detected (usually in lower titers) in about 20% of patients without clinically recognized systemic autoimmune disease. Indiscriminate ordering of the test is costly and may lead clinicians and patients down many a vexing rabbit hole. Up to 40% of patients with autoimmune liver disease have a second systemic autoimmune disorder, perhaps one associated with positive for ANA. But a positive ANA is also present in many patients with autoimmune liver disease (ALD), so when that diagnosis is suspected, ANA and more-specific autoantibodies like anti-smooth muscle and anti-mitochondrial are often ordered, and a positive test result is used to support the diagnosis of ALD. But as in the patient discussed by Prakash et al, the highly positive but less specific ANA test likely reflected the previous diagnosis of Sjögren syndrome. Not accepting the true nonspecificity of this test, and interpreting it in the context of the suspected diagnosis of autoimmune hepatitis, likely led to stronger initial acceptance of the diagnosis of ALD than was warranted.

The discussion by Prakash et al highlights the importance of resisting the reflex use of less-specific tests to anchor a provisional diagnosis without intentionally considering alternative interpretations of those results that might push towards a different diagnosis.



Brian F. Mandell, MD, PhD
Editor in Chief

1. Prakash S, Moore S, Snow A, Brown KE. Elevated aminotransferases in a 62-year-old woman. *Cleve Clin J Med* 2023; 90(11):669–674. doi:10.3949/ccjm.90a.23011

2023

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2024

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THE CLINICAL PICTURE

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A reticular eruption on the thighs

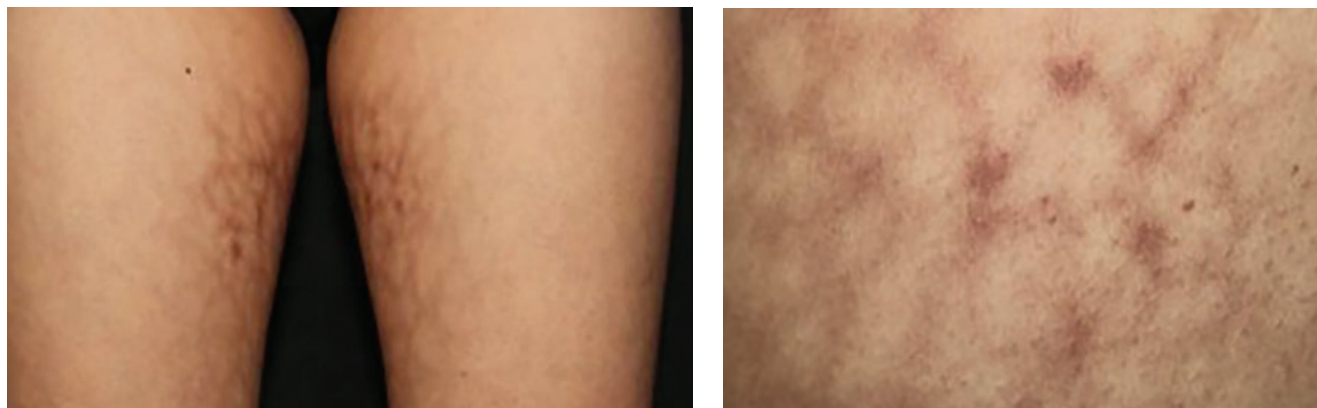


Figure 1. Reticular, nonblanchable, brownish pigmentation with mild erythema and telangiectasias on the patient's inner thighs.

A 17-YEAR-OLD GIRL PRESENTED to our dermatology clinic with a 2-month history of an asymptomatic reticular rash on both thighs. The patient was previously healthy and had not recently taken any new medications. Due to the cold winter weather, she had been wearing an electric heating pad between her thighs for the previous few months.

Physical examination revealed a reticular, non-blanchable, brownish pigmentation with mild erythema and telangiectasias on the inner thighs (**Figure 1**), diagnosed as erythema ab igne. She was advised to discontinue use of the heating pad, and 6 months later the rash had completely resolved without any other intervention.

■ ERYTHEMA AB IGNE

Erythema ab igne is caused by repeated or prolonged exposure to heat from 43°C to 47°C (109°F to 117°F), which is below the thermal burn threshold.¹ Common

heat sources include wood stoves, open fires, laptops, tablets, neurostimulators, telephones, electric heaters, heated blankets, heated patches, and virtual-reality headsets.² Underlying medical conditions for chronic heat exposure must also be considered, such as chronic pain, pancreatitis, and peptic ulcer disease, as patients with these conditions often resort to local hot compresses for pain relief.¹ Our patient had no history of any of these underlying conditions.

The lesions of erythema ab igne appear as reticular hyperpigmentation due to hemosiderin and melanin deposition and may be associated with atrophy, telangiectasia, and bullae.² It is usually asymptomatic, but a few patients report mild burning or itching.² Lesions usually resolve spontaneously within several weeks to months after removal of the heat source and do not require treatment. Although the lesions resolve in most patients, hyperpigmentation in a few patients may not disappear completely after several months. Therefore, laser treatment and topical hydroquinone are considered options for cosmetic purposes.^{2,3}

doi:10.3949/cjfm.90a.23028

The differential diagnosis

Erythema ab igne is usually easy to diagnose from the clinical presentation alone, but care must be taken to distinguish it from livedo reticularis and livedo racemosa.

Livedo reticularis is a cutaneous physical sign characterized by a transient or persistent, reddish-blue to purple, reticular, cyanotic pattern with or without any evidence of systemic disease.⁴ It results from reduced blood flow and lowered oxygen tension at the periphery of the skin segments caused by functional or organic disorders such as vasospasm, arteriolar wall inflammation, and intravascular obstruction.⁵ Compared with livedo reticu-

laris, the reticular pattern of livedo racemosa is permanent and often has irregular and incomplete reticular segments with a more generalized distribution.⁶ Livedo racemosa is always secondary and is often associated with antiphospholipid syndrome, systemic lupus erythematosus, thromboangiitis obliterans, polycythemia vera, and polyarteritis nodosa.^{4,6}

DISCLOSURES

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

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Q: Is the *MTHFR* gene mutation associated with thrombosis?

A: Polymorphisms of the methylene tetrahydrofolate reductase (*MTHFR*) gene are common among the general population, and data from large meta-analyses do not support the association of these variants with elevated prothrombotic risk. Clinicians should educate patients with *MTHFR* polymorphisms about the lack of evidence for association with thrombotic risk and focus on addressing modifiable thrombotic risk factors.

■ BACKGROUND

MTHFR is an essential enzyme that is encoded by the *MTHFR* gene, which catalyzes the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, the primary form of folate in circulation. This substance, 5-methyltetrahydrofolate, is also a necessary cofactor for the conversion of homocysteine to methionine, required for protein synthesis.¹ Reduced expression of *MTHFR* has been implicated in elevated serum homocysteine and reduced serum folate levels, a condition known as hyperhomocysteinemia.²⁻⁴ The relationship between serum homocysteine levels and disease has been investigated across several disease states. In this review, we focus on its putative relationship with venous thromboembolism (VTE).

■ WHAT IS A SINGLE NUCLEOTIDE POLYMORPHISM?

Single nucleotide polymorphisms (SNPs) and single nucleotide variants (SNVs) both refer to single base-pair changes in the nucleic acid sequence of a gene, but they are not interchangeable terms. SNVs are changes that occur in less than 1% of the population,

whereas SNPs occur in at least 1% of the population.⁵ Neither of these terms implies pathogenicity of the genetic change, and both may be colloquially referred to as “mutations.” It should also be noted that databases cataloging human genetic variation are biased towards populations with Northern European heritage. Patients with African, South American, Indigenous, Pacific Islander, and Southeast Asian heritage are underrepresented, complicating the estimation of true population prevalence for a given genetic variant.

■ HOW COMMON IN THE GENERAL POPULATION?

From an epidemiologic perspective—because SNPs in *MTHFR* are common, some occurring in up to 40% of the general population—achieving statistical significance for an association between SNPs and a clinical variable of interest is subject to many potential biases.⁶ It is important for the clinician to recognize potential sources of confounding in these studies.

First, not all *MTHFR* SNPs are equivalent, and different SNPs should be considered independently as risk factors, as should homozygosity and heterozygosity. Second, correlation does not imply causation, and epidemiologic studies can provide correlative evidence, but confounding effects and a biological basis for the association must also be carefully examined.

Crucially, dietary intake of B vitamins influences the measurement of homocysteine, and dietary differences must therefore be considered when comparing populations with *MTHFR* variants.¹ Lastly, both selection bias for patients who have been tested for *MTHFR* variants and ascertainment bias in retrospective cohorts may play a large role in influencing study results.

doi:10.3949/cjfm.90a.23044

■ RISK OF THROMBOSIS AND MTHFR VARIANTS

The most common *MTHFR* SNPs in the general population are the C677T (rs1801133) and A1298C variants (rs1801131), thought to affect the thermostability of the methylenetetrahydrofolate reductase.⁶ The C677T allele has been better studied, and its combined heterozygous and homozygous incidence varies from 20% to 30% in East Asian people to 20% to 40% in White and Hispanic populations in the United States.⁷ The A1298C variant is less well-studied, and its allele frequency is estimated at 10% to 30% in White populations and 20% to 40% in Southeast Asian populations (combined heterozygous and homozygous incidence).⁸ This variant is thought to be milder and less clinically significant.⁶

As mentioned, while these SNPs are associated with reduced methylenetetrahydrofolate reductase enzyme activity and increased homocysteine levels, the relationship between these findings and thrombotic risk has been controversial. Of note, homocysteine levels are impacted by many factors, including concomitant renal disease, thyroid disease, nutritional deficiencies, and alcohol intake.^{1,9}

Early analyses of whether homocysteine levels are associated with VTE came from a 1997 meta-analysis that pooled results of 9 studies and showed an increased risk of VTE in the setting of hyperhomocysteinemia.¹⁰ A larger-scale meta-analysis comprising 11,000 cases and 21,000 controls from 31 databases was published in 2013. It showed that there was no evidence for an association with homozygotes for the *MTHFR* C677T variant and VTE, but due to incomplete data, was unable to examine for an association between homocysteine, *MTHFR* variant, and VTE.¹¹

Likewise, a review of 9 case-control studies involving 382 patients found insufficient evidence to support any association between the *MTHFR* C677T variant and cerebral venous sinus thrombosis.¹² A meta-analysis of 26 studies examining the role of the *MTHFR* C677T variant and recurrent unexplained pregnancy loss showed an association only in 5 studies from China and no association in European studies.¹³ The authors concluded that at most, the presence of this SNP is a risk factor for recurrent unexplained pregnancy loss in Chinese patients, but not European patients.¹³

■ SHOULD PATIENTS BE TESTED FOR MTHFR VARIANTS?

Given the tenuous associations identified in the literature associating *MTHFR* variants with VTE, we do not advocate for the routine testing of patients for *MTHFR*

variants. This approach is supported by the American College of Medical Genetics and Genomics.¹⁴

■ TEST INTERPRETATION

If a patient has had a prior genetic test with a result reported for *MTHFR*, the clinician must carefully consider whether the reported genetic change (whether it is an SNV, SNP, or more complex alteration) is known to be pathogenic and is consistent with the patient's presentation. In cases where the identified genetic change is a common SNP, we do not recommend any further workup or management based on the prior genetic testing. In situations with rarer variants or complex genomic rearrangements identified, consultation with a genetic counselor may be helpful.

■ MANAGEMENT

The propensity to clot is influenced by a myriad of factors in each patient, and a patient's *MTHFR* status is a single, likely noncontributory component of this risk. In patients with VTE, the management of a patient with an *MTHFR* variant should be no different than the standard of care. In those who are at risk of thrombosis, it is essential to recognize that the common *MTHFR* SNPs are not thought to be contributory to VTE risk. Other risk factors such as age, family history, and medical comorbidities such as diabetes and hypertension are greater determinants of VTE risk. We recommend that all patients maintain a healthy weight, stop smoking, limit alcohol consumption, and exercise regularly. Dietary modifications, such as including folate-rich foods like leafy greens, legumes, and fortified cereals, may also be beneficial.

■ THE BOTTOM LINE

The relationship between *MTHFR* variants and thrombosis risk is a complex, multifactorial issue. Early studies reported a potential association between common SNPs in *MTHFR* and VTE, but later, larger meta-analyses have refuted these results. At this time, based on the best available evidence, there is no support for the association of the most common *MTHFR* SNPs with significantly elevated thrombotic risk. We recommend that clinicians focus on modifiable risk factors of thrombosis, such as weight management, smoking cessation, and underlying medical issues. ■

Acknowledgments: Andrew Dhawan, MD, DPhil, is the recipient of a PTEN Research Foundation Young Investigator Award and an American Academy of Neurology Scholar Award. Charis Eng, MD, PhD, is the Sandra J. and Stephen R. Hardis Endowed Chair of Cancer Genomic Medicine and a Lerner Eminent Scholar at the Cleveland Clinic.

DISCLOSURES

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

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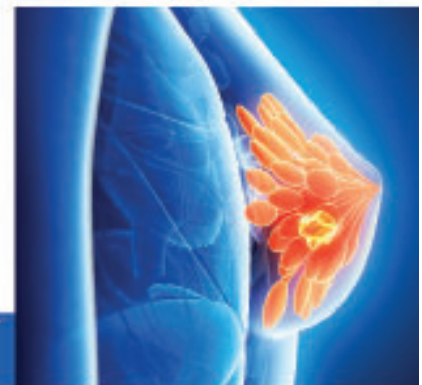
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BRIEF
ANSWERS
TO SPECIFIC
CLINICAL
QUESTIONS

Q: What is the role for terlipressin in hepatorenal syndrome?

A: With careful patient selection, terlipressin, a synthetic analogue of vasopressin, is an effective therapy for hepatorenal syndrome (HRS). The drug has compared favorably with placebo and, based on limited data, other vasoconstrictors.

■ HEPATORENAL SYNDROME: UPDATED DEFINITIONS

HRS is a serious complication of advanced liver disease defined by kidney dysfunction associated with complex changes in the splanchnic circulation resulting in vasoconstriction and renal hypoperfusion.¹ Traditionally, acute HRS, characterized by a rapid decline in kidney function, has been referred to as type 1 HRS; chronic HRS, characterized by progressively worsening kidney function, has been referred to as type 2 HRS.²

The diagnostic criteria for HRS were revised recently based on the International Club of Ascites definition of acute kidney injury (AKI) in patients with cirrhosis (Table 1).¹ The updated definition addresses the potential overestimation of renal function based on the serum creatinine (SCr) level in patients with cirrhosis, where SCr is reduced because of malnutrition and muscle wasting.² The revised definition reclassifies type 1 HRS as HRS-AKI and type 2 HRS as HRS-chronic kidney disease.² HRS-AKI is considered a diagnosis of exclusion.

The ultimate therapy for HRS-AKI may be liver transplant in appropriate candidates. However, because AKI is associated with significantly increased mortality risk,³ therapies are needed that target reversal of HRS-AKI and potentially serve as a bridge to liver transplant. Unfortunately, there are limited treatment options for HRS-AKI. Current therapies

include the combination of midodrine and octreotide, norepinephrine, and terlipressin.

■ TERLIPRESSIN: THE ONLY APPROVED THERAPY FOR HRS-AKI

Terlipressin, available in some parts of the world for several years, was just recently approved by the US Food and Drug Administration (FDA). It is the only drug with an FDA-labeled indication for the treatment of HRS-AKI. The 2021 American Association for the Study of Liver Diseases and the 2018 European Association for the Study of the Liver guidelines both recommend terlipressin in combination with albumin as first-line treatment for patients with HRS-AKI.^{4,5}

■ EVIDENCE FOR TERLIPRESSIN

Terlipressin has been compared with placebo and with other vasoconstrictors. The efficacy and safety of terlipressin for HRS reversal was demonstrated in CONFIRM (Terlipressin Plus Albumin for the Treatment of Type 1 Hepatorenal Syndrome),⁶ a multi-center, randomized, placebo-controlled, double-blind study that led to the FDA approval of terlipressin. It included patients with cirrhosis, ascites, and type 1 HRS, defined as an SCr of at least 2.25 mg/dL without improved renal function within 48 hours of discontinuing diuretic therapy and administration of albumin.⁶ CONFIRM was designed before the new International Club of Ascites AKI definition, so enrolled patients generally had higher SCr levels than would qualify for inclusion based on the new HRS-AKI definition (mean SCr 3.5 mg/dL). Further, patients may have been excluded from CONFIRM who would now qualify for treatment based on the updated HRS-AKI definition.

CONFIRM exclusion criteria included an SCr greater than 7 mg/dL, shock, large-volume paracentesis

doi:10.3949/cjfm.90a.23037

(> 4 L) within 48 hours of randomization, and uncontrolled bacterial infection. Concomitant vasopressors were not permitted. Patients were randomized to receive either terlipressin (N = 199) at an initial dose of 1 mg terlipressin acetate (equivalent to 0.85 mg terlipressin) every 6 hours or placebo (N = 100). Doses were adjusted based on clinical response according to prescribing-information guidelines (Figure 1).⁷ Both treatment arms received daily albumin replacement (median 335 g including 1 g/kg body weight for 2 days prior to receiving the study drug and on day 1, followed by 20–40 g/day while on the study drug) for a median duration of 5 days.⁶

The primary outcome in CONFIRM was verified reversal of HRS, defined as 2 consecutive SCr values of 1.5 mg/dL or less and survival without need for renal replacement therapy for 10 days. This occurred in 32% of patients in the terlipressin group compared with 17% of patients in the placebo group ($P = .006$). In addition, HRS reversal without need for renal replacement therapy for 30 days occurred in 34% of terlipressin patients compared with 17% of placebo patients ($P < .001$). However, there was no difference in 90-day mortality rates (51% terlipressin vs 45% placebo, 95% confidence interval [CI] –6 to 18), nor was there a difference in liver transplant rates (23% terlipressin vs 29% placebo).⁶

Terlipressin was associated with an increased risk of abdominal pain, nausea, diarrhea, and respiratory failure (14% terlipressin vs 5% placebo). In post hoc analyses, populations that were potentially more likely to benefit from terlipressin for HRS reversal included patients with systemic inflammatory response syndrome at baseline, mean arterial pressure less than 70 mm Hg at initiation, and alcohol-associated hepatitis as the cause of cirrhosis.⁶

Terlipressin compared with other vasoconstrictors

The comparative efficacy of norepinephrine and terlipressin was evaluated along with daily albumin replacement in 120 patients with HRS-AKI in a 2020 randomized, open-label trial.⁸ The study included patients who met the recently updated International Club of Ascites criteria for HRS. Consequently, patients in this study had lower SCr levels at initiation than in CONFIRM (mean 1.79 mg/dL in the terlipressin group vs 2.02 mg/dL in the norepinephrine group), so this study may reflect earlier initiation of HRS therapy.¹ The study was conducted in India, where terlipressin was administered as a continuous intravenous infusion, whereas in the United States, FDA-approved dosing is intermittent intravenous administration. Compared with norepi-

TABLE 1

Diagnostic criteria for hepatorenal syndrome with acute kidney injury

Cirrhosis; acute liver failure; ACLF

Increase in serum creatinine:

- ≥ 0.3 mg/dL within 48 hours or
- $\geq 50\%$ from baseline according to ICA criteria and/or
- Urinary output ≤ 0.5 mL/kg ≥ 6 hours.

No full or partial response after at least 2 days of diuretic withdrawal and volume expansion with albumin (1 g/kg body weight per day to a maximum 100 g/day)

Absence of shock

No current or recent treatment with nephrotoxic drugs

Absence of parenchymal disease as indicated by proteinuria > 500 mg/day, microhematuria and/or abnormal renal ultrasonography

ACLF = acute-on-chronic liver failure

Reprinted from *J Hepatol* 2019; 71(4):811–822. doi:10.1016/j.ep.2019.07.002.

Angeli P, Garcia-Tsao G, Nadim MK, Parikh CR.

News in pathophysiology, definition and classification of hepatorenal syndrome: a step beyond the International Club of Ascites (ICA) consensus document, with permission from Elsevier.

nephrine, terlipressin administration was associated with improved reversal of HRS (40% vs 16.7%, $P = .004$), reduced need for renal replacement therapy (56.6% vs 80%, $P = .006$), and improved 28-day survival (48.3% vs 20%, $P = .001$). The rate of adverse effects was significantly higher with terlipressin (23.3% vs 8.3%, $P = .02$), and effects were mainly gastrointestinal.

In a 2015 randomized trial conducted in Italy, terlipressin was administered by continuous infusion to 27 patients, and 22 patients received midodrine and octreotide; both groups also received albumin.⁹ Patients who received terlipressin had higher rates of HRS reversal (19 of 27, or 70.4%) compared with those who received the combination of octreotide and midodrine (6 of 21, or 28.6%, $P = .01$).

Finally, despite limited prospective data comparing terlipressin with other vasoconstrictors, a recent meta-analysis of 26 HRS trials concluded that terlipressin is associated with greater HRS reversal compared with midodrine-octreotide (72.5 more reversals per 1,000; 95% CI > 198 to < 12) and norepinephrine (30.4 more reversals per 1,000; 95% CI > 83 to < 14.6).¹⁰ Based on these data, terlipressin may be more effective than norepinephrine and is likely more effective than the combination of midodrine and octreotide, a conclusion supported by consensus guideline recommendations.^{4,5}

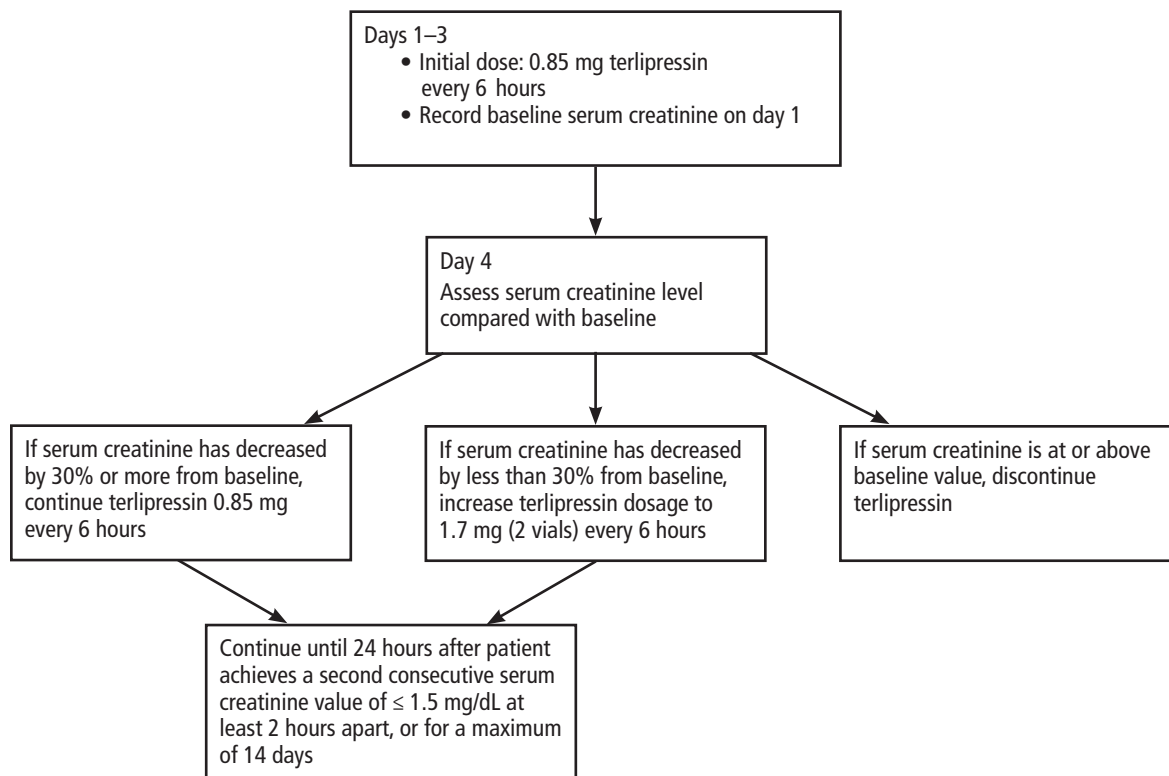


Figure 1. Guide to terlipressin dosing.

Based on information in reference 7.

**■ PATIENT SELECTION CONSIDERATIONS:
POPULATIONS AT RISK OF ADVERSE EFFECTS**

Terlipressin is recommended as a first-line treatment of HRS-AKI and has demonstrated efficacy for HRS reversal over other therapies, but its use is not without hazard. It is associated with respiratory failure, especially in the setting of albumin administration. Other comorbidities can increase the risk of respiratory failure and should be addressed before using terlipressin.^{6,11,12}

Risk of respiratory failure

The risk of respiratory failure with terlipressin in the CONFIRM study was 14% overall vs 5% with placebo, and death from respiratory failure occurred in 11% of terlipressin patients vs 2% of placebo patients.⁶ A similar trend emerged in the pooled data from all phase 3 studies of terlipressin compared with placebo: among 598 patients in placebo-controlled studies, respiratory failure occurred in 11.2% of terlipressin patients vs 4.4% of placebo patients.¹¹

Respiratory failure with terlipressin is hypothesized to result from increased systemic vascular resistance,¹²

which may lead to pulmonary edema in patients with cardiac dysfunction or volume overload. CONFIRM excluded patients with severe cardiovascular disease, including unstable angina, known pulmonary edema, heart failure, and symptomatic peripheral vascular disease.⁶ These patients are unlikely to be good candidates for terlipressin therapy. Further, all patients in CONFIRM received daily albumin replacement of 1 g/kg on day 1, followed by 20 to 40 g per day thereafter. The median total albumin administered during terlipressin administration was 199 g (± 147 g).⁶ Volume overload associated with intravenous albumin dosing has been proposed as a risk factor for respiratory failure in patients receiving terlipressin.¹¹ Consequently, excess volume administration should be avoided, particularly excessive albumin, which is associated with pulmonary edema in vulnerable patients.

Additional factors associated with increased risk of respiratory failure include acute-on-chronic liver failure (ACLF) grade 3, grade 3 to 4 hepatic encephalopathy, aspiration pneumonia, and recent upper gastrointestinal bleeding.¹¹ It is recommended that these patients receive optimized therapy for hepatic

encephalopathy or have a protected airway before initiation of terlipressin to reduce confounding factors for respiratory failure.

Patients with SCr levels above 5 mg/dL are unlikely to benefit from HRS reversal, and this population had a high proportion of fatal adverse events (66% terlipressin vs 39% placebo) in the CONFIRM trial.¹¹ It is not recommended to administer terlipressin to patients whose baseline SCr level is greater than 5 mg/dL. It has been proposed that avoiding terlipressin in these populations would reduce respiratory failure-related adverse reactions by approximately 60%.¹¹ If serious adverse effects such as respiratory failure, ischemic events, or bradycardia occur with terlipressin, therapy should be discontinued. Mild adverse reactions such as nausea and vomiting can be treated while continuing terlipressin therapy.

Cost

The cost of terlipressin is substantial, with an average wholesale cost more than \$1,000 per 0.85-mg vial.¹³ Further, although terlipressin may be administered through peripheral intravenous access and only 15% of patients in CONFIRM were admitted to an intensive care unit at initiation of therapy, some institutions may elect to introduce terlipressin in the intensive care setting in response to safety concerns. The increased utilization of healthcare resources asso-

ciated with this level of care may lead to an overall increase in costs. To support cost-effective practice, consideration should be given to patients most likely to benefit from therapy.

THE BOTTOM LINE

HRS-AKI is a life-threatening complication of advanced liver disease. Although liver transplant may be the eventual treatment in select patients, safe and effective therapies are needed to reverse HRS-AKI to provide a bridge to transplant while avoiding complications associated with renal replacement therapy, as well as to improve survival in patients not being considered for transplant. Terlipressin, the first FDA-approved therapy for treatment of HRS-AKI, has demonstrated efficacy for HRS reversal in randomized controlled trials compared with placebo and, in limited data, compared with other vasoconstrictors. Patient selection is key to minimizing the risk of adverse effects, particularly respiratory failure, including avoidance in patients with known cardiac dysfunction, volume overload, and advanced-grade ACLF.

DISCLOSURES

Dr. Bass has disclosed consulting for Abbvie Pharmaceuticals, and teaching and speaking for Mallinckrodt. Dr. Lindenmeyer has disclosed authorship for Merck. Dr. Kapoor reports no relevant financial relationships which, in the context of her contributions, could be perceived as a potential conflict of interest.

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SYMPTOMS TO DIAGNOSIS

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Elevated aminotransferases in a 62-year-old woman

A 62-YEAR-OLD WOMAN made an appointment to see her primary care physician after returning from a trip to Malaysia. She had experienced a few days of constant right-upper-quadrant abdominal pain while traveling home. The pain had worsened with taking deep breaths and was not instigated by food intake. She also had nausea. By the time of her appointment, 4 weeks after the episode, the symptoms had resolved. She reported no hematochezia, melena, shortness of breath, chest pain, muscle weakness, jaundice, weight loss, or loss of appetite.

The patient had no history of tobacco, alcohol, or illicit drug use. Her medical history included gastroesophageal reflux disease and Sjögren syndrome, diagnosed 10 years earlier based on positive SS-A and SS-B antibody tests, along with symptoms of dry eyes and dry mouth. Her only medications were artificial tears and omeprazole. She also took a multivitamin, a vitamin C supplement, and flaxseed oil. Both parents had hypertension, and her father had type 2 diabetes. She had no history of surgery.

INITIAL EVALUATION AND MANAGEMENT

At the primary care visit, the patient's temperature was 97.6°F (36.4°C), heart rate 72 beats per minute, blood pressure 104/62 mm Hg, respiratory rate 18 breaths per minute, weight 64 kg (141 lbs), and body mass index 25.4 kg/m². She was comfortable, alert, and oriented. Her lungs were clear to auscultation, with no wheezing or crackles. Heart rate and rhythm

Dr. Moore is supported by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health under award number P50NS053672. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

doi:10.3949/cjfm.90a.23011

were regular with no extra heart sounds or murmurs. She had no pain on palpation of her abdomen, and there was no organomegaly.

Laboratory test results

Notable results of blood testing as part of the routine examination were as follows:

- White blood cell count $3.7 \times 10^9/L$ (reference range 4.5–10.8)
- Hemoglobin 13 g/dL (12.3–15.3)
- Hematocrit 39% (38–48)
- Mean corpuscular volume 90 fL (80–100)
- Platelet count $277 \times 10^9/L$ (130–400)
- Alkaline phosphatase 58 U/L (40–129)
- Aspartate aminotransferase (AST) 213 U/L (0–32)
- Alanine aminotransferase (ALT) 120 U/L (0–33)
- Total bilirubin 0.8 mg/dL (0.1–1.2)
- Gamma-glutamyl transferase 91 U/L (28–100)
- Lipase 14 U/L (5–36)
- Right-upper-quadrant ultrasonography: normal-appearing liver.

DIFFERENTIAL DIAGNOSIS

1 Which of the following initial considerations might explain this patient's elevated aminotransferase levels?

- Alcohol use
- Nonalcoholic fatty liver disease (NAFLD)
- Autoimmune hepatitis
- Viral hepatitis

Alcohol-related liver disease

Both AST and ALT can be elevated in alcoholic liver disease, although levels are often less than 300 U/L and rarely exceed 500 U/L.¹ The ratio of serum AST to ALT (the De Ritis ratio) can help differentiate var-

ious causes of liver disease.^{2,3} The ratio in patients with alcoholic liver disease, ranging from cirrhosis to alcoholic hepatitis (which results from chronic, heavy consumption of alcohol), is typically greater than 1.5.¹ The increase in AST relative to ALT with heavy alcohol users is attributed to both of the following:

- Vitamin B6 depletion, which reduces activity of ALT to a greater extent than that of AST
- Mitochondrial damage resulting from alcohol and leading to release of AST.²

Our patient's AST was higher than her ALT, but she denied alcohol use, and her gamma-glutamyl transferase, typically elevated in alcohol-related liver disease, was normal.² Unless she was drinking surreptitiously, alcohol-related liver disease is unlikely to explain her aminotransferase elevations.

Nonalcoholic fatty liver disease

NAFLD is increasingly common, reflecting the rising prevalence of obesity. In patients with obesity, excess adipose tissue is deposited in the liver, leading to oxidation of fatty acids, subsequent inflammation (non-alcoholic steatohepatitis), and eventually cirrhosis in some patients.⁴ Patients who have obesity with other features of metabolic syndrome such as type 2 diabetes or dyslipidemia are at risk for this condition.⁴ In patients with NAFLD, AST and ALT can be normal or elevated to a mild to moderate degree. The AST-ALT ratio is commonly less than 1 but can increase to greater than 1 in the presence of advanced fibrosis.⁵ Our patient had no risk factors for NAFLD such as obesity, diabetes, or hyperlipidemia.

Autoimmune hepatitis

Autoimmune hepatitis, caused by an unregulated immunologic attack on hepatocytes, can present as acute liver failure or chronic indolent disease.⁶ The condition has a predilection toward females and can occur at any age.⁶ At one end of the spectrum, patients can be asymptomatic with mild elevation in aminotransferases (< 5 times the upper limit of normal).⁶ At the other end of the spectrum, patients can present with acute liver failure, with aminotransferases reaching levels greater than 1,000 U/L.⁷

Autoimmune hepatitis is associated with several other autoimmune conditions, including Sjögren syndrome, which this patient had.⁸ It should remain in the differential diagnosis. Immunoglobulin G (IgG) levels and anti-smooth muscle antibody titers can help diagnose autoimmune hepatitis if 2 of 3 of the following features are present:

- ALT greater than 5 times the upper limit of normal
- IgG greater than 2 times the upper limit of normal, or positive anti-smooth muscle antibody titer
- Moderate to severe interface hepatitis (ie, inflammation of the parenchyma near the portal tracts) seen on histology.⁹

Viral hepatitis

Viral hepatitis should be considered as a possible cause of aminotransferase elevation because of the patient's recent travel to Asia, where hepatitis B is the most common viral cause of hepatitis.¹⁰ Hepatitis A and C can also cause hepatocellular injury. In acute viral hepatitis, aminotransferases can rise to several thousand units per liter,¹¹ while in chronic hepatitis C, aminotransferases may increase to a milder degree or even be normal.¹² Our patient had recently experienced an episode of right-upper-quadrant abdominal pain, associated with nausea, which can be a symptom of acute viral hepatitis.

Given her recent travel to Malaysia, the patient should undergo testing for hepatitis viruses as follows:

- For **hepatitis A**, the screening test is the anti-hepatitis A IgM antibody test¹³
- For **hepatitis B**, surface antigen denotes active infection, whereas surface antibody corresponds with cured infection or prior immunization¹⁴; anti-core IgM, which is positive in active infection, marks the window phase when the surface antigen is no longer present but the surface antibody has not yet developed¹⁴
- For **hepatitis C**, screening is done by obtaining the hepatitis C antibody, followed by hepatitis C virus RNA if positive.¹⁵

FURTHER TESTING

The patient was referred to the hepatology clinic. She remained symptom-free, but her laboratory test abnormalities persisted. An evaluation for causes of liver disease was obtained, with the following results:

- Alkaline phosphatase 63 U/L (35–104)
- AST 245 U/L (0–32)
- ALT 141 U/L (0–33)
- Total bilirubin 0.4 mg/dL (< 1.2)
- Alpha-1 antitrypsin 118 mg/dL (90–200)
- Antinuclear antibody greater than 1:2,560 (< 1:40; diffuse cytoplasmic pattern)
- Antimitochondrial antibody negative
- Anti-smooth muscle antibody negative
- IgG 2,000 mg/dL (700–1,600)
- Hepatitis A IgM nonreactive
- Hepatitis B core antibody nonreactive

- Hepatitis B surface antigen nonreactive
- Hepatitis C antibody nonreactive.

In view of her high-titer antinuclear antibody and elevated IgG level, she underwent liver biopsy to evaluate for autoimmune hepatitis. The biopsy showed normal hepatic parenchyma.

■ NEXT STEPS: CONSIDER NONHEPATIC PROCESSES

At the follow-up visit to discuss her liver biopsy results, the patient remained asymptomatic, but her aminotransferase levels were still elevated. Given the absence of any significant findings on liver biopsy, nonhepatic sources of aminotransferase elevation were considered.

2 Which nonhepatic processes could cause her elevated aminotransferases?

- Myocardial infarction
- Myopathy from medications, inflammation, or thyroid disorders
- Muscular dystrophy such as adult myotonic dystrophy
- Hemolysis

The possibility that elevations in aminotransferases reflect a disorder outside the liver should be considered routinely in the differential diagnosis. Nonhepatic causes of AST-dominant aminotransferase elevation include myositis,¹⁶ strenuous exercise,¹⁶ myocardial infarction,¹⁷ hemolysis,¹⁸ renal infarction,¹⁹ and pulmonary embolism.²⁰ AST and ALT are enzymes. AST catalyzes the reversible transfer of an amino group from aspartate to alpha-ketoglutarate to create oxaloacetate, and ALT catalyzes an amino group from alanine to alpha-ketoglutarate to create pyruvate. Glutamate is a byproduct of these processes.²¹ Both AST and ALT serve as metabolic links between carbohydrate and protein metabolism and are involved in aerobic glycolysis.² Because these enzymes are abundant in hepatocytes, they are regarded as “liver enzymes,” but AST and ALT are found in extrahepatic tissues, including the heart, skeletal muscle, kidney, and red blood cells.²²

Myocardial infarction

In myocardial infarction, myocytes die and release their contents, including troponin, a marker used to diagnose acute coronary syndrome.²³ While undergoing necrosis, cardiac myocytes also transiently release AST and, to a lesser extent, ALT.¹⁷ The patient in our case did not have cardiovascular symptoms, so myocardial infarction is unlikely to be implicated in her aminotransferase elevation.

Myopathy

Myopathy, or muscular disease, can result from inflammation, adverse drug reactions, or thyroid disease, among other causes.²⁴ Myositis, or inflammation of the muscle, often leads to weakness.²⁴ Types of myositis include dermatomyositis and immune-mediated necrotizing myopathy (IMNM).²⁴ Dermatomyositis can cause muscle weakness with characteristic rashes, and IMNM often causes severe proximal weakness.^{16,24}

Regardless of the type of myopathy or myositis, levels of creatine kinase (CK) and aldolase rise when myocytes are damaged.²⁴ Aminotransferases, normal constituents of skeletal myocytes, are also released, with AST superseding ALT.²⁵ Acute muscle injury usually causes AST-ALT ratios close to or greater than 4, whereas in chronic myopathies including myositis the elevation of AST and ALT may be more symmetrical because of the shorter half-life of AST.²⁵ Of note, aldolase is not specific to myocytes; as a component of the glycolytic pathway, it is present in significant amounts in hepatocytes. Thus, serum aldolase elevations do not necessarily indicate muscle damage.

Some medications cause myopathy by altering mitochondria or myofibrillar proteins and generate an immune response or change the balance of electrolytes (eg, hypokalemia, hyperkalemia, or hypermagnesemia).²⁶

In patients with significant hypothyroidism, myopathy is related to alterations in glycogenolytic and oxidative metabolism or changes in the contractile proteins; CK and other muscle enzyme elevations are common.²⁷

Our patient did not initially complain of muscle weakness. Myopathy related to omeprazole (which the patient took), although described in the literature, is rare,²⁸ and she did not exhibit signs or symptoms of thyroid disease. Still, given her AST-predominant aminotransferase elevation, subclinical myopathy should be investigated.

Muscular dystrophy

Muscular dystrophies cause progressive weakness and a loss of muscle mass. As with myopathies, muscle damage from dystrophy can result in the release of ALT and AST.²⁹ Myotonic dystrophy is the most common dystrophy seen in adults and is characterized by myopathy and variable myalgias and myotonia, or the inability to relax muscles. Our patient did not exhibit these features.

Hemolysis

AST and ALT normally reside in red blood cells.²² When these cells undergo lysis for any reason, the

result is aminotransferase elevation, with AST being predominant.¹⁸ Our patient had no signs or symptoms of anemia on presentation.

■ RHEUMATOLOGY REFERRAL

Despite the patient's lack of symptoms of IMNM and her negative liver biopsy, her aminotransferase elevations required further investigation. The results of CK testing showed an elevation of 5,857 U/L (26–192). High levels of CK are a specific marker for muscle damage, and aldolase and lactate dehydrogenase can also be elevated due to injury outside the muscle.³⁰ Given the patient's elevated CK level, she was referred for rheumatologic evaluation. By the time of her evaluation, she had developed bilateral proximal arm weakness and, later, proximal leg weakness.

On rheumatology evaluation, electromyography and nerve conduction testing were consistent with a mildly active diffuse myopathic process. Left quadriceps biopsy study showed scattered muscle fibers undergoing necrosis or regeneration, and immunofluorescence testing demonstrated myosin heavy chain class I isoforms following the pattern of myonecrosis and regeneration.

■ SUSPECTED DIAGNOSIS: IMMUNE-MEDIATED NECROTIZING MYOPATHY

3 What features can be associated with IMNM?

- Muscle weakness
- Interstitial lung disease
- Malignancy
- Skin findings

IMNM is characterized by severe proximal muscle weakness and myofiber necrosis with minimal inflammatory cell infiltrate; proximal muscle weakness is the main clinical feature.³¹ There are 3 subtypes, and patients can be antibody-negative or, in 10% of cases, can have 1 of 2 antibodies: anti-signal recognition particle (SRP) or anti-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR).^{30–33}

Interstitial lung disease is associated with anti-SRP myositis in 10% to 20% of patients and with anti-HMGCR myositis in 5% of patients.^{31–34} In these 2 subtypes of IMNM, skin and extramuscular manifestations are uncommon, occurring in fewer than 10% of patients.^{31–34}

Of the 3 subtypes of IMNM, antibody-negative IMNM has the strongest association with cancer.³⁵ Other inflammatory myopathies, most notably der-

matomyositis, also have strong associations with malignancy, particularly in older individuals.³⁶ In comparison, anti-HMGCR IMNM has a weak association with cancer but a strong association with the use of statins, and anti-SRP IMNM has no association with cancers.³⁵

The diagnostic workup for CK elevation with suspected inflammatory myopathy includes electromyography, select immune serologic testing, careful skin examination, consideration to assess for interstitial lung disease with non-contrast computed tomography of the chest, and muscle biopsy of clinically affected muscle.³³ In patients with immune-mediated myopathy, those with IMNM often have higher CK levels. Muscle enzyme elevation can precede the development of weakness.³³ There are several causes of asymptomatic “CK-emia,” including endocrine disturbances, electrolyte abnormalities, strenuous exercise, and medications.³⁷ Unexplained CK-emia is not uncommon. Electromyography can also assist in ensuring that a patient has a myopathy rather than a neuropathy.

4 What are the next steps in the evaluation?

- Steroid therapy
- Methotrexate therapy
- Computed tomography and cancer screening
- Test for anti-HMGCR

Oral corticosteroids can be given for mild to moderate proximal weakness, starting with prednisone 1 mg/kg/day. If symptoms are severe, as when weakness is debilitating and interferes with quality of life, intravenous steroids can be given for 3 to 5 days.³³

Methotrexate is typically started after several months of steroid therapy. (Many rheumatologists and neuromuscular neurologists initiate therapy with several drugs from the outset—in an effort to limit the use of high-dose corticosteroids, as high doses are often required to control myositis—especially if used as monotherapy.) Intravenous immunoglobulin in high doses or rituximab can be given for severe or refractory disease and may need to be continued for 2 years after disease control is achieved. Concurrently, oral corticosteroids should be weaned to the clinical minimally effective dose.³²

Computed tomography in cancer screening

IMNM can manifest as a paraneoplastic condition.³³ There are no evidence-based guidelines regarding cancer screening, but computed tomography of the chest, abdomen, and pelvis and age-appropriate cancer

screenings are recommended for patients with INMN to rule out malignancy.³³ If the patient has pulmonary symptoms, pulmonary function testing and high-resolution computed tomography can elucidate whether there is concomitant interstitial lung disease.³³ Computed tomography of the chest, abdomen, and pelvis in our patient demonstrated no concerning lesions.

Anti-HMGCR antibodies

INMN can result from statin use, a possibility that can be confirmed by testing for serum anti-HMGCR antibodies. About 89% of patients over age 50 with this antibody present have been exposed to statins, but patients can form antibodies without a history of statin use.³⁸ Our patient had never been prescribed statins, and her antibody level was nondetectable.

PATIENT OUTCOME

Our patient received both methotrexate and prednisone. She was tapered off prednisone after 3

years and was transitioned to monotherapy with mycophenolate.³² Her AST and ALT levels downtrended. INMN has a worse prognosis than other types of myopathy. After examination of her chart at the time of this review, she was found to have resumed her medications, and her AST and ALT were still mildly elevated, although she was still asymptomatic.

TAKE-HOME POINTS

- Elevated AST and ALT can be a marker of damage to tissues other than liver, particularly muscle, and especially when AST is higher than ALT.
- INMN can cause muscle enzyme elevations before the onset of recognized muscle weakness. ■

DISCLOSURES

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

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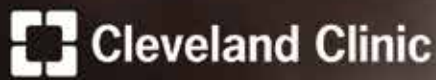
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COVID-19: A management update

ABSTRACT

The management of COVID-19 has evolved through the course of the pandemic to now include options for outpatients, inpatients with life-threatening critical illness, and everyone in between. The goals of therapy include preventing disease progression and preventing worsening disease in those admitted to the hospital, with the hopes of preserving resources and improving patient outcomes. The Infectious Diseases Society of America and the National Institutes of Health have issued guidelines on treating COVID-19, which the authors review here.

KEY POINTS

All patients with COVID-19, no matter how mild or severe it is, should self-isolate or be placed in isolation to avoid spreading the disease.

Nirmatrelvir-ritonavir is recommended for outpatients with mild or moderate COVID-19 who are at risk of progressing to serious disease.

Remdesivir can be considered in patients with mild to moderate disease who are at high risk for progression to severe COVID-19, and in hospitalized patients with oxygen saturation less than 94% breathing room air, but not in those who already need mechanical ventilation or extracorporeal membrane oxygenation.

Dexamethasone 6 mg is the standard of care for hospitalized patients with severe or critical COVID-19.

WHAT STARTED AS A SPRINT has become a marathon with no end in sight. At 3 years into the COVID-19 pandemic, the medical community continues to seek answers through research on how to best manage this disease in its spectrum of presentations, and how to translate the answers into evidence-based guidelines. Numerous drugs have been used or considered for use, and as fast as the virus mutated, so did the efficacy and safety of these drugs, as evidenced in trial data.

Treatment recommendations have rapidly evolved and depend on the patient's medical history, healthcare setting, severity of disease, and other variables. In March 2020, the Infectious Diseases Society of America (IDSA) assembled a multidisciplinary panel to review evidence and make continuing recommendations about treating and managing COVID-19.¹ The National Institutes of Health also issued its own guidelines, which are similar but include recommendations for special populations such as those with preexisting medical conditions (including cancer), different age groups, and ethnic groups.²

To date, the IDSA has made 32 recommendations regarding treating COVID-19 (Table 1).¹ Many of the recommendations are *against* using treatments that don't work, such as hydroxychloroquine. Below, we outline the evidence and recommendations in favor of those that do.

■ INFECTION CONTROL FOR ALL

The estimated incubation period for COVID-19 is up to 14 days, and the virus is transmissible 2 to 3 days before symptoms start—thus the need for masking and social distancing during outbreaks. Isolation is necessary for all patients with COVID-19.

TABLE 1
Treating COVID-19: 32 recommendations from the Infectious Diseases Society of America

Recommended	Not recommended
Dexamethasone for hospitalized critically ill patients	Hydroxychloroquine
Dexamethasone for hospitalized patients with severe but noncritical COVID-19	Hydroxychloroquine plus azithromycin for hospitalized patients with COVID-19
Tocilizumab for hospitalized adults with progressive severe or critical COVID-19 who have elevated markers of systemic inflammation	Hydroxychloroquine for patients exposed to COVID-19
Sarilumab for patients who would qualify for tocilizumab, if tocilizumab is not available	Lopinavir-ritonavir for patients exposed to COVID-19
Convalescent plasma for ambulatory patients with mild to moderate COVID-19 at high risk of progressing to severe disease who have no other treatment options, within 8 days of symptom onset	Lopinavir-ritonavir for ambulatory patients with mild to moderate COVID-19
Remdesivir for patients with mild to moderate COVID-19 within 7 days of symptom onset at high risk of progressing to severe disease	Lopinavir-ritonavir for hospitalized patients
Remdesivir for 5 days rather than 10 days for patients on supplemental oxygen but not on mechanical ventilation or extracorporeal mechanical ventilation	Glucocorticoids for hospitalized patients with mild to moderate COVID-19 without hypoxemia requiring supplemental oxygen
Remdesivir for hospitalized patients with severe COVID-19	Inhaled corticosteroids for ambulatory patients with mild to moderate COVID-19
Baricitinib with corticosteroids for hospitalized adults with severe COVID-19	Convalescent plasma for hospitalized immunocompetent patients
Baricitinib with remdesivir for hospitalized patients with severe COVID-19 who cannot receive a corticosteroid	Routine use of convalescent plasma for hospitalized immunocompromised patients
Tofacitinib for hospitalized adults with severe COVID-19 but not on noninvasive or invasive mechanical ventilation	Remdesivir for those on mechanical ventilation, extracorporeal membrane oxygenation, or both
Fluvoxamine (but only in a clinical trial)	Famotidine for ambulatory patients with mild to moderate COVID-19
Nirmatrelvir-ritonavir within 5 days of symptom onset in ambulatory patients with mild to moderate COVID-19 at high risk of progressing to severe disease	Famotidine for hospitalized patients with severe COVID-19
Molnupiravir within 5 days of symptom onset in ambulatory adults with mild to moderate COVID-19 at high risk of progressing	Ivermectin for hospitalized patients
	Ivermectin for ambulatory patients
	Colchicine for hospitalized patients
	Colchicine for ambulatory patients
	Anakinra for hospitalized patients with severe COVID-19

Based on information in reference 1.

Most patients experience fever, cough, and shortness of breath.¹⁻³ Like those of many other viral illnesses, these symptoms are nonspecific, and some patients experience atypical symptoms, posing diagnostic challenges.^{2,4,5}

While the numbers have gone up and down,⁶ as the pandemic grinds through its third year, COVID-19 was responsible for more than 15,000 hospital admissions in the United States in the week of August 13 to August 19, 2023, and for 2.0% of deaths—and these

numbers are creeping up at the time of this writing.⁷ We will need to continue to discover and study the best therapies to mitigate the effects of the pandemic for the foreseeable future.

■ TREATMENTS FOR OUTPATIENTS

Although outpatients with COVID-19 generally have milder disease than those admitted to the hospital, some have risk factors for progressing to severe disease

(Table 2).² It is this group for whom drug treatment is indicated.

Monoclonal antibodies are not currently available

SARS-CoV-2, the virus that causes COVID-19, is a ball studded with a “spike” protein, by which it attaches to and merges with the host cell.⁸ Early in the pandemic, monoclonal antibodies that target the spike protein were shown to have clinical benefits in treating SARS-CoV-2 infection, and the IDSA recommended them for nonhospitalized patients who had mild to moderate COVID-19 but were at high risk of progression to severe disease or death.¹ Four products received emergency use authorization from the US Food and Drug Administration to treat adult outpatients with mild to moderate COVID-19: bamlanivimab-etesevimab, casirivimab-imdevimab, sotrovimab, and bebtelovimab.^{1,2}

However, the anticipated activity of the different available antibodies varies dramatically depending on the currently circulating COVID-19 variant. The previously authorized antibodies were not expected to be effective against omicron variants of the virus and therefore are not currently authorized for use.²

Outpatient antiviral therapies

Even if the virus has attached itself to the host cell and has gotten in, all is not lost. We can still try to prevent it from replicating and thereby prevent an infection from progressing to more severe disease that could necessitate hospitalization and cause death in patients at high risk. Safe and effective oral agents that do this could help to reduce ongoing strain on healthcare systems and overwhelmed hospital facilities.

Nirmatrelvir-ritonavir is an oral antiviral agent. Nirmatrelvir is a protease inhibitor that targets 3-chymotrypsin-like cysteine protease, an enzyme the virus needs to replicate, whereas ritonavir boosts the activity of nirmatrelvir by inhibiting its metabolism by cytochrome 3A4.

In the Evaluation of Protease Inhibition for Covid-19 in High-Risk Patients (EPIC-HR) trial,⁹ the largest clinical trial of nirmatrelvir-ritonavir, patients at high risk who were treated within 3 days of symptom onset had an 89% lower risk of progression to severe critical illness compared with those who received placebo, without any evident safety concerns.⁹ The IDSA suggests starting this treatment within 5 days of symptom onset in nonhospitalized patients with mild to moderate COVID-19 at high risk of progression to severe disease.¹

TABLE 2
Risk factors for severe COVID-19 illness

Age > 65, or age > 50 and not vaccinated
Chronic lung disease (chronic obstructive pulmonary disease, asthma, interstitial lung disease, pulmonary hypertension, bronchiectasis)
Cardiovascular disease (heart failure, coronary artery disease, or cardiomyopathy)
Type 2 diabetes
Obesity (body mass index > 30 kg/m ²)
Sickle cell disease
Chronic kidney disease
Primary immunodeficiency or immunocompromised state from solid-organ transplantation
Cancer

Based on information in reference 2.

Of importance: numerous medications have clinically relevant interactions with nirmatrelvir-ritonavir, particularly several antiarrhythmic agents, anticonvulsants, and psychiatric medications. Additionally, it is imperative to adjust the dosing for patients with moderate renal impairment based on the estimated glomerular filtration rate. Also, as seen in observational studies and in EPIC-HR,⁹ symptoms can rebound after a course of nirmatrelvir-ritonavir, although the mechanism and frequency remain unclear.

Molnupiravir, another antiviral agent, is approved for outpatient use based on the results of a large clinical trial in unvaccinated patients who had at least 1 risk factor for severe COVID-19 illness and who could not receive nirmatrelvir-ritonavir, remdesivir, or monoclonal antibodies, in which early treatment (within 5 days of symptom onset) with molnupiravir reduced the risk of hospitalization and death.¹⁰

Nirmatrelvir-ritonavir or molnupiravir should be considered for patients with COVID-19 who are age 65 or older or who are age 12 or older with an underlying condition that increases the risk of severe outcomes of COVID-19. The current recommendations advise against treating patients who have no symptoms or who have symptoms but no high-risk features. There are no recommendations for repeat courses of therapy in patients previously treated with antivirals who experience rebound symptoms.

TABLE 3
Recommended treatment for outpatients with COVID-19

	Asymptomatic or mild with no high-risk features	Mild with high-risk features (see Table 2)	Moderate with high-risk features
Features	None	Fever, cough, change in taste or smell, no difficulty breathing	Symptoms and clinical or radiographic evidence of lower respiratory tract disease Oxygen saturation \geq 94%
Isolation	Yes	Yes	Yes
Treatment	None	Molnupiravir or remdesivir	Molnupiravir or remdesivir

Based on information in reference 1.

Given the risk of rebound illness, particularly with nirmatrelvir-ritonavir, the decision to treat should not be based solely on the goal of hastening recovery. Rather, the focus should be on mitigating the risk of progression to severe disease. Patients and prescribers should have a shared medical decision-making discussion to clearly outline the goals of therapy and the risks before starting.

Patients being treated with antivirals in the outpatient setting (Table 3)¹ still need to isolate themselves to reduce transmission.

■ TREATMENT FOR HOSPITALIZED PATIENTS

While most COVID-19 cases are either asymptomatic or mild, a substantial percentage of patients develop severe respiratory illness requiring hospitalization.¹¹ Indications for treatment vary depending on severity of illness (Table 4).¹

Remdesivir, an antiviral medication

Remdesivir inhibits viral replication by terminating its RNA transcription, and hopes were high that it would help critically ill patients with COVID-19 who had evidence of hypoxemic respiratory failure. However, 4 main trials of remdesivir in patients with moderate to severe disease found no significant benefit compared with the standard of care in terms of in-hospital mortality.¹² Furthermore, a 2021 study found no clinical benefit from remdesivir in hospitalized patients who had had COVID-19 symptoms for more than 7 days and needed oxygen support.¹³ In a more positive direction, in a 2022 trial in patients with COVID-19 spanning the disease spectrum, fewer patients who received remdesivir needed mechanical ventilation compared with those who did not receive the drug.¹⁴

The IDSA recommends that remdesivir be considered in patients with mild to moderate disease who are at high risk of progression to severe COVID-19 and in hospitalized patients with oxygen saturation less than 94% breathing room air, and that it not be considered in those who already need mechanical ventilation or extracorporeal membrane oxygenation.¹ When used in those with severe or critical illness, it should be considered an adjunct therapy, given in addition to glucocorticoids (see below).

Steroids: Dexamethasone 6 mg, the standard of care

COVID-19 is associated with diffuse lung injury through an inflammation-mediated response within the lung parenchyma. It is not the infection itself that causes most of the damage but rather the body's exaggerated reaction to it—the “cytokine storm.”¹⁵ Glucocorticoids have long been used to modulate inflammation, and several studies have investigated their use in hospitalized patients with COVID-19.¹¹

Dexamethasone. The Randomized Evaluation of Covid-19 Therapy (RECOVERY) trial¹¹ established dexamethasone as the standard of care in patients with COVID-19. Patients were assigned to receive either dexamethasone 6 mg daily for 10 days or usual care alone. Overall, the mortality rate at 28 days was significantly lower with dexamethasone. However, no difference was detected in the subgroup of patients who did not need supplemental oxygen at baseline. This led the IDSA to recommend that dexamethasone be used only in patients with a pulse oximeter reading of less than 94% on room air or in those requiring supplemental oxygen.¹¹

Because dexamethasone 6 mg was good, further studies sought to determine if 12 mg would be better. It wasn't. In a trial in patients hospitalized with

TABLE 4

Recommended treatment for hospitalized patients with COVID-19

	Mild or moderate	Severe	Critical	
Features	Symptoms Oxygen saturation ≥ 94%	Oxygen saturation < 94% Respiratory rate ≥ 30 breaths/min Lung infiltrates on chest radiography > 50%	Respiratory failure requiring high-flow nasal cannula or noninvasive mechanical ventilation	Respiratory failure requiring invasive mechanical ventilation or extracorporeal membrane oxygenation
Isolation	Yes	Yes	Yes	Yes
Treatment	Remdesivir	Remdesivir plus dexamethasone	Dexamethasone with or without remdesivir Consider an immune modulator	Dexamethasone plus baricitinib, tofacitinib, or tocilizumab

Based on information in reference 1.

COVID-19 who needed supplemental oxygen, there was no significant difference in clinical outcomes between the dosing groups, confirming the original dose of 6 mg per day.¹⁶ A more recent study looked at the effects of high-dose vs low-dose dexamethasone therapy on all-cause mortality at 60 days, and at the effect of different oxygenation strategies vs standard of care on the need for invasive mechanical ventilation at 28 days.¹⁷ The findings suggest that neither make any significant difference in these outcomes.

Interleukin 6 inhibitors

To curb the immune response to COVID-19, in addition to giving steroids, experts began looking at agents that inhibit interleukin 6 (IL-6), a cytokine produced by macrophages that induces an inflammatory response and is often elevated in patients with COVID-19.¹⁸ One of the attractions of targeting IL-6 is that approved agents already exist that inhibit either the cytokine itself (anakinra, canakinumab, and rilonacept) or its receptor (tocilizumab and sarilumab). Enthusiasm for these agents was high, although it was unclear whether IL-6 inhibitors were safe in COVID-19, as they make patients more vulnerable to infection.

Several studies of IL-6 inhibitors in hospitalized patients with COVID-19 had positive results and shaped practice: in-hospital mortality was reduced, as was the amount of organ support required.¹⁹ As

use in practice continued, further studies looked at another outcome, ie, the patient's clinical status by day 28 (ranging from discharged to dead), with death as a secondary outcome. Unfortunately, there was minimal difference in either outcome between those receiving tocilizumab vs placebo.^{19,20} Other trials similarly found no profound effect on the mortality rate.

However, in the RECOVERY trial, tocilizumab use was associated with a lower risk of progression to either mechanical ventilation or death (35% vs 42%).²¹ This was further supported by a meta-analysis of 27 randomized controlled trials that evaluated IL-6 inhibitors (usually tocilizumab) and found that their use was associated with a lower rate of 28-day all-cause mortality.²²

Regarding sarilumab, the largest trial of this agent to date included more than 400 patients with COVID-19 who needed supplemental oxygen or intensive care unit admission. This trial found no difference in clinical outcomes with sarilumab vs placebo, and sarilumab is recommended only if tocilizumab is unavailable.²³

In summary, for hospitalized adults with progressive severe COVID-19 (with low oxygen levels requiring supplemental oxygen) or critical illness (requiring mechanical ventilation or in multiorgan failure) who have elevated markers of systemic inflammation, the IDSA suggests giving tocilizumab in addition to the standard of care (ie, steroids) rather than standard of care alone.¹

Janus kinase inhibitors

Baricitinib, an oral selective Janus kinase 1 and 2 inhibitor, is another agent that inhibits the inflammatory response in viral illness.

COV-BARRIER (Study of Baricitinib [LY3009104] in Participants With COVID-19),²⁴ a randomized, double-blind, placebo-controlled trial, analyzed 1,525 hospitalized patients with COVID-19 in 12 countries who had elevations of 1 or more inflammatory biomarkers. The patients were randomized 1-to-1 to receive a once-daily oral dose of baricitinib 4 mg or placebo in addition to the local standard of care for up to 14 days or until hospital discharge. Standard of care included systemic corticosteroids such as dexamethasone and antivirals such as remdesivir. The trial found no significant reduction in the trajectory of disease progression overall. By day 28, 8% of the patients in the baricitinib group had died compared with 13% in the placebo group, a 38% relative risk reduction. The incidence of serious adverse events, infections, and venous thromboembolic events was similar between the baricitinib group and the placebo group.

In the Adaptive COVID-19 Treatment Trial 2, the combination of baricitinib and remdesivir shortened the time to recovery in hospitalized patients with COVID-19 compared with remdesivir alone. The acceleration to improvement was most pronounced in the patients who were receiving high-flow oxygen or noninvasive ventilation. Of note, when analyzed by severity of disease, the median time to recovery in the noninvasive ventilation or high-flow oxygen delivery group who received combination therapy was 10 days, compared with 18 days in the control group (which was receiving remdesivir alone).²⁵

The recommended dose of baricitinib is 4 mg once a day (adjusted for renal impairment) for up to 14 days or until discharge from the hospital.²⁵

Tofacitinib is another agent of interest in the same class. In the STOP-COVID trial (Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19),²⁶ tofacitinib was associated with a decreased risk of respiratory failure and death. Approximately 80% of participants in each treatment group also received corticosteroids, and thus this trial supports that tofacitinib plus steroids is effective in improving outcomes in hospitalized patients with COVID-19.²⁶

Baricitinib is favored over tofacitinib because it has more data to support its use. However, tofacitinib can be considered if baricitinib is unavailable.²⁶ The IDSA recommends that if tofacitinib is used, it should be in addition to the standard of care for patients hospitalized for severe COVID-19, and that patients should receive at least prophylactic doses of anticoagulants while in the hospital in view of the risk of venous thromboembolism with tofacitinib.¹ Moreover, patients who receive Janus kinase inhibitors should not receive tocilizumab or other immunomodulators, owing to inadequate evidence for combined treatment.^{1,2}

In summary, baricitinib and tofacitinib appear to provide the most benefit in those with severe COVID-19 on supplemental or high-flow oxygen support.¹

LONG COVID

The COVID-19 pandemic is the biggest public health crisis of the 21st century. In addition to the acute symptoms of active illness, the long-term health complications of COVID-19 pose significant challenges.²⁷

The National Institute for Health and Care Excellence defined post-COVID-19 syndrome (“long COVID”) as “signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis.”²⁸ Up to half—or maybe more—of all COVID-19 survivors experience long COVID symptoms after initial recovery from acute infection. These symptoms include but are not limited to fatigue, muscle pain, palpitations, cognitive impairment, dyspnea, anxiety, chest pain, and arthralgia. About one third of these patients experience these lingering symptoms for about 2 months after their initial infection.²⁹

Currently, no treatments have been shown to prevent the development of or decrease post-COVID-19 syndrome, although trials are ongoing.³⁰ ■

DISCLOSURES

Dr. Sacha has disclosed consulting for Wolters-Kluwer. 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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The new GFR equations: How will eliminating the race coefficient affect Black patients?

LABORATORIES HAVE BEEN USING new (2021) equations to estimate the glomerular filtration rate (GFR). Notably, the new equations differ from earlier ones in that they do not include a coefficient for race. The change was motivated by a desire to reduce racial inequities and improve the health of Black patients. As a result, Black patients are getting lower estimated GFRs than they did with preexisting equations. But will there be unintended consequences? Here, we discuss the history of GFR equations and the potential clinical consequences of the new ones.

HEALTH DISPARITIES IN BLACK AMERICANS

About 37 million Americans—more than 1 in 7—have chronic kidney disease, and a disproportionate number are Black.¹ In fact, Black Americans are almost 4 times more likely to have kidney disease than White Americans.^{1,2}

Some of this disparity can be attributed to the prevalence of *APOL1* genetic variants that confer risk for kidney disease in people of African ancestry.³ *APOL1* risk variants were significantly associated with more severe kidney disease in patients with hypertension-attributed nephropathy, lupus nephritis, sickle cell disease, and human immunodeficiency virus-associated nephropathy.⁴⁻⁷ However, social determinants of health such as economic stability, education, access to food, neighborhood and physical environment, social context, and healthcare systems play a significant and complex role in health outcomes.⁸ For example, Black patients are less likely to have medical insurance, undergo screening, or be referred to a nephrologist before starting dialysis.⁹⁻¹¹

Influenced by America's social justice movement, medical communities are examining how they may be

contributing to healthcare inequities.¹² As a result, the widely accepted equations for estimating the GFR, a key number in assessing kidney function, came under scrutiny because they included race as a categorical variable. In August 2020, the National Kidney Foundation (NKF) and the American Society of Nephrology (ASN) formed a task force to evaluate this issue, and 1 year later, they released their recommendations with a new set of equations that do not include race.¹³

DIRECTLY MEASURING THE GFR: THE GOLD STANDARD, BUT CUMBERSOME

Kidney function is primarily assessed by measuring the rate kidneys can remove solutes from plasma. While *renal clearance* is the net rate of removal by glomerular filtration plus tubular secretion minus tubular reabsorption, the GFR specifically describes the flow of plasma from the glomerulus into the Bowman space per unit of time and is a surrogate of kidney function. In other words, substances freely filtered by the glomerulus that are not absorbed or secreted by the nephron are equal to GFR. Unfortunately, isolating an endogenously produced substance has been elusive, and therefore we have had to use exogenous substances (inulin, isotopes) or estimate the GFR using endogenous substances (creatinine, cystatin).

The GFR can be directly measured by injecting exogenous substances:

Inulin, a fructose polysaccharide discovered more than 200 years ago in many plant species, is in many ways the ideal marker for directly measuring GFR.¹⁴ Infused into the circulation, it is freely filtered by the glomerulus, is not reabsorbed or secreted by the tubules, and is therefore completely excreted. It achieves a steady plasma concentration and is neither

doi:10.3949/cjcm.90a.22061

TABLE 1
Non-GFR determinants of creatinine and cystatin C

Increase serum creatinine concentration

Muscle mass
 Protein intake
 Rhabdomyolysis

Increase serum cystatin C

Male
 Older age
 Obesity
 Smoking
 Hyperthyroidism (hypothyroidism decreases it)
 Glucocorticoid therapy
 Inflammatory markers (C-reactive protein)
 Malignancy

Consider ordering serum cystatin C GFR

In patients at the extremes of muscle mass or cachexia
 When the serum creatinine concentration is elevated without urinary or radiologic evidence of kidney damage
 When a more precise GFR measurement will change treatment decisions

GFR = glomerular filtration rate

produced nor metabolized by the kidneys. Thanks to these properties, inulin’s renal clearance is equal to its GFR. Unfortunately, measuring the inulin GFR is time-intensive and technically challenging, requiring constant infusion of the exogenous substance with frequent urine and serum collections.

Other exogenous substances, including iothalamate compounds containing radioactive (“hot”) or nonradioactive (“cold”) isotopes of iodine, are now considered the gold-standard markers for measuring GFR. Nonradioactive iothalamate is preferred in order to avoid radiation exposure and regulations associated with proper handling and storage of the radioactive material. However, iothalamate GFR measurement is costly, time-consuming, not widely available, and often limited to research.

CREATININE AND CYSTATIN C ARE ENDOGENOUS MARKERS

Creatinine

Creatinine, an endogenous waste product of the breakdown of creatine, is widely used as a marker of kidney function. We can measure 24-hour creatinine clear-

ance in the urine or estimate the GFR using a variety of equations based on the serum concentration of creatinine (see below), avoiding the intensive process of measuring GFR directly. Like inulin, creatinine is freely filtered, but unlike inulin, it is also secreted by the tubules, so creatinine clearance is higher than the actual GFR. The 24-hour urine creatinine clearance is still widely used as an estimate of GFR, but the results may be 10% to 20% higher than the true GFR because of active creatinine secretion by the tubules.¹⁵

Moreover, several other processes affect serum and urine creatinine levels (**Table 1**). These include generation of creatinine, kidney tubular secretion, and reabsorption and vary from person to person, depending on muscle mass, exercise, diet, hydration, and other factors.¹⁶ Additionally, creatinine secretion is increased in advanced chronic kidney disease, further limiting its accuracy as a filtration marker.^{17,18}

Black patients on average have higher serum creatinine concentrations at the same measured GFRs compared with non-Black patients.^{19,20} It has been speculated that this difference is due to differences in biometric variables such as muscle mass. However, Hsu et al²¹ studied this and found that even after controlling for biometric variables such as height, weight, body mass index, body surface area, fat-free mass, and urinary creatinine excretion, Black patients still had 8.7% higher creatinine concentrations than non-Black patients. This suggested that additional non-GFR determinants have not been accounted for, such as the gastrointestinal creatinine excretion or the rate of creatinine generation per unit of lean muscle.

Cystatin C

Cystatin C, an endogenous protein produced at a constant rate by all nucleated cells, can be used as an alternative or adjunct marker.²² It is freely filtered by the glomerulus and is neither reabsorbed nor secreted by the tubules. We used to think that its serum concentration, unlike that of creatinine, was not affected by sex, age, race, muscle mass, or protein intake.²²

However, that may not be entirely true. Knight et al,²³ in a study with 8,058 participants, found that older age, male sex, greater weight and height, current cigarette smoking, and higher serum C-reactive protein levels were independently associated with higher cystatin C levels. Manetti et al,²⁴ in a small study, found that cystatin C levels were higher in patients with hyperthyroidism and lower in patients with hypothyroidism (**Table 1**). Lack of availability, high cost of testing, and lack of insurance reimbursement have limited its use.

SERUM CREATININE-BASED AND CYSTATIN C-BASED EQUATIONS

Serum creatinine has a nonlinear relationship to GFR (Figure 1). A small increase of serum creatinine at higher levels of GFR represents a larger decline in kidney function while a larger increase in serum creatinine at lower levels of GFR represents smaller declines in kidney function. Measuring serum creatinine concentration levels in isolation without consideration for other non-GFR determinants such as age, sex, weight, and race to estimate body habitus would be a very crude measure of estimated GFR. Therefore, researchers over the decades have been trying to develop equations that would be able to estimate GFR without having to obtain a burdensome 24-hour urine collection or inject an exogenous substance to better refine this relationship.

The 1976 Cockcroft-Gault equation for creatinine clearance

Published in 1976, the Cockcroft-Gault equation was derived from a study in 249 men whose race or ethnicity was not reported.²⁵ Using simple arithmetic, it estimates creatinine clearance (not GFR) based on age, lean body weight, and serum creatinine concentration. It is not adjusted for body surface area, and it presumes that women have 15% less muscle mass. Therefore, for women, the results are multiplied by 0.85. The Cockcroft-Gault equation remained in clinical use until newer equations were released and is still used in drug development and dosing.

The 1999 Modification of Diet in Renal Disease equation

The Modification of Diet in Renal Disease (MDRD) study²⁶ assessed the impact of protein restriction and blood pressure control on the progression of chronic kidney disease. Unfortunately, the benefit of a low-protein diet was small, but the study served as the data source for the development of the future set of GFR equations. Patients had serial blood samples, 24-hour urine collections, and ¹²⁵I-iothalamate testing to accurately measure the GFR. The post hoc analysis included 1,628 patients from the United States (80.1% White, 12.1% Black, 39.6% female, 6% patients with diabetes, mean age 51, mean weight 79.6 kg, and mean body surface area 1.91 m²).¹⁹ One-third of the population was randomized to be the training sample, while the remaining group was the validation sample.

The MDRD investigators developed several equations to estimate the GFR, including a 6-variable equation

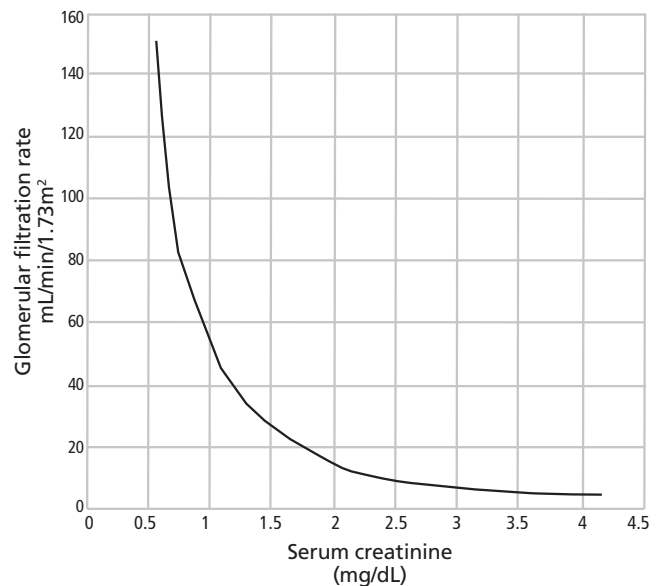


Figure 1. Nonlinear relationship of serum creatinine to the glomerular filtration rate.

based on urinary laboratory values, and a 7-variable equation based on expanded serum laboratory values. However, a simplified 4-variable equation based on age, sex, race (Black or non-Black), and serum creatinine concentration became the most widely used.¹⁹

Criticisms of the MDRD equations included poor precision (variability between multiple measurements), poor performance if the GFR is higher than 60 mL/min/1.73 m² (since the parent study enrolled only patients who already had chronic kidney disease), and underrepresentation of Black, Asian, and Latino populations.

The 2009 and 2012 Chronic Kidney Disease Epidemiology Collaboration equations

Results of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study—funded by the National Institute of Diabetes and Digestive and Kidney Disease to develop a new equation to improve shortcomings of the MDRD equation—were published in 2009.²⁰ Investigators used 10 studies involving 8,254 patients from North America and Europe and randomized them into an equation-development group (n = 5,504) and an internal validation group (n = 2,750). Another 3,896 patients in 16 other studies served as an external validation group. All patients underwent iothalamate GFR measurement. In the development group, the mean age was 47, 43% were women, 32% were Black, 5% were Hispanic, 1% were Asian, and the mean GFR was 68 mL/min/1.73 m².²⁰

The 2009 CKD-EPI equation performed better than the MDRD equation in all GFR ranges (including those higher than 60 mL/min/1.73 m², though precision was still limited at this range), and it was recommended as a replacement for the MDRD equation. Similar to the MDRD equation, the 2009 CKD-EPI creatinine-based equation included age, sex, and a race coefficient (Black or non-Black).²⁰

In 2012, the CKD-EPI investigators published an equation based on cystatin C alone and another one based on cystatin C and creatinine combined.²⁷ Although 40% of the 5,352 participants in the development and internal validation cohort were Black, only 3% were Black in the external validation group. The cystatin C equation did not include a race coefficient, although the combined equation did, and the combined equation outperformed the CKD-EPI equations that used either cystatin C or creatinine alone.²⁷

Major nephrology societies supported the use of the CKD-EPI equations,²⁸ but because few laboratories could measure cystatin C, the equations incorporating this marker were infrequently used.

The 2021 CKD-EPI creatinine equations remove the race coefficient

America's social justice movement led the nephrology community to reexamine the universal use of estimated GFR equations incorporating a race coefficient. The leading US organizations for patient advocacy (the NKF) and healthcare professionals (the ASN) partnered to create a task force to address this issue. The NKF-ASN task force undertook an exhaustive review of the medical literature and expert and patient-advocacy testimony and concluded that race-based equations should be replaced.¹³ Included in the review of equations by the NKF-ASN task force were new equations developed by the CKD-EPI workgroup that did not include race coefficients.²⁹

The 2021 CKD-EPI equations were developed using methods similar to those of the 2009 and 2012 CKD-EPI equations and included versions based on creatinine alone, cystatin C alone, and combined creatinine and cystatin C. Black participants made up 31.5% of the development group for the creatinine-based equation and 39.7% of the development group for the combined creatinine-cystatin C equation, which was comparable to their representation in the 2009-2012 CKD-EPI study (40%). Black patients also accounted for 14.3% of the external validation group for the creatinine equation, whereas in the 2009 and 2012 studies they accounted for only 3%.^{20,27,29}

The NKF-ASN task force endorsed the adoption of the 2021 CKD-EPI equations and encouraged clinicians to use the combined creatinine-cystatin C equation.^{28,29} Many laboratories have incorporated the new equations and report the estimated GFR based on them, and on-line calculators are readily available (https://www.kidney.org/professionals/kdoqi/gfr_calculator).

CLINICAL CONSEQUENCES

The CKD-EPI 2021 equations may have clinical consequences. For example, many drugs that are excreted by the kidneys (eg, sodium-glucose transporter 2 inhibitors, metformin, bisphosphonates, and some antibiotics and chemotherapeutic agents) come with warnings that they should be avoided, given in lower doses, or stopped if the GFR is below certain thresholds. What if a patient's GFR results, if calculated by different equations, differ enough to affect their medication recommendations?

Will the change help or hurt Black patients?

The Black population is disproportionately affected by chronic kidney disease.¹ From a population-health perspective, the change to the 2021 CKD-EPI creatinine equation will shift estimated GFR values lower in Black patients, which will increase the prevalence and severity of CKD staging. Inker et al²⁹ reported that compared with direct measurement, the new creatinine-based equation underestimated the GFR in Black patients by a median of 3.6 mL/min/1.73 m², and it overestimated it in non-Black patients by a median of 3.9 mL/min/1.73 m². In contrast, when the race coefficient was omitted from the previous 2009 CKD-EPI creatinine-based equation, it overestimated the GFR for Black patients by 3.7 mL/min/1.73 m² and underestimated it for non-Black patients by 0.5 mL/min/1.73 m².^{20,29}

This shift in estimated GFR has potential benefits for Black patients, including earlier detection and treatment of kidney disease to reduce its progression, earlier referral to nephrologists, and more transplant referrals and listings (**Table 2**). Black patients are more likely than White patients to develop kidney failure but are less likely to be put on transplant waiting lists or receive transplants.^{11,30} The typical threshold for referral for transplant evaluation is an estimated GFR of 20 mL/min/1.73 m² or lower, so with the newer, lower estimated GFRs, Black patients may be referred earlier.

Conversely, there may be unintended negative consequences as a result of "renalism," a term used to describe the therapeutic nihilism that requires

patients suffering with kidney disease to have to wait longer for effective interventions.³¹ More Black patients may be excluded from clinical trials because of a GFR cutoff or a diagnosis of chronic kidney disease or may be excluded as living kidney donors.³² Owing to strict GFR cutoffs, more Black patients may be denied non-kidney solid-organ transplants (lung, heart, intestine, bone marrow) and advanced heart therapies such as ventricular assist devices.

The lowering of GFR in Black patients may make patients ineligible for first-line cancer treatments, antiviral medications, or disease-modifying diabetic drugs such as sodium-glucose cotransporter 2 inhibitors. A retrospective study comparing dosing and eligibility of anticancer drugs in Black patients when comparing estimated GFR equations with and without race reported that 18% of patients would have been given discordant recommendations.³³

Additional concerns include inferior drug therapy due to dose reductions in chemotherapy, antivirals (for influenza, hepatitis C, human immunodeficiency virus), and lifesaving antibiotics. Moreover, inferior enhancement of radiographic images due to avoidance or reduction of intravenous contrast (eg, for computed tomography) or intra-arterial contrast (angiography) may lead to inappropriate therapy, delays in diagnosis, and adverse clinical outcomes. Also, the shift in estimated GFR may lead to a new diagnosis (increase in prevalence) or reclassification to a more advanced stage of chronic kidney disease, causing anxiety, as we have seen in patients in our clinics (Table 2). Contrarily, the new equations overestimate GFR in non-Black patients by a median of 3.9 mL/min/1.73 m².

We suspect that these changes may also have unintended consequences in the non-Black population with respect to nephrology care, drug therapy and dosing, choice of imaging, and eligibility in transplant.

Follow estimated GFR over time

The imprecision of these equations must be considered when interpreting a single creatinine value. We therefore suggest that clinicians follow the general trend in estimated GFR over time.

Precision is measured by the P30—the percent of estimated GFR values that are within 30% of the measured GFR. The 2021 CKD-EPI equations have P30 values of 87% for the creatinine-only equation, 85% for the cystatin C-only equation, and 91% for the creatinine-cystatin C equation.^{22,29} These values are higher than those of the earlier equations (80.6% for the MDRD equation, 84.1% for the CKD-EPI

TABLE 2

Potential patient impacts of the 2021 CKD-EPI equations

Positive impacts

Earlier nephrology referral for Black patients
 Earlier recognition and treatment of chronic kidney disease in Black patients
 Earlier referral for transplant evaluation
 Increased patient trust in the healthcare system

Negative impacts

Exclusion of medications restricted by GFR cutoff (eg, metformin, sodium-glucose cotransporter 2 inhibitors, and some chemotherapy agents)
 Dose reductions of critical medications (eg, antibiotics, antivirals, and some chemotherapy)
 Exclusion from clinical trials or organ donation based on chronic kidney disease, chronic kidney disease stage, or GFR cutoff
 Substandard imaging due to avoidance or reduction of contrast use
 Increased medical insurance, life insurance costs
 Increased patient anxiety from the diagnosis

Neutral or unclear impacts

Reclassification of chronic kidney disease stage
 Changes in estimates of prevalence of chronic kidney disease

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration study;
 GFR = glomerular filtration rate

2009 equation).^{19,20}

Nevertheless, a patient with an estimated GFR of 50 mL/min/1.73 m² could have a measured GFR between 35 and 65 mL/min/1.73 m². With this limited precision, it is possible for these estimated GFR equations to assign patients into an inaccurate stage of chronic kidney disease. In fact, the new equations have only slightly greater than 60% accuracy at assigning chronic kidney disease stage.²⁹ Therefore, several measurements over time should be obtained to better assess the accuracy of GFR. Additional research is needed for better markers to improve the precision and overall assessment of kidney health.

■ TAKE-HOME POINTS

- Recently, calls to reevaluate the basis for using a race coefficient in GFR-estimating questions prompted a reevaluation of GFR estimation.
- Currently, creatinine is the most widely used biomarker to estimate GFR, but serum creatinine levels are influenced by factors other than GFR.

- Over the last several decades, a coefficient for race has been used in GFR equations in an attempt to account for these non-GFR determinants. However, this practice introduces a bias between Black and non-Black patients in GFR estimation.
- The new CKD-EPI 2021 equations were developed without a race coefficient and perform with improved precision compared with previous equations. The NKF-ASN task force called for the immediate implementation of these equations and an increased focus on using cystatin C to assist with GFR estimation.
- The change in these GFR-estimating equations will have important clinical impacts on chronic kidney disease prevalence estimates, access to transplant, and drug dosing for individual patients.

- These creatinine-based and cystatin C-based equations have significant limitations in their precision. We believe that additional research and focus is needed to improve the assessment of kidney function, given the increasing prevalence of kidney disease.³⁴

DISCLOSURES

Dr. Mehdi has disclosed teaching and speaking for AstraZeneca and serving as advisor or review panel participant for Fresenius. Dr. Nakhoul has disclosed consulting for Amgen, ChemoCentryx, GSK, and Otsuka Pharmaceuticals; and teaching and speaking for ChemoCentryx. Dr. Taliercio has disclosed serving as advisor or review panel participant for Otsuka America Pharmaceuticals, GSK, Boehringer Ingelheim. 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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REVIEW

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Cirrhosis: Primary care approaches to screening, immunization, and lifestyle modifications

ABSTRACT

For patients with decompensated cirrhosis, health maintenance is critical to improve survival rates and prevent adverse outcomes. We review the primary care management of cirrhosis and its complications, such as esophageal varices, hepatocellular carcinoma, and chemical or medication exposures. We also highlight specific immunizations and lifestyle modifications to prevent decompensation, and we summarize current screening guidelines.

KEY POINTS

The 2-year mortality rate for decompensated cirrhosis is as high as 26.4%, and the 5-year rate is as high as 85%.

Factors independently associated with cirrhosis include diabetes, alcohol abuse, hepatitis B virus, hepatitis C virus, men who have sex with men, and older age.

Primary care clinicians are often the first to diagnose and manage patients with liver cirrhosis.

CIRRHOSIS IS THE 12TH MOST COMMON cause of death worldwide and the eighth highest cost-to-treat illness worldwide.^{1,2} In the United States, the prevalence of cirrhosis is 0.27%, corresponding to approximately 633,323 adults.³ There are few comprehensive resources available that outline primary care management of patients with liver cirrhosis. Hence, this review discusses management in the primary care setting, screening for complications, immunizations, exposure reduction, and lifestyle modifications in patients with liver cirrhosis.

DIAGNOSIS

Cirrhosis of the liver is both a pathologic and clinical diagnosis. Pathologically, it is defined as the histologic disruption of the architecture of the liver owing to fibrous replacement of normal liver tissue, and leads to portal hypertension and end-stage liver disease that is typically irreversible in advanced stages.^{4,5}

Clinically, a patient is usually diagnosed when presenting with decompensation, or clinical decline, showing evidence of variceal bleeding, renal failure, spontaneous bacterial peritonitis, hepatic encephalopathy, or ascites.⁴ It is essential to recognize and diagnose decompensated cirrhosis early, as it has a high mortality rate without transplant, with a 2-year mortality rate as high as 26.4%, and 5-year mortality as high as 85%.^{3,4}

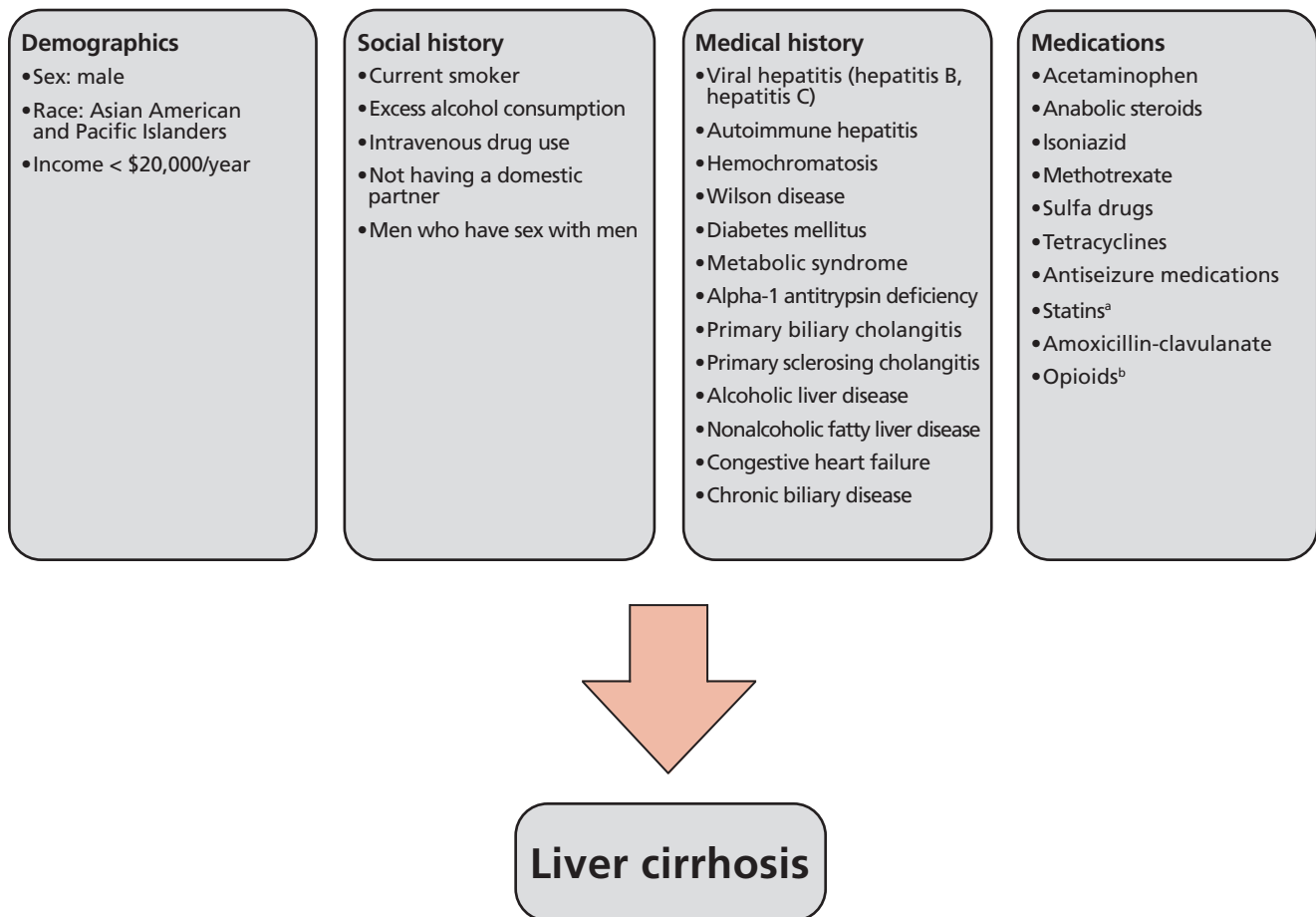


Figure 1. Risk factors for development of liver cirrhosis.

^aNewer studies have suggested possible benefit of statins in patients with cirrhosis.

^bOpioids have been shown to be associated with increased readmission rates in patients with cirrhosis.

Based on information in references 3–6.

■ DIAGNOSTIC TESTING

Cirrhosis is often clinically asymptomatic and insidious in the initial stages. It has been reported that up to 20% of patients with hepatitis C virus infection may develop cirrhosis before clinical signs are present.⁴ As many as 10% of patients with nonalcoholic steatohepatitis may develop cirrhosis with no clinical signs or symptoms.⁴ In asymptomatic patients, incidental detection of elevated aminotransferases or imaging suspicious for hepatic disease should stimulate further workup to determine the likelihood of liver disease.⁵ This includes a thorough history to screen for cirrhosis risk factors, as described in **Figure 1**.^{3–6}

In addition, laboratory tests to evaluate for liver injury should be ordered for patients with a high

suspicion of liver disease.⁵ These tests include a complete blood cell count (platelet count < 150 × 10⁹/L), aspartate aminotransferase, alanine aminotransferase, albumin, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, prothrombin time, and international normalized ratio (INR) (**Table 1**).^{4,5}

Once the presence of liver disease is evident, patients should undergo a complete evaluation to determine disease course and potential etiology, as these are essential prognostically. For instance, patients with hepatitis C virus-induced cirrhosis have a lower annual decompensation rate than those with hepatitis B virus, ie, 4% compared with 10%.⁴ Patients with alcohol-induced liver cirrhosis have higher decompensation rates than patients with other forms of cirrhosis.⁷

TABLE 1
Initial laboratory tests when evaluating for chronic liver disease

Laboratory test	Function	Rationale
Complete blood cell count	Patients with liver disease are more prone to bleeding due to decrease production of liver clotting factors	May manifest as anemia Often decreased platelet levels
Alanine aminotransferase (ALT)/ aspartate aminotransferase (AST)	ALT is an enzyme found in the liver AST is an enzyme found in the liver, heart, muscle, and kidneys	ALT increased during liver injury AST increased in the presence of liver injury Elevated AST is less specific than ALT for liver injury
Albumin	Albumin is a protein made by the liver	Often decreased in chronic liver disease
Alkaline phosphatase	Alkaline phosphatase is an enzyme often produced by bile ducts, also produced by bone	May be normal or elevated in liver disease
Total bilirubin	Bilirubin, a breakdown product of heme, is conjugated by the liver to allow for removal from the body Damage to the liver may result in inability to process bilirubin	May be increased in liver disease
Gamma-glutamyl transferase	An enzyme found primarily in the liver Can be used in elevated alkaline phosphatase to determine if origin is hepatic or bone	May be elevated in liver disease
Prothrombin time (PT)/international normalized ratio (INR)	Measure amount and function of clotting factors	Because clotting factors are produced by the liver, PT and INR may be prolonged in patients with liver disease

Interpreting results of aminotransferase testing

The American College of Gastroenterology recommends that if aminotransferases are elevated during routine testing, additional laboratory testing is required, including hepatitis B surface antigen, hepatitis B core antibody, hepatitis B surface antibody, hepatitis C virus antibodies, and iron studies (Table 2).^{4,6} Because alanine aminotransferase is found in cells other than hepatocytes, testing creatine kinase and determining the ratio of creatine kinase to alanine aminotransferase is important.

Age also plays a key role in the interpretation of elevated aminotransferases. For example, in a young individual with significantly elevated aminotransferases, genetic disorders such as Wilson disease or hemochromatosis should be on the list of differential diagnoses and require additional workup. Furthermore, abdominal ultrasonography, with particular

focus on the right upper quadrant (liver), should also be ordered to rule out an acute or structural disease process.

If the laboratory tests are unremarkable and aminotransferases remain elevated after a period of 3 to 6 months, further investigation with antinuclear antibody and antismooth-muscle antibody, gamma-globulin, ceruloplasmin, and alpha-1 antitrypsin phenotype should be ordered to evaluate for additional causes.⁶

Biopsy and noninvasive testing

The diagnostic test for liver cirrhosis is biopsy.^{4,5} Noninvasive testing modalities to evaluate for liver cirrhosis include vibration-controlled transient elastography and magnetic resonance elastography. It should be noted that noninvasive measures, especially transient elastography, are replacing biopsy as the preferred tests for fibrosis staging.⁵ Transient elastography

TABLE 2
Diagnostic tests for evaluation of the etiology of liver cirrhosis

Diagnostic test	Disease process
Hepatitis B surface antigen, immunoglobulin M anti-hepatitis B core antigen	Acute hepatitis B
Hepatitis B surface antigen, positive viremia on highly sensitive hepatitis B virus DNA assay ...	Chronic hepatitis B
Anti-hepatitis C virus, hepatitis C virus RNA (confirmatory)	Hepatitis C
Antismooth muscle antibody, antinuclear antibody	Autoimmune hepatitis
Antiliver kidney microsomal antibody, antisoluble liver antigen antibody (both less common)...	Autoimmune hepatitis
Iron level, serum ferritin, transferrin saturation	Hemochromatosis
Ceruloplasmin	Wilson disease
Alpha-1 antitrypsin phenotype	Alpha-1 antitrypsin deficiency
Lipid panel, hemoglobin A1c, hepatic ultrasonography	Nonalcoholic fatty liver disease, nonalcoholic steatohepatitis
Aspartate aminotransferase > alanine aminotransferase, elevated gamma-glutamyl transferase, elevated mean corpuscular volume	Alcoholic liver disease
Antimitochondrial antibody	Primary biliary cholangitis

Based on information in references 4 and 6.

determines liver stiffness by measuring the velocity of low-frequency ultrasound waves traveling through the liver.⁵ It is both sensitive and specific to establish the diagnosis of liver cirrhosis.⁸ In fact, guidelines from the National Institute for Health and Care Excellence (NICE) recommend that liver biopsy be performed if elastography is unsuitable or inconclusive.⁹

■ SCORING SYSTEMS FOR THE DEGREE OF LIVER INJURY

Several classification systems aim to predict the degree of liver injury and the prognosis. The Child-Pugh-Turcotte scoring system (Table 3) is among the most widely used, with an excellent predictive value that uses albumin, total bilirubin, INR, and degree of ascites and encephalopathy to assess the severity of cirrhosis.^{10,11} Additionally, NICE recommends using the Model for End-Stage Liver Disease (MELD) score every 6 months, as it predicts 3-month mortality in patients with end-stage liver disease.^{9,12} The MELD score, initially created to predict the survival of patients undergoing transjugular intrahepatic portosystemic shunts, uses creatinine, bilirubin, and INR.¹²

The Child-Pugh-Turcotte and MELD scoring systems are commonly used together in clinical practice because studies of the discriminative ability of Child-Pugh-Turcotte vs that of MELD have had variable results.¹² A systematic review of observational studies found that Child-Pugh-Turcotte had a higher sensitivity than MELD in predicting outcomes in patients with acute-on-chronic liver fail-

ure (0.81 vs 0.63), but MELD had higher sensitivity (0.77 vs 0.51).¹² However, the MELD score was found to have better discriminative ability to predict outcomes in intensive care unit patients. Moreover, in patients undergoing surgery, the Child-Pugh-Turcotte had higher specificity (0.82 vs 0.71).¹² It should be noted that no significant difference was found when comparing sensitivity and specificity in predicting 12-month mortality between the 2 scores. For this reason, we recommend using the clinical context to decide which classification system to use in clinical practice.

■ ESOPHAGEAL VARICES: SCREENING AND PREVENTION

One of the most important and fatal complications of liver cirrhosis is the rupture of gastroesophageal varices secondary to portal hypertension.¹³⁻¹⁵ Studies have demonstrated cumulative incidence of the development of esophageal varices in patients with cirrhosis to be 5% at 1 year and 28% at 3 years, progression was 12% at 1 year and 31% at 3 years, and the 2-year risk of bleeding was 12% vs 2% with small varices vs none at baseline.¹³

Esophageal varices can be diagnosed with esophago-gastroduodenoscopy, which is usually recommended in high-risk varices.^{14,15} Initial screening may be performed by platelet count and liver elastography (Table 4).^{9,16-18} Patients with compensated cirrhosis who are not candidates for nonselective beta-blocker for prevention of decompensation should undergo esophago-gastroduodenoscopy for variceal screening if liver

TABLE 3
Child-Pugh-Turcotte score

Score ^a	Bilirubin	INR	Albumin	Ascites	Encephalopathy
A	< 2 mg/dL	< 1.7	> 3.5 g/dL	Absent	Absent
B	2–3 mg/dL	1.7–2.2	2.8–3.5 g/dL	Mild	Mild
C	> 3 mg/dL	> 2.2	< 2.8 g/dL	Severe	Severe

^aClass A = < 6 points; class B = 7 to 9 points; class C = > 10 points.

INR = international normalized ratio

From information in references 10 and 11.

stiffness measurement is less than 20 kPa or the platelet count is less than $150 \times 10^9/L$.¹⁵ Patients avoiding screening endoscopy can be followed every year by repetition of transient elastography and platelet count. If liver stiffness measurement increases (< 20 kPa) or platelet count declines (< $150 \times 10^9/L$), these patients should undergo screening endoscopy.¹⁵

For patients with no varices or small varices, controlling the underlying cause and managing the complications of cirrhosis effectively prevents the progression of variceal rupture.¹⁴ For example, keeping hepatitis viral load low to prevent worsening fibrosis can prevent worsening variceal engorgement. For patients with large varices, nonselective beta-blocker therapy (carvedilol [preferred], nadolol, or propranolol) dramatically reduces risk of variceal bleeding from 30% to 14%.^{14,19} For those with medium or large varices, NICE recommends endoscopic variceal band ligation to prevent bleeding.⁹

HEPATOCELLULAR CARCINOMA

One of the most feared complications of cirrhosis is the development of hepatocellular carcinoma, with an annual incidence as high as 8% in patients with liver cirrhosis.^{20,21} Risk factors in the development of hepatocellular carcinoma include hepatitis B or C virus infection, aflatoxin exposure, alcohol use, tobacco use, and obesity.²² The risk of developing hepatocellular carcinoma is also higher in patients age 55 and older, patients with 75% or less prothrombin activity, and patients with platelet counts below $75 \times 10^9/L$.²²

The role of imaging

Owing to relatively low cost, ultrasonography is most commonly used as an initial imaging tool compared with computed tomography (CT) or magnetic resonance imaging (MRI) for screening of hepatocellular carcinoma. As such, current guidelines from NICE and the American Association for the Study of Liver

Diseases recommend that patients with cirrhosis undergo routine imaging every 6 months to screen for hepatocellular carcinoma.^{9,21} This recommendation is based on low-quality evidence from several studies suggesting a benefit of at least 3 months of life-years gained in patients undergoing surveillance with ultrasonography every 6 months.²¹

CT and MRI are alternate options as they have a higher sensitivity and specificity than ultrasonography.¹⁶ However, they have limited availability and higher associated costs. Therefore, only in select cases where ultrasonography results are challenging to interpret (patients with morbid obesity, those with fatty liver, or those with advanced liver disease), CT and MRI can be considered.²³ Ultrasonography only shows a sensitivity of 47% when detecting early-stage hepatocellular carcinoma in patients with cirrhosis, so a negative imaging result should not dismiss high clinical suspicion or replace serial ultrasonography.²⁴ If ultrasonography detects a mass under 10 mm, repeat ultrasonography is warranted in 3 months to monitor the growth.²⁴ For lesions greater than 10 mm, further imaging with CT or MRI and the risks and benefits of biopsy should be discussed with a specialist.¹⁹ However, it should be noted that biopsy of suspected hepatocellular carcinoma is generally avoided for fear of tumor seeding, thereby making localized disease more widespread.

Use of tumor markers

In addition to imaging, tumor markers such as serum alpha-fetoprotein can also be used to screen for hepatocellular carcinoma.^{19,25} Generally, alpha-fetoprotein levels greater than 20 ng/mL are considered a positive test. Patients with evidence of a 10-mm or larger lesion and a serum alpha-fetoprotein level greater than 20 ng/mL should undergo diagnostic testing with a contrast-enhanced multiphase CT or MRI.¹⁹ In addition, clinicians should remember that although

TABLE 4
Screening recommendations for patients with liver cirrhosis

Complication	Screening recommendations
Esophageal varices	Initial screening may be performed by platelet count and transient elastography All patients with high-risk varices should be offered esophagogastroduodenoscopy For those with medium to large varices, endoscopic variceal band ligation is appropriate for prevention of bleeding ⁹
Hepatocellular carcinoma	All patients with cirrhosis should undergo routine ultrasonography every 6 months to screen for hepatocellular carcinoma ^{9,16}
Hepatic encephalopathy	Clinical diagnosis based on exclusion of other causes of brain dysfunction ¹⁸ Ammonia levels should not be used to diagnose or stage patients with hepatic encephalopathy ^{17,18}

elevated alpha-fetoprotein levels are expected in patients with liver cirrhosis, even in the absence of hepatocellular carcinoma, alpha-fetoprotein levels greater than 400 ng/mL warrant additional workup to rule out hepatocellular carcinoma.²⁵

Decreasing the risk of hepatocellular carcinoma

Chemopreventive strategies and dietary agents have been proposed to decrease the risk and delay the onset of hepatocellular carcinoma.²⁶ Universal immunization and antiviral therapy for patients with hepatitis B and hepatitis C virus infection reduce the risk of hepatocellular carcinoma development.

Aspirin and statins have antineoplastic and anti-inflammatory properties that may have a protective effect on hepatocellular carcinoma development.²⁷ However, there is still a substantial lack of data on aspirin and statin use in hepatocellular carcinoma, and additional studies are needed to determine benefit in this patient subset.

SCREEN FOR HEPATOTOXIC MEDICATIONS

Although no specific recommendations have been published regarding the use of medications in patients with cirrhosis, it can be generalized that hepatotoxic medications should be prescribed with caution.²⁸ A list of drugs that should be avoided or prescribed with caution is summarized in **Table 5**.^{5,29-32}

OFFICE EVALUATION OF HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy refers to cognitive dysfunction resulting from liver disease that manifests as a broad spectrum of neurocognitive symptoms ranging

from subclinical abnormalities to coma.³³ Hepatic encephalopathy is a major cause of morbidity, mortality, and healthcare spending in the United States.³⁴ Primary care clinicians can play a key role in recognizing the signs and symptoms of hepatic encephalopathy and initiating early treatment before the need for hospitalization.

The clinical presentation of hepatic encephalopathy varies widely. Patients with minimal disease may have few symptoms, such as subtle personality changes or abnormal psychometric tests.^{18,33} Testing of patients for minimal hepatic encephalopathy or covert hepatic encephalopathy is important because these conditions are reported to be as high as 50% in patients with chronic liver disease.³⁵ Early diagnosis of minimal hepatic encephalopathy can help predict the likelihood of the development of overt hepatic encephalopathy and can allow for the initiation of treatment and lifestyle modifications to slow or prevent disease progression.

The International Society for Hepatic Encephalopathy and Nitrogen Metabolism has suggested that patients undergo testing using two separate psychometric tests, as each test may evaluate different components of cognitive functioning, and impairment in patients with minimal hepatic encephalopathy may vary from patient to patient.³⁵ Some available testing strategies include the Animal Naming Test, Psychometric Hepatic Encephalopathy Score, Critical Flicker Frequency test, Continuous Reaction Time test, Inhibitory Control Test, Stroop Test, Trail Making Test, the computerized Scan test, and examination using electroencephalography.³⁵ Some of these tests are time-consuming and require specialized equipment and staff training. Hence, they cannot be

TABLE 5
Medications to use cautiously in patients with liver cirrhosis

Antimicrobials: azithromycin, cefoperazone, ceftazidime, ceftriaxone, chloramphenicol, erythromycin, griseofulvin, ketoconazole, metronidazole, nalidixic acid, nitrofurantoin (chronic use), piperacillin, roxithromycin, telithromycin, tetracycline	Avoid or use with caution any medications that undergo first-pass metabolism or detoxification in the liver ²⁹
Acetaminophen	Should not exceed 2 g per day or 500 mg per dose ^{5,30}
Nonsteroidal anti-inflammatory drugs	Contraindicated in patients with advanced cirrhosis due to risk of further hepatotoxicity and higher risks of renal failure ⁵
Antihypertensives	Monitor patients for evidence of hypotension or ascites; discontinue as necessary ⁵
Metformin	Recent studies have shown metformin may be beneficial in treatment of steatohepatitis and may protect against hepatocellular carcinoma ^{5,29} Continue metformin in patients with diabetes ^{5,29}
Statins	May be safely used and possibly beneficial to prevent decompensation, despite common practice to hold or deprescribe ^{5,29,31}
Vitamin A	Restrict to < 5,000 IU daily ⁵
Opioids and benzodiazepines	Should be avoided ^{5,32}
Proton pump inhibitors	Avoid due to the potential risk of potentiating spontaneous bacterial peritonitis ^{5,29}

performed in a busy outpatient primary care setting. However, the Animal Naming Test has a high degree of accuracy, can be administered quickly, and is feasible in an outpatient setting.

Symptoms of overt hepatic encephalopathy are more apparent and include personality changes, irritability, disinhibition, sleep disturbances, sleep cycle alteration or excessive daytime sleepiness, disorientation, inappropriate behavior, confusion, stupor, and coma.³⁵ Additionally, motor symptoms such as hyperreflexia and hyperreflexia, in addition to extrapyramidal signs such as muscular rigidity, bradykinesia, hypokinesia, slowed speech, Parkinson-like tremor, and dyskinesia are expected.³⁵ Finally, asterixis is usually seen in patients in early to middle stages of the disease.

The diagnosis of overt hepatic encephalopathy is primarily based on findings of a clinical examination and is made only after excluding other causes of brain dysfunction.¹⁷ A key test to determine the clinical severity of hepatic encephalopathy is the West Haven criteria, which help stratify patients into the following grades based on clinical presentation and neuropsychiatric state:

- Unimpaired: normal, no subclinical or clinical impairment of mental state
- Covert: minimal encephalopathy and lack of disorientation and asterixis (ie, grade I)
- Overt (grades II–IV).³⁵

It should be noted that high blood ammonia levels are not diagnostic for hepatic encephalopathy, nor are they helpful in determining prognosis or staging.^{17,35} Hence, they should not be used to follow hepatic encephalopathy.

■ IMMUNIZATION AND EXPOSURE REDUCTION

For healthcare clinicians, it is essential to ensure that patients with liver cirrhosis receive proper vaccinations to ensure health.³⁶ According to the US Centers for Disease Control and Prevention guidelines, patients with chronic liver disease should receive the following vaccinations: influenza vaccine annually, hepatitis A and hepatitis B vaccine, herpes zoster vaccine, Tdap vaccine, and 1 dose of pneumococcal conjugate vaccine (PCV15, PCV20) if age 65 or older, or age 19 to 64 after a diagnosis of liver disease is

established.³⁶ If PCV15 is used, it should be followed by a dose of pneumococcal polysaccharide vaccine 23.

■ **LIFESTYLE MODIFICATIONS**

Diet and exercise

A Mediterranean diet and avoidance of red and processed meat, high-fructose corn syrup, and foods high in saturated fats have shown the most promising results in reducing the risk of nonalcoholic fatty liver disease (NAFLD) and preventing progression to nonalcoholic steatohepatitis and eventual cirrhosis.³⁷ In a randomized clinical trial, patients with NAFLD who followed a low-glycemic-index Mediterranean diet with no caloric restrictions for 6 months were found to have reductions in their NAFLD score as determined by liver ultrasonography.³⁸ Furthermore, patients who adhered to a Mediterranean diet showed more significant weight loss than a control group.^{37,38} Those who adhered to a Mediterranean diet and exercised at least 30 minutes a day (eg, aerobic exercise consisting of fast walking, slow or fast running, dancing) showed not only more significant weight loss, but also improvement in elevated aminotransferases and liver stiffness than in controls.^{37,38}

In patients with cirrhosis, hyperammonemia, muscle autophagy, and low levels of branched-chain amino acids have been hypothesized to be the cause of sarcopenia.³⁹ To prevent or reverse this catabolic state, high-protein diets can help maintain nitrogen levels needed to avoid sarcopenia.

The European Association for the Study of the Liver clinical practice guidelines recommend 1.2 to 1.5 g/kg/day of protein and at least 35 kcal/kg/day of calorie intake for patients with hepatic encephalopathy.⁴⁰ Furthermore, the European Association for the Study of the Liver recommends avoiding fasting for longer than 6 hours, putting the patient at high risk of entering a catabolic state during the night. Meals should therefore be given in small, frequent amounts, with late-night snacks containing high amounts of carbohydrates and proteins to improve nitrogen balance throughout the night.³⁹

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Sodium and fluid restriction

For patients with liver cirrhosis and ascites, sodium restriction is a mainstay in managing symptoms.⁴⁰ Sodium intake should be limited to less than 2 g/day or 88 mmol/day, as it has been noted that the development of ascites is secondary to renal retention of sodium.⁴⁰ Patients can generally achieve this recommendation by avoiding added salt and pre-prepared meals that are often high in sodium.⁴⁰ However, extreme restriction less than 2 g/day is not recommended as it can reduce food intake, worsening coexisting malnutrition and the catabolic state common in patients with cirrhosis.⁴⁰ In addition, for patients taking diuretics, a marked reduction in sodium intake can exacerbate hyponatremia.⁴¹

Fluid restriction of 1 to 1.5 L/day should be reserved for patients with clinical hypervolemia and severe hyponatremia (serum sodium < 125 mmol/L).⁴¹ Fluid restriction is most effective when fluid intake is less than the urinary volume. However, urinary volume is usually low in patients with cirrhosis, so adequate fluid restriction is nearly impossible to achieve and is therefore not recommended.⁴¹

■ **TAKE-HOME MESSAGES**

The careful evaluation of patients with cirrhosis in the primary care setting includes identifying risk factors that can lead to decompensation, attention to proper immunization and exposure reduction, and counseling on lifestyle modifications, with a low threshold for referral to appropriate specialists. Primary care clinicians can play a key role in reducing the morbidity and mortality of liver cirrhosis, improving patient outcomes and survival rates. ■

Acknowledgments: We thank Jeffrey Jackson, MD, MPH, from the Medical College of Wisconsin for critically reading and encouraging us during the preparation of this manuscript.

■ **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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