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Ignazio Grattagliano, MD, and Enzo Ubaldi, MD
Italian College of General Practitioners, Florence, Italy

Piero Portincasa, MD, PhD, and Giuseppe Palasciano, MD
Department of Internal and Public Medicine, University Medical School, Bari, Italy

i.grattagliano@semeiotica.uniba.it

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TRANSPLANT NEWS FROM UNOS
John Lake, MD, Director, Liver Transplantation, University of Minnesota Medical Center

Liver disease: Early signs you may be missing

Maximizing your care starts with zeroing in on lab values you may be overlooking and taking advantage of algorithms that can help detect fibrosis.

PRACTICE RECOMMENDATIONS

› *Suspect compensated liver cirrhosis in a patient with abnormal liver function tests, a low platelet count, and prolonged prothrombin time.* (C)

› *Use ultrasonography as a first-line diagnostic tool for liver cirrhosis.* (C)

› *Prescribe beta-blockers as prophylaxis for patients at risk for variceal bleeding.* (A)

› *Work collaboratively with hepatic specialists to manage the care of patients with cirrhosis.* (B)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence
(B) Inconsistent or limited-quality patient-oriented evidence
(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE 1 ▸ A patient with mildly elevated ALT and AST

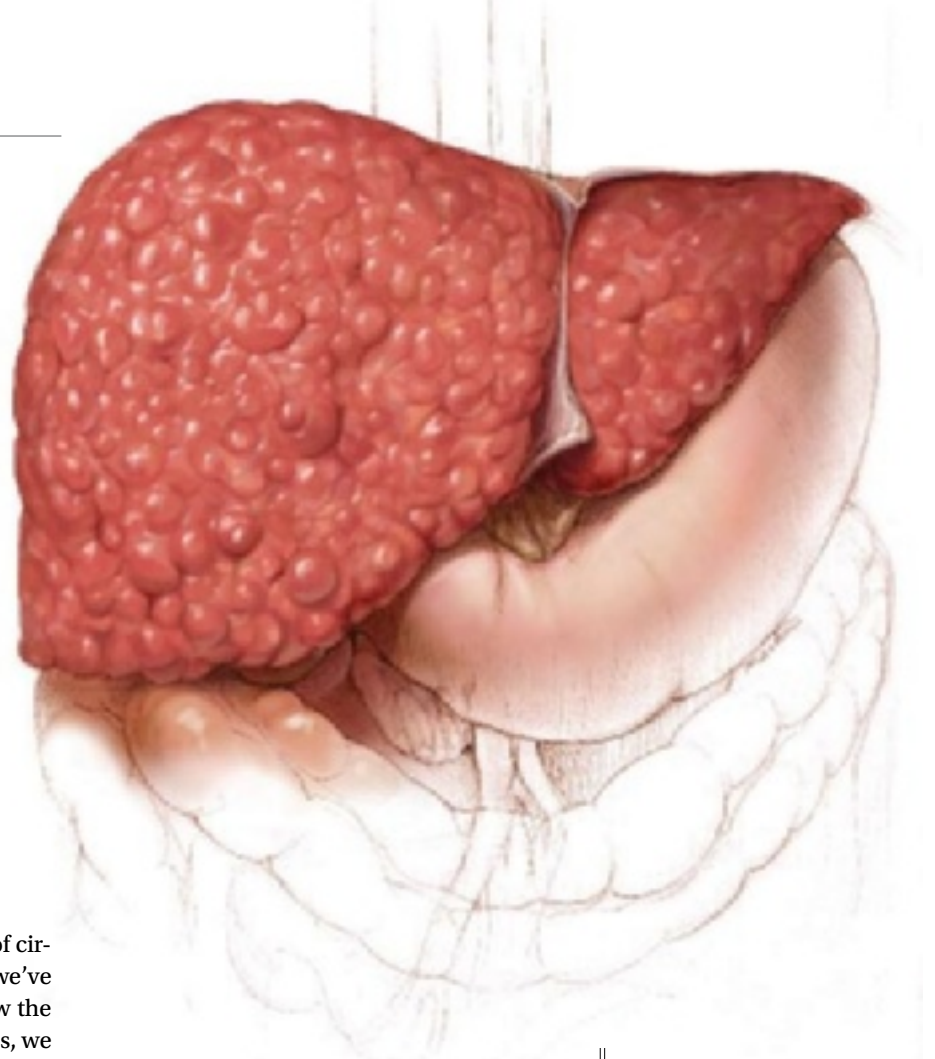
John M., a 63-year-old truck driver with a family history of diabetes and arterial hypertension, is complaining of persistent fatigue—again. He has type 2 diabetes and takes metformin and repaglinide, but his blood pressure is normal. Lab tests reveal a recurrent mild elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels of unknown origin; Mr. M. has no history of virus or hepatotoxic drugs, and reports only modest alcohol intake. He is obese, however, with a BMI of 34.5 and a waist circumference of 41 inches.

CASE 2 ▸ A patient with abdominal swelling

Anna B., a slim 68-year-old, comes in with 2 acute conditions: About a week ago, she noticed abdominal swelling and low back pain that began suddenly, after she carried a heavy load. She's taken nonsteroidal anti-inflammatory drugs for 6 days, but the pain has not improved. The patient's only significant clinical history is a hysterectomy, with oophorectomy, at age 38, and a recurrent elevation of serum transaminase levels that has never been investigated. Examination reveals an important kyphosis, and finger pressure on the vertebral spine or a position change exacerbates the pain. Her abdomen is swollen and tense, with a tympanic sound on the upper abdomen and a dull sound on the lower portion.

If John M. and Anna B. were your patients, would you suspect that they both have advanced liver disease? What diagnostic tests would you order, and how would you manage their care?

Cirrhosis has always been associated with high rates of morbidity and mortality. It is the 12th most common cause of death in the United States;[1] in some parts of the world, its ranking as a cause of death is considerably higher.[2,3] In recent years, however, cirrhosis has become the focus of greater attention both here and abroad, for 2 reasons: The first is the increasing prevalence of viral hepatitis and steatohepati-



Because abnormal ALT values are common and frequently resolve, many primary care physicians pay little attention to this potentially important finding.

tis, both of which are prominent causes of cirrhosis. The second is the improvement we've made in treatment: Not only can we slow the progression of cirrhosis, but in some cases, we can even restore hepatic function.[4]

The key to successful management of cirrhosis lies in spotting subtle signs and symptoms well in advance of the serious complications that can arise down the road. Here's what to look for.

Early warnings you can't afford to overlook

While the clinical presentation of a patient with liver cirrhosis is often asymptomatic, serum transminases—included in many standard laboratory tests as part of a routine examination—often provide the first sign of a problem.

Mildly elevated ALT in an asymptomatic patient may be transient and benign, or an indication of chronic liver disease.[5] In fact, signs suggestive of significant liver disease have been reported in more than 20% of patients with ALT elevation.[2] But because abnormal ALT values are common and frequently resolve, many primary care physicians pay little attention to this potentially important finding—and miss a key opportunity for early identification and treatment.[6]

Look at other lab values, risk factors, as well

Additional lab values that suggest the possibility of cirrhosis include an elevated AST/ALT ratio, a low platelet count (<150,000/L), elevated alkaline phosphatase, elevated bilirubin (>1.1 mg/dL), low serum albumin (<2.5 g/dL), and decreased prothrombin time (<100%). Potential causes include viral hepatitis, heavy alcohol use, hepatotoxic drugs, steatosis, and steatohepatitis.

The next step for a patient with any of these abnormal values is a thorough medication review and medical history. Identify all prescription and nonprescription drugs the patient is taking, as well as any herbal products and supplements, in search of hepatotoxic agents. Amiodarone and valproic acid, among other drugs, may cause steatosis, and some herbal products—particularly kava kava extract, used to treat anxiety and insomnia—have been linked to hepatitis and even liver failure.[7] Question the patient about alcohol consumption and a history of conditions associated with liver disease, such as diabetes, hyperlipidemia, and thyroid disorders, as well.

CONTINUED

TABLE 1

Child-Pugh: Classifying cirrhosis, predicting survival*

	1 point	2 points	3 points
Bilirubin (mg/dL)	<2	2-3	>3
Prothrombin time (INR)	<4 sec (<1.7)	4-6 sec (1.7-2.3)	> 6 sec (>2.3)
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
Ascites	Absent	Mild	Severe
Encephalopathy	Absent	Mild	Severe

INR, international normalized ratio.

*Total the number of points for all 5 indicators (1 point for every answer in column 1, 2 points for every answer in column 2, and 3 points for every answer in column 3). Patients with ≤6 points (Grade A) have an estimated 1-year survival rate of 100%; patients with 7-9 points (Grade B) have an estimated 1-year survival rate of 80%; and patients with ≥10 points (Grade C) have an estimated 1-year surival rate of 45%.

Adapted from: Infante-Rivard C, et al. *Hepatology*. 1987.[14]

Schedule repeat testing within 6 months for every patient with ALT elevation.

At a minimum, schedule follow-up testing of asymptomatic patients with abnormal laboratory findings in no more than 6 months. Persistent ALT elevation in such patients is most commonly caused by major viruses, alcohol abuse, nonalcoholic fatty liver disease (NAFLD), or nonalcoholic steatohepatitis (NASH).[8] Nonalcoholic fatty liver is especially likely in patients with clinical and demographic risk factors—those who, like John M., suffer from obesity or diabetes, or both.

Ultrasound yields further information

Further screening should be limited to patients who continue to have abnormal test results for 6 months or more or have multiple risk factors. While biopsy is still considered the gold standard for diagnosing and staging chronic liver disease, it should be considered, according to the American Gastroenterological Association, only if ultrasound and other tests have not been helpful in reaching a diagnosis.[9]

Often, though, ultrasonography aids in diagnosis. In the case of John M., ultrasound revealed an enlarged liver with diffuse echostructural dyshomogeneity and signs of severe steatosis and mild splenomegaly, but no increase in portal vein diameter and no ascites. For asymptomatic patients with cirrhosis or an earlier stage of liver disease, ultrasound at 6-month intervals, combined with blood alpha-fetoprotein measurement, can be used to track disease progression and screen for hepatocellular carcinoma.[10]

Newer, noninvasive methods aid in diagnosis

Noninvasive means of evaluating the presence and extent of liver fibrosis and differentiating cirrhosis from noncirrhosis, developed in recent years, have been found to have positive predictive values greater than 85% to 90%.[11] Transient elastography (FibroScan, London, England), which assesses liver stiffness, is 1 such method. Although it is often used successfully, however, morbid obesity, small intercostal spaces, and ascites limit the diagnostic capability of this medical device.[12]

Fibrosis can also be detected with the use of 1 or more algorithms—each testing blood samples for a different combination of serum surrogate markers for liver disease. Some widely used algorithms include the APRI (AST-to-platelets ratio index), the Fibrotest (aptoglobin, alpha-2 macroglobulin, apolipoprotein A1, gamma-glutamyl transpeptidase, and bilirubin), the Hepascore (bilirubin, gamma-glutamyl transpeptidase, haluronic acid, alpha-2 macroglobulin, age, sex), and the BARD (BMI, AST/ALT ratio, diabetes).

Hepatologists often use the results of ultrasonography, followed by transient elastography in conjunction with findings from 1 or more of these algorithms, to determine which patients are candidates for liver biopsy.[11,12]

Staging is crucial, with or without biopsy

The decision to perform a liver biopsy should be based on a number of factors, including

the patient's age, lifestyle, liver chemistry abnormalities, desire for prognostic information, and associated comorbidities.[9] Despite the value of biopsy, it is a costly procedure with potentially serious side effects and risks—and not always accepted by patients. In a recent survey of 1177 primary care physicians in France, as many as 59% of patients with chronic hepatitis C refused to undergo liver biopsy; what's more, 22% of the doctors surveyed shared the patients' hesitancy.[13] Whether patients refuse biopsy or it is deemed unnecessary because ultrasound and other noninvasive tests result in a probable diagnosis, staging is necessary, both to guide therapy and to arrive at a prognosis.

Liver enzyme levels reveal little about organ integrity and are not useful for staging. But other parameters (specifically, bilirubin, albumin, and prothrombin time), combined with the presence (or absence) and severity of physical findings such as encephalopathy and ascites, are included in the Child-Pugh classification system (**TABLE 1**),[14] a widely used system that roughly indicates disease severity.[15]

The Model for End-stage Liver Disease (MELD)—and PELD, the pediatric model—use bilirubin, creatinine, and international normalized ratio values to classify disease severity. MELD and PELD scores are considered more accurate than the Child-Pugh score in determining short-term mortality,[16] and are used by the United Network of Organ Sharing (UNOS) for liver allocation. You'll find a calculator at http://www.unos.org/resources/MeldPeldCalculator.asp?index=98.[17]

Despite the progress in diagnostic techniques, the life expectancy and quality of life for patients with advanced cirrhosis remains poor. Patients routinely experience fatigue, pruritus, ascites, encephalopathy, and bleeding; dyspepsia and malnutrition are common, as well. Cirrhosis also carries the risk of life-threatening complications, partly due to comorbidities—most notably, osteoporosis, malabsorption, and rheumatic diseases. Liver transplantation has the potential to change the life expectancy of these patients, but because of the extensive waiting lists, candidates for transplant often die before a liver becomes available.

But for many patients who are in stable condition—those with compensated cirrhosis, that is—the prognosis is far more hopeful: In addition to providing standard medical care, including immunization, if necessary, and nutritional counseling, targeted therapy is crucial to slow, or stop, disease progression.

Treatment for cirrhosis depends on the cause

Although primary care physicians can often provide most, or all, of the care for those in stable condition, a specialist may be helpful in determining further testing to identify the underlying cause of the cirrhosis, which is essential to determining the most appropriate treatment. What's more, research has shown that patients with cirrhosis whose care is managed by a primary care physician and a hepatologist have better outcomes than those who are treated by a primary care doctor alone.[18]

What to test for?

Tests to determine the cause of cirrhosis are listed in **TABLE 2**. For an individual patient, diagnostic tests would be based on the suspected cause. A patient with a family history of hereditary hemochromatosis would be tested for elevated serum ferritin levels and hepatic iron content on liver biopsy sample; the transferrin saturation index would also be obtained, and the patient might be tested for specific gene mutations. A patient who drinks heavily would be tested for elevated gamma-glutamyl transpeptidase and mean corpuscular volume. For someone with obesity, diabetes, and an enlarged liver, standard lab tests, including high-density lipoprotein (HDL) cholesterol, glucose, and triglycerides, may be sufficient.

Keep in mind, however, that cirrhosis may have more than 1 contributing factor—obesity or chronic alcohol use and a virus, for example; alcohol abuse and metabolic fatty liver; or virus and hemochromatosis. Thus, it may require more than 1 type of treatment.

Alcohol abuse is the cause of 25% of cases of liver cirrhosis, and a contributor to another 25% to 50%.[19] The key treatment here—and an ideal role for a family physician—is to refer the patient to a detoxification and treatment program and provide ongoing monitoring and

Cirrhosis may have more than 1 contributing factor—obesity and a virus, or chronic alcohol use and metabolic fatty liver, for example.

TABLE 2

Liver cirrhosis: Common causes, diagnostic tests, and treatments[4,34-38]

Cause	Test (result)	Therapy
Alcohol	GGT (↑), MCV (↑)	Abstinence
HBV + delta virus infection	HBsAg (+) HBV-DNA(+) HBc-IgM (+) HDV-RNA (+)	Interferon alpha-2b, nucleoside (lamivudine, telbivudine, entecavir) and nucleotide (adefovir, tenofovir) analogs
HCV infection	HCV-RNA (+)	Interferon + ribavirin
Primary biliary cirrhosis	GGT (↑) Alkaline phosphatase (↑) AMA (+)	Ursodeoxycholate
Autoimmune hepatitis	ANA (+) ASMA (+) LKM (+)	Prednisone, azathioprine
Hemochromatosis	Ferritin (↑) Transferrin saturation index (>45%) Hepatic iron content (↑) HFE gene mutation (C282Y, H63D)	Phlebotomy, chelating agents
Wilson's disease	Ceruloplasmin (↓) Serum copper (↓) 24h urinary copper excretion (↑)	D-penicillamine, zinc
NAFLD/NASH	HDL cholesterol (↓) Glucose (↑) Triglycerides (↑)	Low-calorie diet, physical activity, insulin-sensitizer drugs or insulin

AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth-muscle antibody; GGT, gamma–glutamyl transpeptidase; HBc-IgM, immunoglobulin M antibody to hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HBV-DNA, hepatitis B virus DNA; HCV-RNA, hepatitis C virus RNA; HDL, high-density lipoprotein; HDV-RNA, hepatitis delta virus RNA; LKM, liver kidney microsomes; MCV, mean corpuscular volume, NAFLD/NASH, nonalcoholic fatty liver disease/nonalcoholic steatohepatitis.

Recovering alcohol abusers may not be considered for a liver transplant until they have had 6 months of continuous abstinence.

support. Antiviral treatment may be helpful for a recovering alcoholic who also tests positive for hepatitis B or C virus, but because of potential problems with compliance, some physicians delay therapy until the patient has had at least 6 months of continuous abstinence. Although this is not an absolute criterion, the same period of abstinence may be required before a patient becomes eligible for a liver transplant.

NAFLD/NASH is typically diagnosed on the basis of lab values and physical presentation. For a stable patient, the primary treatment includes lifestyle change—a low-calorie, low-carbohydrate diet and an exercise regimen—and a possible switch to insulin for better glycemic control.

For patients who are not candidates for such targeted treatments, either because their disease is too advanced or they're unable to tolerate the recommended therapy, numerous pharmaceutical preparations claiming antioxidant or anti-inflammatory properties are available. But only 1—an herbal extract known as silymarin, derived from the milk thistle plant and taken with vitamin E—has been found to have some protective effects.[20]

Address systemic problems along with targeted treatment

Malnutrition is a serious problem for many patients with cirrhosis. Causes range from poor oral intake or malabsorption to ongoing alcohol use, chronic nausea, or early satiety because of compression from ascites. Dental problems that prevent the patient from chewing properly may be a contributing factor, as well.

Regardless of the cause, malnutrition is associated with muscle wasting, hypoalbuminemia, decreased resistance to infections, and variceal bleeding, and addressing it is a key part of treatment. Assess the nutritional status of every patient with cirrhosis, and stress the importance of multivitamin supplementation.[21] If dental care is needed, take steps to see that the patient receives it.

Nutritional support, however, should be reserved for severely malnourished patients awaiting transplantation.[22]

Osteoporosis. Reduced bone formation—the result of vitamin D deficiency, hypoparathyroidism, and hypogonadism—is a well-known complication of end-stage cirrhosis. However, osteopenia may occur in an earlier stage of disease, especially in patients with cholestatic disease and those receiving antiviral therapy. Prescribe bisphosphonates, together with calcium and vitamin D_3, to improve bone mineral density.[23]

Diabetes. The relationship between diabetes and cirrhosis is particularly complex, because diabetes can be both a causal factor and a consequence of cirrhosis. Diabetes is common in patients with NASH, and prevalent among those with hepatitis C and hemochromatosis. Multivariate analyses have found that diabetes has an independent negative effect on the progression of liver disease.[24]

Diet remains the first-line treatment for hyperglycemia, with metformin as the drug of choice if diet alone is unsuccessful. Sulfonylureas can be used, but require caution to avoid hypoglycemia. Glitazones are a newer alternative, but their value in patients with liver cirrhosis has not been studied. However, the use of any oral antidiabetic agent requires extra caution in patients with cirrhosis, and should be avoided in those with advanced liver disease. Although insulin requires intense self-monitoring of serum glucose levels, it is preferable to oral agents for this patient population.[25]

Managing complications of cirrhosis

Hospital, home, or long-term care? Whether patients with advanced cirrhosis can be maintained at home or require hospitalization or long-term care is best decided in consultation with patient, family, and other members of the health care team. One helpful tool is the Karnofsky Performance Scale Index (http://www.medal.org/visitor/www%5CActive%5Cch1%5Cch1.01%5Cch1.01.01.aspx), which scores patients from 0 to 100 based on their functional impairment.[26] (Patients with decompensated liver cirrhosis and limited self-sufficiency typically score <50, indicating that they require home health care, hospice, or institutional care.) Whatever the outcome, the patient may need to be reevaluated as the disease progresses and complications occur.

Ascites, the most common complication of cirrhosis,[27] is a primary reason for hospitalization, but may be managed on an outpatient basis, depending on the patient presentation. Determining factors include the presence or absence of portal hypertension, impaired albumin synthesis, decreased plasma oncotic pressure, and sodium retention. Diagnosis is based on physical exam and ultrasonography.

Initial treatment for ascites includes salt restriction[28,29] and avoidance of NSAIDs, which promote renal sodium retention, followed by spironolactone (100–400 mg/d). Add furosemide (40-160 mg/d) if the fluid retention does not begin to resolve after 3 to 5 days of treatment. If the condition persists despite maximum tolerable doses of diuretics, large-volume paracentesis to remove transudative fluid (albumin <1 g/dL; serum/ascites albumin gradient >1.1) may be needed. A patient with recurrent or refractory ascites should see a specialist for further evaluation and the possibility of a transjugular intrahepatic portosystemic shunt (TIPS).

Abdominal pain and an ascitic granulocyte count >250/mm^3 suggest spontaneous bacterial peritonitis (SBP)—a severe complication of ascites that can result in renal and liver failure. In addition to pain, patients may present with tense ascites and fever, followed by encephalopathy, shock, and increased serum creatinine levels. Hospitalization is required for SBP; therapy includes high-dose albumin and intravenous antibiotics, typically cephalosporin. Long-term prophylaxis with norfloxacin to prevent the recurrence of SBP is indicated.[30]

If your patient has ascites and is being cared for at home, talk to the patient and his

In addition to salt restriction, prescribe spironolactone for patients with ascites; add furosemide, if needed.

Without transplantation, patients with decompensated cirrhosis have an 85% mortality rate over 5 years.

or her family about the importance of a daily weight check. Tell them to contact you if the patient gains more than 4 to 8 lbs within a few days. Frequent electrolyte checks are needed, as well. An albumin infusion is required when serum levels are particularly low, or after large-volume paracentesis.[31] Patients with SBP or refractory ascites generally have more advanced disease and a poor prognosis.

Portal hypertension/esophageal varices. The main aim of treating portal hypertension is to prevent esophageal variceal bleeding. The appearance of varices should be checked by endoscopy every 2 to 3 years, or yearly for patients at high risk of bleeding. Patients with varices can be managed with nonselective beta-blockers at doses that are sufficient to elicit a 25% reduction in resting heart rate. Those at high risk for bleeding and patients who have already had esophageal bleeding may require endoscopic band ligation.[32] TIPS is an alternative for those whose previous treatments have failed.[33]

Hepatic encephalopathy. This potentially reversible decrease in neuropsychiatric function mainly affects patients with portal hypertension. Caused by reduced hepatic clearance of gut-deriving neurotoxins, hepatic encephalopathy is associated with a range of signs and symptoms—from subtle personality changes to coma, with flapping tremor as a frequent initial finding. Acid-base and electrolyte disturbances, constipation, infections, gastrointestinal bleeding, and sedatives can precipitate encephalopathy. Hepatic encephalopathy is a diagnosis of exclusion, however, requiring the exclusion of all other etiologies of altered mental status.

Treatment consists of identifying and correcting the precipitating factors, and includes electrolyte correction, colon cleansing, and acidification with lactulose. Dietary protein restriction is no longer advocated, because it may facilitate malnutrition and complications. Oral rifaximine is useful and well tolerated for suppression of intestinal bacterial flora. Venous infusion of branched-chain amino acids or flumazenil may be effective in case of coma.

Fever and sepsis. Infection is a high-risk factor for mortality in patients with cirrhosis, as it can lead to renal and liver failure, variceal bleeding, and hepatic encephalopathy. However, individuals with cirrhosis often do not develop the typical signs and symptoms of infection; leukocytosis may be absent because of severe leukopenia, for instance, and patients may be afebrile.

Thus, the general appearance of systemic illness is an indication for antibiotics, with quinolones and cephalosporins as first-line agents. Infections most commonly involve the urinary tract (25%-55%) or the respiratory tract (20%), or are related to SBP (10%-30%).[33] Hospitalization is suggested in case of poor general health status or the appearance of organ dysfunction.

When medical therapy and other interventions fail to control complications, transplantation is the only alternative. Primary care physicians can play a role here, too, in referring potential candidates for liver transplants to specialists for further consideration.

CASE 1 ▸ Resolution

As we've already seen, John M.'s ultrasound revealed an enlarged liver. The results led to a probable diagnosis of an advanced form of NASH. Other lab tests indicated that he had poorly controlled diabetes, high triglyceride levels, and—for the first time—a low platelet count. His physician stressed the importance of following a low-calorie, low-carbohydrate diet and exercising regularly, prescribed insulin, and referred the patient to a hepatologist for further noninvasive evaluation of fibrosis and to determine whether liver biopsy was needed.

CASE 2 ▸ Resolution

Blood tests revealed that Anna B. had a low platelet count (64,000/mm^3), elevated liver enzymes (AST 2x upper limit of normal [ULN], ALT 1.5x ULN, GGT 2.5x ULN), and high gammaglobulins (33.6%) with no monoclonal bands. Ultrasound revealed an enlarged liver with diffuse echostructural dyshomogeneity, portal vein dilatation, and moderate ascites. She also tested positive for HCV and had an HCV-RNA reading of 15x10^6 IU/mL. No other cause of chronic liver disease emerged. Ms. B.'s physician told her that she had an osteoporotic vertebral fracture—a frequent comorbidity in patients with liver cirrhosis—and decompensated liver cirrhosis from an old HCV infection. He added that her abdomen was distended because of fluid retention. The physician recommended bed rest, prescribed paracetamol (1 g tid) and spironolactone (100 mg/d), and referred the pa-

tient to an orthopedist for treatment of the fracture and to a hepatologist to be evaluated for transplantation. JFP

CORRESPONDENCE
Ignazio Grattagliano, MD, Department of Internal Medicine, University Medical School of Bari, P.zza G. Cesare, 11 – 70124, Bari, Italy; i.grattagliano@semeiotica.uniba.it

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