A JOHNS HOPKINS PRESS HEALTH BOOK

Your Complete Guide to LIVER HEALTH

Coping with Fatty Liver, Hepatitis, Cancer, and More

Paul J. Thuluvath, MD, FRCP

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JOHNS HOPKINS UNIVERSITY PRESS

Baltimore

***Note to the Reader*:** This book is not meant to substitute for medical care, and treatment should not be based solely on its contents. Instead, treatment must be developed in a dialogue between the individual and their physician. Our book has been written to help with that dialogue.

Drug dosage: The author and publisher have made reasonable efforts to determine that the selection of drugs discussed in this text conforms to the practices of the general medical community. The medications described do not necessarily have specific approval by the US Food and Drug Administration for use in the diseases for which they are recommended. In view of ongoing research, changes in governmental regulation, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert of each drug for any change in indications and dosage and for warnings and precautions. This is particularly important when the recommended agent is a new and/or infrequently used drug.

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To my mother, Selena, my best teacher; my father, Joseph, my silent supporter; my wife and best friend, Reeja, the inspiration behind my scholarly activities; and my children, Nimisha and Avesh, who followed my path in medicine

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Your Complete Guide to Liver Health

CHAPTER 1

Understanding Liver Disease

The liver is one of the body's hardest-working organs, helping to digest food and get rid of toxins. To understand more about how liver disease affects the liver, it's important to learn more about the liver and what it does.

UNDERSTANDING HOW THE LIVER WORKS

The liver, one of the body's largest organs, is in the upper right side of the belly and has two large sections: the right and left lobes (figure 1.1). The liver works together with other organs —like the gallbladder, pancreas, and the intestines—to help the body process food (figure 1.2).

Many important jobs are performed by the liver (table 1.1), including:

1. Making proteins
2. Making, storing, and processing fats
3. Processing and storing carbohydrates
4. Creating and secreting bile to help the intestines absorb fats and fat-soluble vitamins
5. Getting rid of potentially harmful chemicals the body produces
6. Getting rid of toxins, such as drugs, alcohol, and harmful substances from the environment

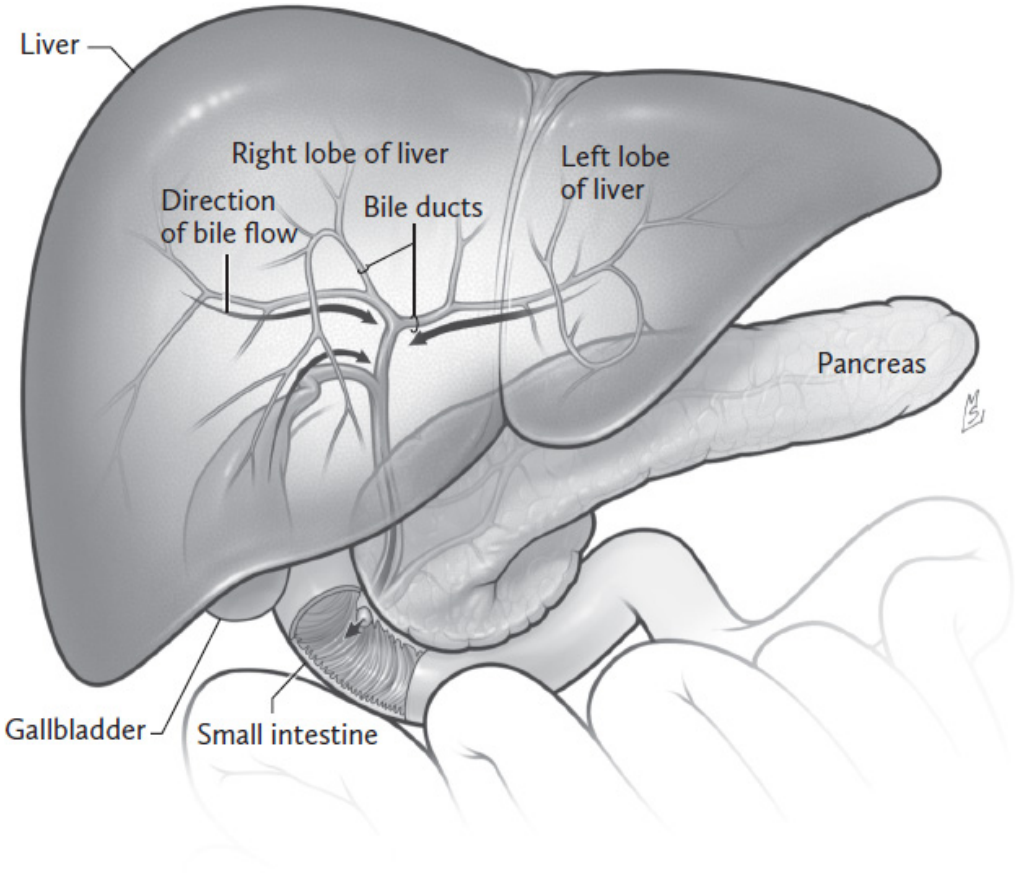

FIGURE 1.1. The liver, gallbladder, and pancreas

TABLE 1.1. Important jobs of the liver

Plays a major role in processing carbohydrates, proteins, and fats
Makes proteins, including: • albumin (helps maintain the volume of blood) • fibrinogen (needed for blood clotting) • transferrin (helps the blood carry iron) • prothrombin (helps the blood clot)
Processes many drugs, so the body can use them
Gets rid of many toxins, including drugs, alcohol, ammonia formed from breaking down proteins, and bilirubin formed from breaking down old red blood cells
Gets rid of tumor cells, bacteria, yeasts, viruses, and parasites
Stores many vitamins and minerals

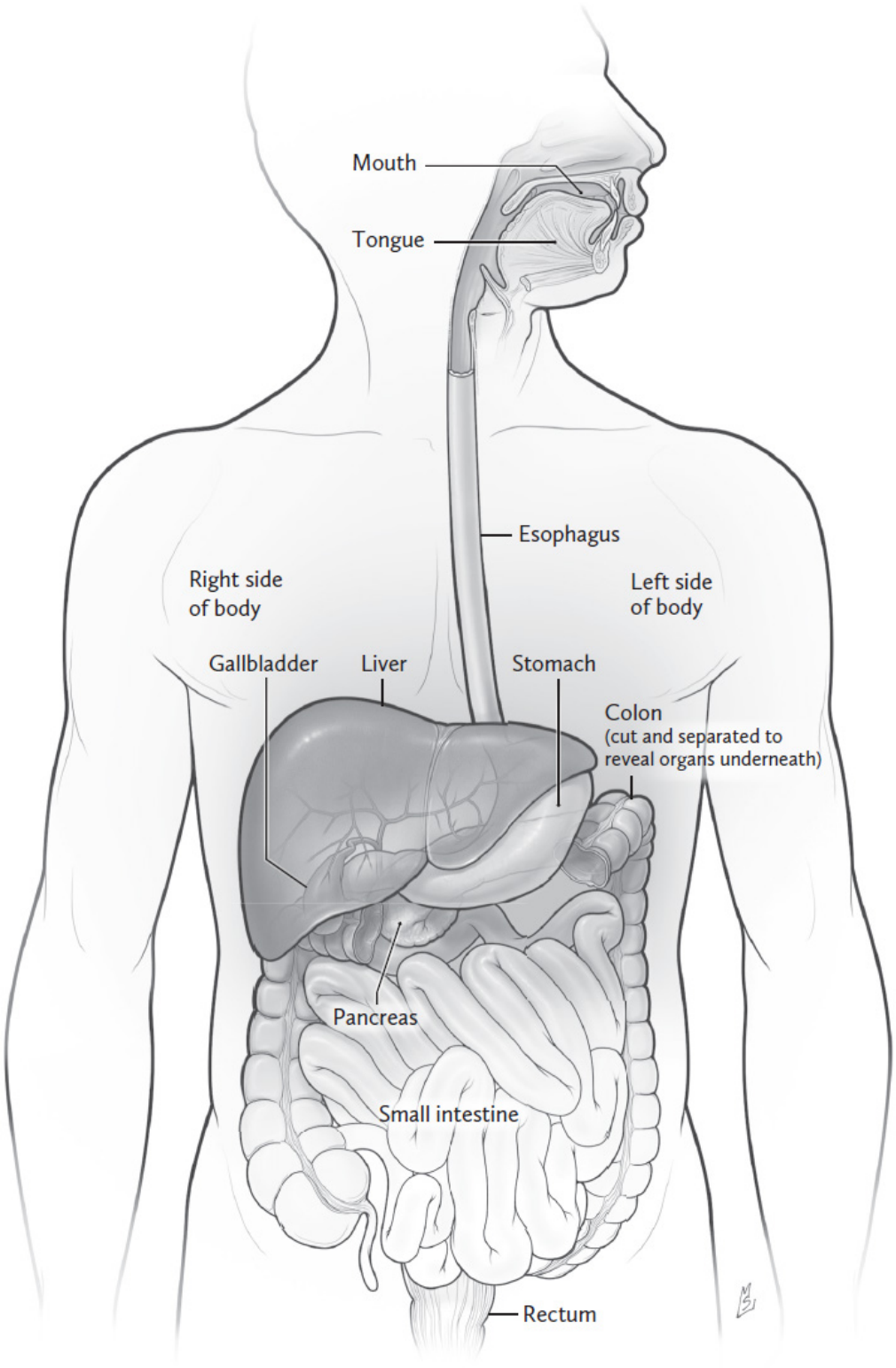

FIGURE 1.2. The digestive system

LIVER DISEASE, DAMAGE, OR INJURY

Liver disease is any condition that damages the liver and prevents it from doing its jobs properly. There are many

different types of liver disease and several causes of that disease. The most common causes include viruses, inherited conditions, non-alcoholic fatty liver disease, or alcohol (table 1.2). Additionally, cytomegalovirus, or CMV (which can cause serious birth defects), Epstein-Barr virus, or EBV (which causes "mono," or infectious mononucleosis), and herpes simplex virus, or HSV, can also trigger an *acute* (new) liver injury. CMV and EBV infections are common and often *asymptomatic* (without symptoms), but these viruses may cause more severe injury in individuals who are *immunocompromised* (have a weakened immune system). Although liver enzyme abnormalities are common in COVID-19, it is not known whether these abnormalities are the direct result of a viral infection.

Any of the above conditions can damage the liver cells, but no matter what the cause, the damage prevents this organ from working normally.

STAGES OF LIVER DAMAGE

The liver is usually able to repair itself when it gets damaged. It can withstand a lot of harm before a person may start to feel any symptoms. In other words, most people who have liver damage do not have any symptoms in the early stages of the disease or its harmful changes.

Fibrosis

In situations where the damage is caught early, the liver can repair itself (regenerate new liver cells) and start working normally again. The healing process may result in the formation of scar tissue (*fibrosis*).

TABLE 1.2. Causes of liver disease

Condition	Types
Inherited disorders	hemochromatosis alpha-1 antitrypsin deficiency Wilson disease
Infections caused by viruses*	hepatitis A

	hepatitis B hepatitis C hepatitis D hepatitis E
Autoimmune disorders	autoimmune hepatitis primary biliary cholangitis primary sclerosing cholangitis
Other causes	alcohol non-alcoholic fatty liver disease medications and supplements

*Viruses such as the herpes simplex virus (HSV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) may also cause acute liver injury.

Cirrhosis

After a long period of continued damage, the liver cannot always repair itself. The amount of scar tissue may just be too high. Because scar tissue does not work like healthy tissue, the liver gradually will not be able to do its jobs well. When the liver has a significant amount of scar tissue that has replaced the healthy tissue, the liver slowly becomes shrunken, lumpy, and hard—a condition known as *cirrhosis* of the liver. With long-term damage, symptoms do not start to show up until the liver has sustained a lot of harm. Many people do not develop symptoms until the late stages of cirrhosis, after many years of liver damage.

So, whether or not you have symptoms, it is important to diagnose and manage liver disease. If you wait until symptoms start to appear, it may be too late to fix the problem.

Is Fibrosis (Scarring) Reversible?

Until recently, physicians and research scientists believed that scarring of the liver was irreversible. Some recent observations, however, suggest that scarring can be reversed to some extent if the cause of the scarring is removed. Studies of chronic hepatitis B have clearly demonstrated the possibility that even early cirrhosis can be reversed after the hepatitis B virus is *cleared* (eliminated) from the body. Many studies of

people who have hepatitis C with significant scarring also show that clearance of the hepatitis C virus reduces the severity of fibrosis. Trials are in progress for individuals with fatty liver disease to determine whether scarring could be reversed. Despite the possibility that early cirrhosis is potentially reversible, no convincing evidence has suggested that long-standing cirrhosis can be reversed.

SIGNS AND SYMPTOMS OF LIVER DISEASE

No matter what the cause of liver damage, the symptoms—what a person experiences—and physical signs—what a doctor finds during a physical examination—of all types of liver disease are similar. The common general symptoms of liver damage and the possible causes of that damage are shown in table 1.3.

If people experience pain as a main symptom, more than likely they have a problem that is not related to liver disease. For example, if a person has yellowing skin and feels severe pain after eating meals, they may have a bile duct blockage because of gallstones.

- People who have early stages of liver disease usually don't have any symptoms.
- When a person has symptoms, they usually have had liver disease for many years (late-stage liver disease).
- As soon as an individual has any symptoms, they should see a doctor right away for help.

TABLE 1.3. General symptoms and possible causes of liver disease

Symptoms	Possible cause
• Poor appetite • Loss of taste • Nausea • Discomfort or pain in the upper right belly • Yellowing skin (jaundice) • Dark-colored urine • Itching	acute hepatitis
• Severe pain in the upper right belly,	bile duct blockage due to gallstones

especially after meals • Yellowing skin	
• Painless yellowing skin • Pale-colored stools • Weight loss • Age older than 50 years	cancer of the pancreas, gallbladder, or bile ducts
• Yellowing skin • Fluid in the legs • Swelling of the abdomen (ascites) • Memory loss	liver scarring (cirrhosis)

CHRONIC LIVER DISEASE

During the early stages of long-term (*chronic*) liver disease, people rarely have any symptoms. In general, individuals develop symptoms only during the later stages of liver disease, so it is important for everyone to see their doctor regularly for checkups. Sometimes people will refuse treatment, because they do not have any symptoms, but it's best to manage the disease as early as possible for better health.

People who have chronic liver disease may have general symptoms, such as feeling tired and mild discomfort in the upper right belly. The symptoms of later stages of liver disease, which may have progressed to advanced scarring of the liver (cirrhosis), are listed in table 1.4.

TABLE 1.4. Symptoms and signs of advanced liver disease

Symptoms
• severe fatigue • short-term memory problems • jaundice • impotence in men • enlarged breasts in men (gynecomastia) • swelling of the abdomen or legs • vomiting blood or passing black stools
Signs
• spider-like collections of blood vessels (spider nevi) on the face, arms, or chest • loss of armpit or pubic hair • redness (erythema) of the palms • decrease in size of the testicles • prominent veins on the abdominal wall

- fluid in the belly (ascites)
- flapping tremors (asterixis)
- wasting away of muscles

All of the symptoms of later stages of liver disease can appear with other conditions, meaning none of them occur only in people who have liver disease. For example, some pregnant women have redness in their palms and some red spots with "spidery legs" that turn white when pressed. These spots may be related to the hormone estrogen, which is usually processed by the liver (which is why pregnant women may develop this sign). People who have any of these listed symptoms should talk to a doctor first before coming to any conclusions.

As liver disease progresses, people may notice swelling in their legs (pitting *edema*) and swelling in their belly (*ascites*). Some of the serious signs of liver disease (ascites, bleeding, and confusion) are explained in more detail in later chapters.

COMPLICATIONS OF LIVER DISEASE

From Cirrhosis

As we mentioned before, when the liver suffers damage from liver disease or injury for a long time, it forms scar tissue to replace the healthy tissue. This condition, called cirrhosis, can happen after many years in people who experience liver disease or injury. If the cirrhosis is diagnosed early and its cause is treated, the damage may be reversed. In general, cirrhosis is the presence of a lot of scar tissue throughout the liver, with normal liver tissue appearing as nodules (rounded or irregularly shaped small masses). To the naked eye, a healthy liver normally has a smooth surface, but a liver that has cirrhosis has lumps and bumps.

As cirrhosis progresses and more scar tissue forms, the liver cannot work properly, resulting in serious complications, including swelling in the belly and legs, confusion, and bleeding from the stomach or esophagus. When these complications occur in people who had a previously stable liver disease, it is described as *decompensation of liver*

disease.

Other Serious Complications

Liver cancer is the commonest and most serious complication of cirrhosis. People who have hepatitis B and do not have any fibrosis may also develop liver cancer, because the hepatitis B virus is a cancer-causing virus.

Advanced liver disease may also cause damage to other organs. Kidney failure, which is one of the most serious complications of advanced cirrhosis, is caused by increased blood pressure in the *portal vein*—the blood vessel that takes blood from the digestive system to the liver—and decreased blood flow to the kidney.

Rarely (in less than 5 percent of cases of cirrhosis), people with liver disease may develop lung issues, including shortness of breath, not enough oxygen in their blood (because blood is bypassing the lungs, a condition known as *hepatopulmonary syndrome*), or increased pressure in the blood vessel going to the lungs (*portopulmonary hypertension*).

Advanced liver disease may also cause the heart to stop working (*cirrhotic cardiomyopathy*). This condition is extremely rare. Advanced cirrhosis sometimes results in a wasting away of muscles, malnutrition, vitamin deficiencies, and bone disease (*osteopenia*, or bone thinning, and *osteoporosis*).

In chapter 2, we describe how liver disease is diagnosed.

FURTHER READING

The progression of liver disease. American Liver Foundation. https://liverfoundation.org/for-patients/about-the-liver/the-progression-of-liver-disease/.

Viral hepatitis and liver disease. US Department of Veterans Affairs. https://www.hepatitis.va.gov/basics/liver-single-page.asp.

Schuppan D and Afdal NH. Liver cirrhosis. Lancet. 2008 Mar 8;371(9615): 838–851. https://doi.org/10.1016/S0140-6736(08)60383-9/.

CHAPTER 2

Diagnosing Liver Disease

A doctor can check for liver disease by first taking a history of your symptoms and performing a physical examination. The doctor will ask about your family history or habits that may raise your risk of developing liver disease. The doctor will also do blood tests, imaging tests, or a liver biopsy. This chapter will explain how a doctor checks for liver disease.

BLOOD TESTS

When the liver becomes damaged or infected, the liver cells release more liver enzymes into the blood. Having higher than normal levels of these liver enzymes in the blood can mean the liver is damaged. Sometimes, people who may believe they are healthy learn that they have higher liver enzymes levels when they have a yearly physical examination or other routine blood work. Often the levels are only slightly higher than normal, but such levels do not necessarily correlate with the seriousness of any liver disease. Even having slightly higher than normal levels of liver enzymes could indicate something serious, so it is important to see a doctor about having more tests.

Liver function tests are the most commonly used blood tests to check for liver injury and disease (table 2.1). The liver function tests measure the levels of liver enzymes, proteins, and bilirubin in the blood. The last test listed in the table is prothrombin time, which measures how long it takes for blood to clot.

Liver Enzymes

Liver function tests show the amounts of different liver enzymes in the blood. A doctor uses these tests to learn about the type of liver injury or infection, measure the severity of the

damage, and check to see how a person responds to treatment. The most commonly elevated enzymes are aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT). The doctor can make a better diagnosis from these tests, based on which enzymes are higher than normal and the amount to which they are higher. For example, if a person has higher than normal levels of AST and ALT, this usually indicates that their liver cells have been damaged. The meaning of each test is shown in table 2.2.

TABLE 2.1. Common liver function blood tests to check for liver diseases

albumin
immunoglobulins (Ig)
bilirubin (total, direct, and indirect)
aspartate aminotransferase (AST)
alanine aminotransferase (ALT)
alkaline phosphatase (ALP)
gamma-glutamyl transpeptidase (GGT)
lactic dehydrogenase (LDH)
prothrombin time (PT)

TABLE 2.2. What do the test results mean?

Test	**Meaning of results**
Aspartate aminotransferase (AST)	higher than normal levels mean liver cell damage (it can also come from muscles)
Alanine aminotransferase (ALT)	higher than normal levels mean liver cell damage
Alkaline phosphatase (ALP)	higher than normal levels mean damage to the tube (bile duct) that carries bile from the liver (it can also come from bones or, rarely, the intestine)
Gamma glutamyl transpeptidase (GGT)	higher than normal levels mean damage to the tube (bile duct) that carries bile from the liver (it can come from drinking alcohol or taking other

	medicines)
Albumin	lower than normal levels mean major liver damage
Bilirubin	higher than normal levels mean damage to or blockage of the tube (bile duct) that carries bile from the liver, or significant liver damage
Prothrombin time (PT) or international normalized ratio (INR)	higher than normal levels mean major liver damage (or the person is taking blood-thinning medicines)

People who take a high dose of Tylenol (acetaminophen) may have levels of AST and ALT that are 20 to 200 times higher than normal. People who have chronic hepatitis B or C may have levels of AST and ALT that are 2 to 20 times greater than normal. Both the normal enzyme levels and higher than normal levels that happen with different stages of liver disease are listed in table 2.3.

TABLE 2.3. Levels of liver enzymes associated with specific liver diseases

Test	Normal values	Abnormal values with diseases
Aspartate aminotransferase (AST), alanine aminotransferase (ALT)	men: 0–30 U/L (units per liter) women: 0–18 U/L	*1 to 20 times higher than normal (20–600 U/L)* • chronic hepatitis B • hepatitis C • hepatitis caused by the immune system attacking the liver (autoimmune hepatitis) • medication-related *20 to 50 times higher than normal (600–1500 U/L)* • acute hepatitis C • hepatitis caused by the immune system attacking the liver (autoimmune hepatitis) *20 to 200 times higher than normal (600–6000 U/L)* • acute hepatitis A • acute hepatitis B • too much acetaminophen (Tylenol) • hepatitis caused by not enough blood getting to the liver

Test	Normal values	Abnormal values with diseases
Alkaline phosphatase (ALP)	30–130 U/L	*1 to 2 times higher than normal (30–260 U/L)* • any liver disease • medication-related *2 to 4 times higher than normal (60–520 U/L)* • primary biliary cholangitis • primary sclerosing cholangitis • medication-related *more than 3 times higher than normal (90–390 U/L)* • bile duct obstruction • intrahepatic cholestasis • medication-related

Based on the patterns and levels of different liver enzymes, a doctor can better figure out the nature of the liver injury and know how to possibly treat that person. But because the range of abnormalities in liver enzymes can vary widely, there are no set values that can be used to diagnose any particular disease.

Albumin, Prothrombin Time, and Bilirubin

The liver makes *albumin*, which is a protein in the blood that can do many things, such as carrying vitamins and minerals in the blood. Measuring the amount of albumin in the blood can help a doctor know if there is a serious problem with the liver. Levels of albumin become low after there has been long-term damage to the liver.

Prothrombin is one of the proteins that the liver makes to help the blood clot. The prothrombin time test measures how long it takes for a person's blood to clot. A longer clotting time means the liver has more damage.

Bilirubin is a yellow substance in the blood that is made when red blood cells break down normally. The liver processes bilirubin and stores it in the gallbladder. Bilirubin is part of bile, which helps you digest your food. Levels of bilirubin could be higher for many reasons, including more red blood cell breakdown, liver injury or cirrhosis, blockage of

bile ducts, infection, or the use of some medications.

Measurements of albumin and bilirubin levels and prothrombin time can provide information about how advanced the liver damage may be. For example, people who have cirrhosis may have a lower albumin level and a higher prothrombin time, which means their condition is getting worse.

HEPATITIS TESTING

In addition to doing the blood tests and liver function tests described above, a doctor will request several other blood tests to check for infections, including hepatitis A, B, and C. The common tests for hepatitis A, B, and C are shown in table 2.4.

TABLE 2.4. Tests for hepatitis A, B, and C infections

Test	If present, the results mean
Hepatitis A	
Hepatitis A IgM antibody	the person has an acute hepatitis A infection
Hepatitis A IgG antibody	the person has been exposed to hepatitis A (through an infection or vaccination)
Hepatitis A total (IgM + IgG) antibody	the person either has a new infection or has had the infection before, but if that person doesn't have any symptoms, the results mean they previously had an infection
Hepatitis B	
Hepatitis B DNA	the person has an active virus infection
Hepatitis B core IgM antibody	the person has a new hepatitis B infection
Hepatitis B core IgG antibody	the person has had an infection before or has an ongoing long-term infection
Hepatitis B surface antigen	the person has an active infection

Test	If present, the results mean
Hepatitis B surface antibody	the person is completely immune, either by having had the infection before or by being vaccinated
Hepatitis B virus e antigen	the person has an active infection, but if that person does not have this antigen, it does not mean they don't have an active infection (a mutated virus may not release this protein into the blood, a condition also known as hepatitis Be antigen negative disease)
Hepatitis B virus e antibody	the person may have some immunity, but the presence of this antibody does not always mean immunity; people who do not have the hepatitis B virus e antigen but have an active virus may have this antibody if the virus has mutated (a condition also known as hepatitis Be antigen negative disease)
Hepatitis C	
Hepatitis C antibody	the person has an active infection or has had a hepatitis C infection before
Hepatitis C RNA by PCR	the person has an active infection
Hepatitis C genotype and subtype	an indication of what type of hepatitis C infection the person has (types 1 to 6)
Hepatitis D	
Hepatitis D antibody	the person has been exposed to hepatitis D
Hepatitis D RNA	the person has an active infection
Hepatitis E	
Hepatitis E IgG antibody	the person has been exposed to hepatitis E (through an infection)
Hepatitis E IgM antibody	the person has an acute infection

When a person is exposed to any infection, their body's immune system makes antibodies against that infection.

Antibodies are a type of protein that the body makes to help fight the infection by clinging to surface proteins (*antigens*) on a virus. Special blood tests look for particular antibodies for certain types of hepatitis.

Hepatitis A Testing

A doctor can request a simple blood test to check for hepatitis A. If a person has recently been infected with the hepatitis A virus, they will have immunoglobulin M (IgM) antibodies in their blood. A person who has had hepatitis A for a long time or who has had the hepatitis A vaccine will have immunoglobulin G (IgG) antibodies in their blood.

Hepatitis B Testing

To check for a hepatitis B infection, a doctor will look for several different things in a person's blood to be entirely certain they are infected (see table 2.4). People who currently have hepatitis B or who have ever had the infection will always have some hepatitis B DNA in their liver cells. All of the results of the following tests give your doctor a full picture about your infection:

1. *Hepatitis B surface antigen* (HBsAg): This test determines whether the virus is present in your blood by checking for the specific hepatitis B virus protein (antigen).
2. *Hepatitis B surface antibody* (HBsAb): This test shows that the person has antibodies against hepatitis B, either from having and recovering from a past hepatitis B infection or from being vaccinated for hepatitis B.
3. *Hepatitis B core IgM antibody* (anti-HBcAb IgM): This test checks for a new, current hepatitis B infection.
4. *Hepatitis B core IgG antibody* (anti-HBcAb IgG): This test will show if a person has had a past or chronic hepatitis B infection.
5. *Hepatitis B DNA*: This test measures how much hepatitis B virus DNA is in your blood.
6. *Hepatitis B virus e antigen* (HBeAg): The hepatitis B virus makes this protein in the infected liver cells and

releases the protein into your blood. In general, the presence of this protein in the blood indicates very high levels of virus in the blood and a very active infection. But a negative test does not mean the virus is not making copies of itself; a negative result could mean that there is a mutation of the hepatitis B virus.

7. *Hepatitis B virus e antibody* (HBeAb): This is an antibody made in response to the hepatitis Be antigen. The presence of this antibody may suggest the person is recovering. It is also present in mutations of the hepatitis B virus (known as hepatitis Be antigen negative disease). It is not a protective antibody, and its presence does not mean that the person is less infectious.

Your doctor may request other blood tests to determine the specific type of hepatitis B infection and the amounts of virus in your blood. Your physician may also check for hepatitis D (HDV), as it may coexist with hepatitis B.

Hepatitis C Testing

When a person is infected with hepatitis C, their immune system produces antibodies against the hepatitis C virus. A doctor will request the following tests to check if a person has hepatitis C infection:

1. *Hepatitis C antibody test*: This test checks for hepatitis C antibodies in the blood. The test can't tell the difference between an active hepatitis C infection and a past hepatitis C infection. Anyone who has ever had a hepatitis C infection will have hepatitis C antibodies in their blood. Sometimes (although it rarely happens), people who have hepatitis C will not have antibodies, either because they have a new (*acute*) infection or because they may be immunocompromised from an HIV infection.
2. *Polymerase chain reaction (PCR) test*, to check for hepatitis C virus ribonucleic acid (RNA): If a person has antibodies in their blood, this test will prove that the person has hepatitis C by checking for the amount of hepatitis C genetic material (RNA) in the blood. The

amount of virus RNA does not indicate whether the infection is mild or severe.

The doctor may request more hepatitis C tests to find out the specific type of hepatitis C (known as a *genotype*) you have.

Hepatitis D Testing

Hepatitis D testing is done only for those with hepatitis B, as these two viruses may coexist. A positive antibody test indicates that the person has been exposed to hepatitis D, and a positive RNA test would suggest an ongoing active infection.

Hepatitis E Testing

Hepatitis E is not common in developed countries, but sporadic infections have been reported. In an acute infection, a test for the hepatitis E IgM antibody will be positive. The presence of the IgG antibody suggests previous exposure to hepatitis E. A hepatitis E RNA test is available only for research purposes.

OTHER BLOOD TESTS

To check for other types of liver damage or injury, a doctor can use other blood tests, which include checking for anti-nuclear antibodies, anti–smooth muscle antibodies, anti-mitochondrial antibodies, and other proteins. Some of these tests are listed in table 2.5.

TABLE 2.5. Other blood tests used to diagnose liver diseases

Test	Why it's important
Immunoglobulins	higher than normal levels may mean the person has hepatitis caused by the immune system attacking the liver (autoimmune hepatitis)
Anti-nuclear antibody	higher than normal levels may mean the person has hepatitis caused by the immune system attacking the liver (autoimmune hepatitis); also seen in lupus
Anti–smooth muscle antibody	higher than normal levels may mean the person has hepatitis caused by the immune system attacking the liver

	(autoimmune hepatitis)
Anti-mitochondrial antibody	if present, may mean the person has immune-mediated damage to small bile ducts (primary biliary cholangitis, or PBC)
Ferritin	higher than normal levels may mean the person has a condition where too much iron builds up in the body (hemochromatosis), and levels can be higher in those with an acute (new onset) liver inflammation from any cause
Iron saturation	higher than normal levels may mean the person has a condition where too much iron builds up in the body (hemochromatosis)
Alpha-fetoprotein	higher than normal levels may mean the person has liver cancer (if higher than 400 IU/ml, they almost definitely indicate cancer)

Hemochromatosis gene analysis is a useful test for people who may have *hemochromatosis* (too much iron in their blood), and it could be used to screen family members of individuals with hemochromatosis who have an identified gene mutation.

RADIOLOGICAL TESTS

A doctor can request radiological tests to check for liver disease, including ultrasound, a computed tomography (CT) scan, and magnetic resonance imaging (MRI). These tests can look for fat, tumors, or cirrhosis in the liver.

Other special tests can look at the tubes (bile ducts) that take bile from the liver to see if they are damaged or blocked: magnetic resonance cholangio-pancreatography (MRCP), endoscopic retrograde cholangio-pancreatography (ERCP), or percutaneous transhepatic cholangiography (PTC).

The doctor can also take special X-rays of the blood vessels (angiograms) to see if the vessels are narrowed or *occluded* (blocked).

If a doctor finds anything in these tests that is not normal, they may do a liver biopsy to make a firm diagnosis.

LIVER BIOPSY

Doctors may take a sample of liver tissue (*liver biopsy*) to check for liver disease. In a liver biopsy, a needle is inserted into the liver and a small sample of tissue is taken. This tissue will be tested to check for the type of disease and the amount of damage to the liver.

During a liver biopsy, the doctor first numbs the patient's skin with an anesthetic and then passes a needle between their ribs (figure 2.1). The doctor usually does the biopsy with the assistance of an ultrasound device, to help guide the procedure.

Problems after having a liver biopsy rarely happen (less than 1 in 2,000). Possible problems include bleeding, damage to an organ close to the liver (colon, gallbladder, lungs), pain, or infection. Because these complications are very rare, most doctors consider the benefits of having a liver biopsy to be greater than the possible risks.

Before doing a liver biopsy, the doctor will do some more blood testing to check if it is safe to perform this procedure using the above method. Otherwise, the doctor can get the tissue sample by passing a tube through the neck vein (*transjugular*) and getting a tissue sample using a special needle. People should not take aspirin or similar medications (ibuprofen or other nonsteroidal anti-inflammatory medicines, also known as NSAIDs) for one week before the biopsy and for 48–72 hours afterward. These medicines increase the risk of bleeding because of their effects on platelets in the blood.

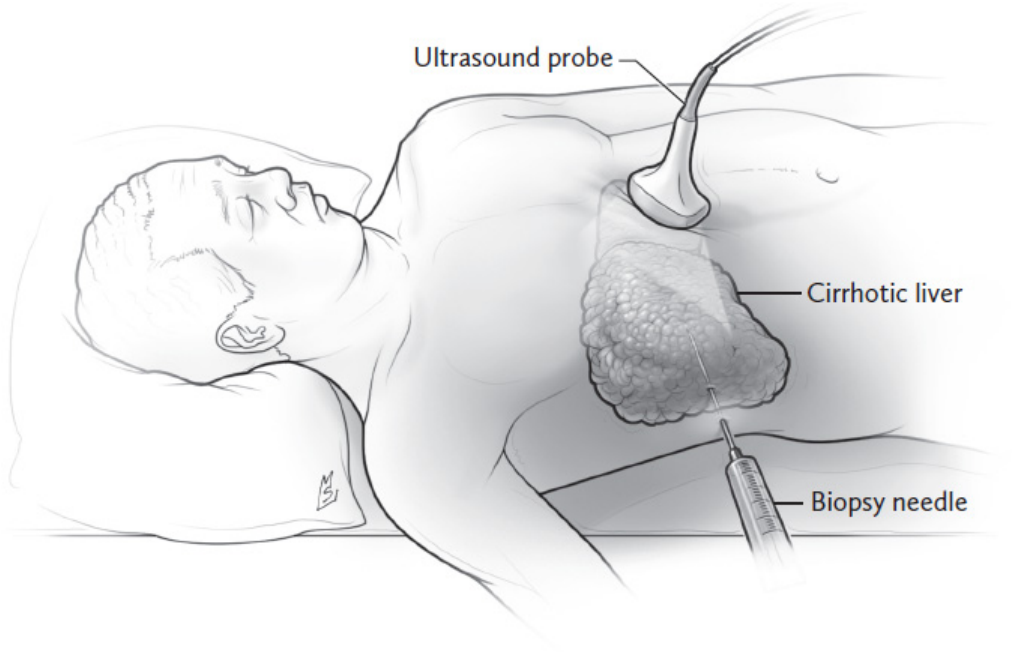

FIGURE 2.1. A liver biopsy

OTHER TESTS TO ASSESS THE SEVERITY OF SCARRING

Because of the possible problems that can happen after having a liver biopsy, doctors can use other tests, like FibroSURE and FibroScan, to check for the severity of liver damage and scarring. Compared with having a liver biopsy, these tests are not as accurate (about 75–85 percent accuracy) in checking for scarring and the amount of liver damage, but these tests don't use any needles and could be administered to a patient more often, if necessary.

There are many blood tests that are commercially available, and they use a combination of serum markers to predict the severity of scarring. There are many pitfalls with blood tests in assessing the severity of scarring, as shown below:

- The presence, not of biological markers (*biomarkers*), but surrogates, which reflect either liver functions or the turnover of scar tissue (*matrix*), but not the deposit of scar tissue.
- Biomarkers that are related not just to the liver, but instead reflect any inflammatory conditions.
- Biomarkers that are affected by the liver's clearance of the

marker and influenced by the severity of the inflammation.
- Biomarkers that cannot differentiate mild to severe (F1 to F3) scarring in a reliable manner but are relatively good at signaling either a normal liver or cirrhosis.

The relative accuracy of these tests is shown in table 2.6.

More often, radiological (either ultrasound or MRI-based) tests are used these days to assess the severity of scarring by measuring the stiffness of the affected tissue. This is an evolving area, and currently there are many options, as shown below. The physics behind these techniques is that scarred tissue responds differently when it is *excited* (stimulated). The devices produce shear waves (electronic sound waves), which travel faster in scarred tissue. Scarred tissue also shows less strain when it is compressed by pressure from the waves. Many other factors, however, also affect liver stiffness, including liver inflammation, heart failure, amount of liver fat, type of liver disease, and *jaundice* (yellowing skin or eyes). These factors reduce the accuracy of these tests.

TABLE 2.6. Accuracy of non-invasive blood tests used to assess fibrosis

Test	Accuracy
AST:ALT ratio	60% to 70%
AST / platelet count	70% to 80%
FibroSURE	75% to 85%
FibroMeter	80% to 85%

Ultrasound-Based Tests

These are:

- Shear wave elastography (SWE)
  - Transient elastography (TE)
  - Acoustic radiation force impulse (ARFI) elastography
- Strain elastography
  - Supersonic shear imaging (SSI)

- Hitachi real-time elastography (HI-RTE)

The main difference between shear wave elastography and strain elastography is the method of excitation. The most commonly used ultrasound technique is transient elastography. With TE, an external device, called a transducer, produces shear waves with low-frequency (50 Hz) vibrations and amplitudes (displacements created by the vibrations). As a shear wave is transmitted through the liver, TE measures its average speed by pulse-echo ultrasound acquisition (the pulses that travel through the tissue and the echoes from those pulses). That speed is then expressed in kilopascals, or kPa (a unit of pressure), and measurement cut-offs have been developed to assess the severity of scarring.

This test is approximately 80 percent accurate, but its results are even better for people with cirrhosis. A diagram of how transient elastography is done is shown in figure 2.2. The procedure, which only takes five minutes, is begun after a person has fasted for three hours. There are no potential complications associated with this test.

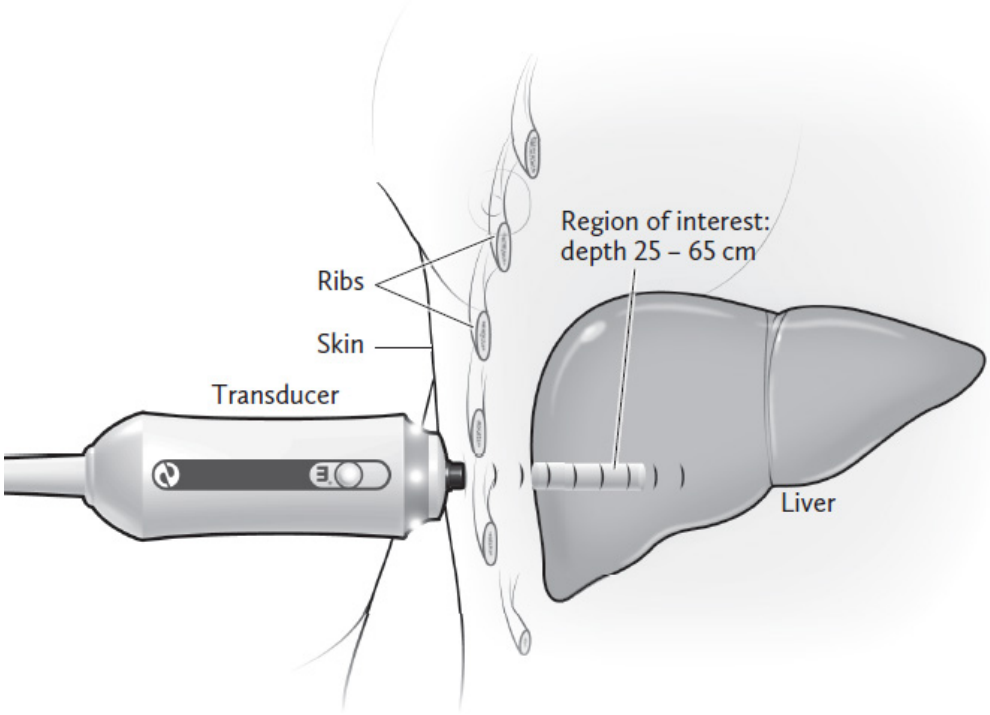

FIGURE 2.2. How transient elastography is done

MRI-Based Test

MR elastography is another technique using MRI, but it scans the entire liver. This procedure is more expensive than ultrasound-based techniques, and its accuracy is only marginally better.

Physicians may use a combination of tests to understand the nature and severity of liver damage.

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CHAPTER 3

What Is Viral Hepatitis?

Hepatitis means “inflammation of the liver.” Bacteria, viruses, toxins, or medications can cause this inflammation. It could be even caused by your immune system damaging itself (in a process called *autoimmunity*). The most common causes of hepatitis are viruses—namely, the hepatitis A, hepatitis B, hepatitis C, and hepatitis E viruses. These viruses all have one thing in common: They invade normal liver cells and take over those cells to make copies of themselves.

Viral infections, including hepatitis A, B, C, and E, are the most common causes of hepatitis. Hepatitis E is very uncommon in the United States. Hepatitis D, also known as delta virus, needs the hepatitis B virus to make copies of itself, so hepatitis D is only seen in people who are infected with hepatitis B.

VIRAL HEPATITIS

In the United States, the most common viruses that cause hepatitis are hepatitis A, hepatitis B, and hepatitis C. According to the Centers for Disease Control and Prevention (CDC), in 2018, hepatitis C infected more than 50,300 new people, and hepatitis B infected more than 22,600 new people; hepatitis A infects about 24,000 people each year.

The tests used for the diagnosis of viral hepatitis are shown in table 2.4 (chapter 2).

SYMPTOMS

It can take weeks or months after a person has been exposed to the hepatitis virus to have the infection. Most people with any type of hepatitis infection (whether it’s acute or chronic) have

no symptoms, don't feel sick, and don't know they are infected. People who have new (acute) infections will often have no symptoms. The symptoms for hepatitis A, hepatitis B, and hepatitis C are similar. Symptoms people infected with hepatitis may experience are:

- Fatigue
- Loss of appetite
- Yellowing skin or eyes
- Nausea / upset stomach
- Vomiting
- Abdominal pain
- Joint pain
- Dark-colored urine
- Light-colored stools

TYPES OF VIRAL HEPATITIS

Hepatitis A

Hepatitis A, caused by the hepatitis A virus, is very contagious. A person infected with hepatitis A has the virus in their blood and their stools. It is usually spread when a person eats food or drinks water contaminated with feces from a person who has hepatitis A. It can also be spread through close or sexual contact with an infected person. Hepatitis A infections are always short lasting (acute), but they can be present from a few weeks to a few months. Sometimes the illness can be serious. No treatment exists for hepatitis A infections, but medications can help relieve some of the symptoms, such as an upset stomach and vomiting. Hepatitis A infections can be prevented with a vaccine (2 doses, 6 months apart). Practicing good hygiene by washing your hands before cooking and eating will help prevent infection.

TABLE 3.1. Types of hepatitis infections

Infection	Duration	How is it spread?	Is there a cure?	Is there a vaccine?

Infection	Duration	How is it spread?	Is there a cure?	Is there a vaccine?
Hepatitis A (HAV)	short-term	• food or water contaminated with feces from an infected person	no	yes
Hepatitis B (HBV)	short-term or long-term	• infected mother to baby (common) • sex with an infected person • sharing needles or other drug equipment with an infected person	no, but the virus can be slowed or stopped very efficiently	yes
Hepatitis C (HCV)	short-term or long-term	• sharing needles or other drug equipment with an infected person • sex with an infected person • infected mother to baby (rare)	yes (more than 95% can be cured)	no
Hepatitis D (HDV)	short-term or long-term	• sharing needles or other drug equipment with an infected person • sex with an infected person	no	no
Hepatitis E (HEV)	short-term	• food or water contaminated with feces from an infected person • blood transfusion from an infected person (very rare) • infected mother to baby (extremely rare)	no	none available in the United States

Note: Viruses such as the herpes simplex virus (HSV), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) may also cause acute liver injury. Liver enzyme abnormalities are common in SARS-CoV-2 (COVID-19) infections, but it is not known whether such abnormalities are the direct result of the infection.

Hepatitis B

Hepatitis B, caused by the hepatitis B virus, can be spread through having sex with an infected person or by sharing

needles, syringes, or other drug-injection equipment. Hepatitis B can also be passed from an infected mother to her baby at birth. Hepatitis B infections can be either short lasting (acute) or long lasting (chronic). Acute infections will happen within a few weeks after a person is infected with the hepatitis B virus. These infections can be mild or severe. Most adults (around 95 percent) become immune to the virus and recover from the infection. Most children and babies (roughly 90 percent) who are infected have the infection for the rest of their lives. No cure exists for hepatitis B, but medications can stop or slow the virus from causing damage to the liver. Hepatitis B can be prevented with a vaccine (2 doses, 1 month apart).

Hepatitis C

Hepatitis C, caused by the hepatitis C virus, spreads when blood from a person infected with the virus enters the body of an uninfected person. The most common way of spreading hepatitis C is by people sharing syringes or needles to inject drugs. A less common way is through sexual contact. Hepatitis C infections can be either short lasting (acute) or long lasting (chronic). About half of the people who become infected develop a lifelong infection. Several treatments exist for hepatitis C. Unlike hepatitis B, hepatitis C can be easily cured.

Hepatitis D

Hepatitis D, which is sometimes called the “delta virus,” is only found in people who have hepatitis B. The hepatitis D virus spreads when blood from a person infected with the virus enters the body of an uninfected person. Both viruses can infect a person at the same time (*coinfection*), or people with hepatitis B may contract hepatitis D later (*superinfection*). Hepatitis D infections can be either short lasting (acute) or long lasting (chronic). Hepatitis D could be treated with interferon, but success rates are not very high. No vaccine exists to prevent hepatitis D, but preventing hepatitis B infections will also help prevent hepatitis D infections.

Hepatitis E

Hepatitis E is usually spread when a person eats food or drinks

water contaminated with feces from a person infected with hepatitis E. Rarely, it can be spread by a transfusion of blood products contaminated with hepatitis E. Hepatitis E can also be passed from an infected mother to her baby. In the United States, hepatitis E is rare; it is mostly seen in South Asia. Hepatitis E is usually short lasting, although occasional chronic infections have been reported in immunocompromised people. No reliable vaccine exists to prevent hepatitis E infections.

Other Viruses

Other viruses—such as herpes simplex virus (HSV), Epstein-Barr virus (EBV), and cytomegalovirus (CMV)—may also cause acute liver injury. These infections are usually asymptomatic or self-limiting. CMV infections are the most common opportunistic infections in organ transplant recipients. In immunocompromised people, these infections could be very severe.

Chapters 4 and 5 contain more information about hepatitis B and C.

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CHAPTER 4

Understanding Hepatitis B

Worldwide, hepatitis B is a much bigger problem than hepatitis C. There are approximately 250 million people with hepatitis B, and it causes more than 500,000 deaths per year. Hepatitis B is more common in parts of Africa and Asia, where many people, while in the womb, contract the infection from their mother (vertical transmission). Up to 10 percent of the people in Asia, and as many as 50 percent in sub-Saharan Africa, are exposed to hepatitis B. Hepatitis B is also more common in those with hepatitis C or HIV because of a similar spread of these infections. According to the CDC, approximately 900,000 people in the United States have chronic hepatitis B.

Hepatitis B and hepatitis C are similar in many ways, but there are also many differences. Hepatitis C is a RNA virus, while hepatitis B is a DNA virus. Both are spread in a similar manner, but hepatitis B is more infectious than either HIV or hepatitis C. Another major difference is that hepatitis C is curable, whereas hepatitis B is not. Nonetheless, hepatitis B can be suppressed very effectively with medications.

Hepatitis B is a very complex DNA virus (figure 4.1). A hepatitis B infection, caused by the hepatitis B virus, can be a short-lasting (acute) illness or a long-term (chronic) illness.

Acute hepatitis B infection: When someone first becomes infected with hepatitis B, they have an acute infection. These infections usually last six months or less.

Chronic hepatitis B infection: These types of infections are when the hepatitis B virus stays active for more than six months.

Whether a person develops a long-term (chronic) illness depends partly on their age. Most adults (90–95 percent) who

have a hepatitis B infection recover without treatment and without suffering from a long-term illness. But most babies (90 percent) and children younger than 5 years old who become infected with hepatitis B will have the disease for the rest of their lives (also known as immune tolerant hepatitis B). Infected babies and young children usually do not develop liver disease, but they have a higher risk of liver cancer occurring when they get older.

Worldwide, hepatitis B is the most common cause of liver cancer.

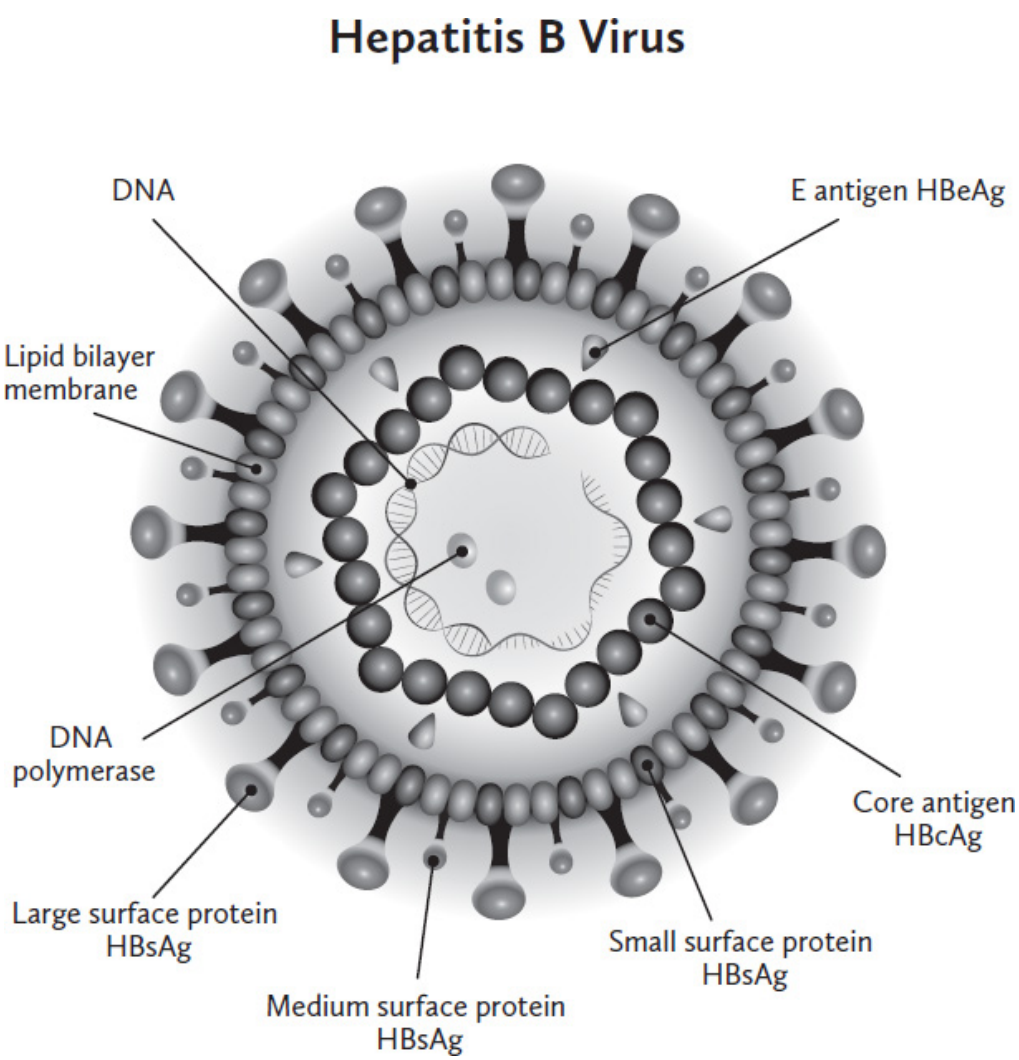

FIGURE 4.1. The structure of the hepatitis B virus

SYMPTOMS

People may or may not have any symptoms when they first become infected with the hepatitis B virus (acute infection).

Whether they start to feel symptoms partly depends on their age. Most children with acute infections are asymptomatic, but most adults with acute hepatitis B will have some signs of the disease.

A person who has a hepatitis B infection may have some of the following symptoms:

- Fever
- Fatigue
- Poor appetite
- Nausea
- Vomiting
- Discomfort or pain in the upper right belly
- Joint pain
- Yellowing skin or eyes
- Dark-colored urine
- Light-colored stools

Most people with long-term hepatitis B have no symptoms until the disease has progressed to cirrhosis.

HOW HEPATITIS B IS SPREAD

The hepatitis B virus spreads when blood, semen, or other body fluids from a person infected with the hepatitis B virus enters the body of someone who is not infected with the virus. This can happen when a person:

1. Shares intravenous needles, syringes, or drug equipment with an infected person
2. Has sex with an infected person
3. Shares toothbrushes, shaving razors, or medical supplies with an infected person
4. Is accidentally exposed to the hepatitis B virus by a needlestick or spill

In addition, a mother who has hepatitis B can pass the infection to her baby during birth.

Some people who have a higher risk of getting infected include:

- Those who share needles during intravenous drug use
- Those who live with an infected person
- Health care workers who may be exposed to infected blood and other body fluids
- Those who travel to a part of the world where hepatitis B is common (the transmission routes are the same as above).

Anyone who has a higher risk of becoming infected can prevent the infection with the hepatitis B vaccine. Ideally, everyone should receive the hepatitis B vaccine.

DIAGNOSING HEPATITIS B

To check if you have a hepatitis B infection, a doctor will test for several different things in your blood to be entirely certain you are infected (tables 2.4 and 4.1). People who currently have hepatitis B or who have ever had the infection will always have some hepatitis B DNA in their liver cells, so it's important to have the full set of tests to know whether you have a current or past infection. The results of these tests will give your doctor a complete picture about your infection, including if you have a short-term or a long-term infection.

TABLE 4.1. Tests for a hepatitis B infection

Test	If present, the results mean
Hepatitis B DNA (HBV DNA)	the person has an active virus infection
Hepatitis B core IgM antibody (HBcIgM)	the person has a new hepatitis B infection
Hepatitis B core IgG antibody (HBcIgG)	the person has had an infection before or has an ongoing long-term infection
Hepatitis B core total antibody (measures both IgG and IgM)	the person has an acute or chronic infection (if an acute infection is suspected, your doctor will request an IgM antibody test)

Hepatitis B surface antigen (HBsAg)	the person has an active infection
Hepatitis B surface antibody (HBsAb)	the person is completely immune by either having had the infection before or by being vaccinated
Hepatitis B virus e antigen (HBeAg)	the person has an active infection, but if that individual does not have this antigen, it does not mean they don't have an infection (a mutated virus may not release this antigen into the blood)
Hepatitis B virus e antibody (HBeAb)	the person may have some immunity, but the presence of this antibody does not always mean immunity; people who do not have the hepatitis B virus e antigen but have an active virus could have this antibody if the virus has mutated and does not release the hepatitis B virus e antigen

For most people, their doctor can tell the difference between an acute and a chronic infection, based on the results of the hepatitis B core IgM antibody test. IgM antibodies are usually present in the blood when a person has an acute hepatitis B infection.

People who have hepatitis B should also be tested for:

1. Hepatitis C
2. HIV
3. Hepatitis D

People who have hepatitis B have a higher risk of having liver cancer. So anyone who has a hepatitis B infection should talk to their doctor about whether they should have regular cancer screenings (about every six months), depending on their age, health, and family history of liver cancer or liver disease.

TREATMENT

There is no cure for hepatitis B, but treatment can help people recover from the infection.

For Acute Hepatitis B

Most people who have acute hepatitis B usually get better without any treatment. In about 90–95 percent of adults who have this infection, they will recover without any problems. To help with recovery, their doctor may recommend getting sufficient rest, eating well, avoiding alcohol, and staying hydrated.

In some people who have severe acute infections, their doctor may recommend starting treatment with medicines (table 4.2). It is extremely rare (less than 1 percent) for someone to need a liver transplant.

- All those without immunity to hepatitis B (the presence of hepatitis B surface antibodies) who are in contact with a person with acute hepatitis B, either in their household or sexually, should have treatment with hepatitis B immune globulin and a vaccination to prevent this infection.

For Chronic Hepatitis B

About 5 percent of adults who have acute hepatitis B infections develop a long-term (chronic) infection, meaning the infection lasts longer than six months. Those who have a chronic infection may develop severe liver damage (chronic hepatitis) and cirrhosis. The complications of cirrhosis from this type of infection are the same as those for cirrhosis from any other causes.

Many people who have long-term infections will need medications to help them feel better, prevent the progression of liver disease, and reduce the risk of liver cancer. Treatment, however, will not help everyone who has a long-term hepatitis B infection. For example, taking medication may not help people who don’t have any signs of damage to their liver, based on blood tests or a liver biopsy. Talk to your doctor to decide if treatment is right for you.

Visit Your Doctor

Tell your doctor that you have had a hepatitis B infection if you need:

- Chemotherapy
- An organ transplant
- Treatment for hepatitis C.

A hepatitis B infection can flare up and get worse.

If You Take Medicine for Hepatitis B

Once a person starts treatment for a hepatitis B infection, they may need to take medication for the rest of their lives. They should visit their doctor every three to six months to check if the treatment is working well, find out if their liver disease may be getting better or worse, and be tested for liver cancer (every six months).

If You Don't Take Medicine for Hepatitis B

Even if you don't need to take medication, you still should see your doctor regularly to make sure the infection is not getting worse because of the following possibilities:

1. The infection can flare up for no reason.
2. You still have a risk of developing liver cancer.

IS TREATMENT RIGHT FOR YOU?

Talk to a doctor to figure out if treatment is the best option. There are many different things to consider when deciding whether to start treatment.

In general, most people who have a long-term hepatitis B infection should take medication if:

- They have higher than normal levels of liver enzymes and very high levels of hepatitis B virus DNA in their blood.
- They have signs of liver damage.
- They have cirrhosis.
- They have liver cancer.
- They are going through chemotherapy or planning to have an organ transplant, even if they do not have an active

hepatitis B infection and the levels of the hepatitis B virus in their blood are very low.
- They are pregnant and have very high levels of the hepatitis B virus in their blood (if so, they should get treatment in the third trimester to lower the risk of passing the infection to the baby).
- They have hepatitis C and have hepatitis B virus DNA in their blood.

In addition, the doctor will consider many other factors, such as whether the person has the hepatitis Be antigen in their blood, the levels of hepatitis B virus DNA in their blood, and whether they have a family history of liver cancer.

The doctor may also take a sample of liver tissue (liver biopsy) to check for liver disease, depending on the results of other tests and the levels of liver enzymes.

TYPES OF TREATMENTS

There is no cure for hepatitis B, but there are very effective treatments to suppress the replication of the virus.

The two most common medicines used to treat hepatitis B are entecavir and tenofovir. Other treatments—such as telbivudine, adefovir, and lamivudine—are not used today, because entecavir and tenofovir are more effective and safer. Both entecavir and tenofovir are very potent in treating hepatitis B infections by preventing the hepatitis B virus from multiplying in the body, which can then help prevent the progression of liver damage and lower the risk of developing liver cancer.

Both entecavir and tenofovir are pills, taken once daily. They are very safe and have hardly any side effects. Entecavir and tenofovir could be used without dose adjustments, even in the presence of liver failure, but the dose may need to be changed in the case of kidney dysfunction.

There are two preparations of tenofovir available in the market, and both are equally effective. There may be a marginal benefit with tenofovir alafenamide (25 mg, daily) in

older people and those with renal insufficiency when compared with tenofovir disoproxil fumarate (tenofovir DF, 300 mg daily). Tenofovir alafenamide may generate less osteoporosis and is less likely to cause renal insufficiency.

- There is no safety data on tenofovir alafenamide or entecavir in pregnant women. Therefore, tenofovir DF is the drug of choice in pregnancy.

Side Effects of Entecavir or Tenofovir

Side effects are minimal or none with both medications. Very rarely, tenofovir DF may cause kidney dysfunction or bone thinning (osteopenia). Using tenofovir alafenamide could minimize these side effects.

Unusual side effects of these medications include muscle weakness or peripheral neuropathy. In those with advanced cirrhosis, especially with kidney failure, lactic acid can build up in the body (lactic acidosis).

Treatment Monitoring

It is important to take these medicines exactly as instructed by your doctor and to talk to your doctor regularly. Rarely, the hepatitis B virus can change (mutate), so the medicines don't work any more in treating the infection.

- People who test positive for the hepatitis Be antigen may be able to stop taking medicines for a hepatitis B infection, based on their progress. Always talk to your doctor about any changes to your treatment.
- For people who have active liver disease and do not have the hepatitis B virus e antigen in their blood, there are no tests to determine when to stop treatment. Most physicians will consider continuing treatment for the rest of the person's life, or until the hepatitis B surface antigen disappears.

In general, the majority of people with an active hepatitis B infection will need lifelong treatment and follow-ups. Those with hepatitis B also need to be screened for liver cancer on a

regular basis for the rest of their life, irrespective of whether they have liver disease, since hepatitis B is a cancer virus.

TABLE 4.2. Medicines to treat hepatitis B

Antiviral medication	How it is taken	Preferred groups	Side effects
Entecavir	pill taken once a day on an empty stomach	people with renal insufficiency	RARE but can include the following: • in those with advanced cirrhosis, especially with kidney failure, lactic acid can build up in the body (lactic acidosis)
Tenofovir alafenamide, 25 mg daily	pill taken once a day with food	older people people with renal insufficiency	RARE but can include the following: • in those with advanced cirrhosis, especially with kidney failure, lactic acid can build up in the body (lactic acidosis)
Tenofovir disoproxil fumarate, 300 mg daily	pill taken once a day, with or without food	pregnant women (pregnancy category B)	RARE but can include the following: • kidney dysfunction • thinning of bones (osteopenia) • peripheral neuropathy • in those with advanced cirrhosis, especially with kidney failure, lactic acid can build up in the body (lactic

			acidosis)
Interferons	injection weekly	those who prefer short-term (1 year) treatment	COMMON • flu-like illness, mood disorders, loss of appetite, weight loss, low blood counts

Note: Side effects (such as nausea, vomiting, diarrhea, headache, skin rash, fatigue, dizziness, and sleep problems) have been reported with both entecavir and tenofovir, but these are very infrequent.

OTHER MONITORING

Hepatitis B is a chronic (lifelong) disease. Even if a person does not require treatment, there is a possibility that the disease could flare up without any precipitating cause. It is therefore important to follow up with their physician as recommended (usually every 3–12 months, depending on multiple factors). Surveillance for liver cancer is also necessary, even if the person does not require hepatitis B treatment.

If a person has had exposure to hepatitis B, it is important to inform their cancer specialist of this if they ever need chemotherapy. Inactive hepatitis B could flare up during chemotherapy or if the immune system is suppressed with medications (such as after an organ transplant). This also applies to people who have both HCV and hepatitis B. Before any treatment of hepatitis C, it is important to discuss the management of hepatitis B with your physician, as inactive hepatitis B could flare up during treatment for hepatitis C.

PREVENTION

The most effective way to prevent an infection with hepatitis B in people who have not had this disease before is to get the hepatitis B vaccine. This vaccine is safe, and the side effects are very rare.

Once individuals have had hepatitis B, they do not benefit from vaccination. In the United States, hepatitis B vaccination

has become routine only recently, so most adults do not have immunity against hepatitis B. The new hepatitis B vaccine is given as 2 doses, 1 month apart.

Because it is common for mothers to pass the hepatitis B infection to their babies at birth, every pregnant woman should be tested for hepatitis B. If a pregnant woman has a hepatitis B infection and has high levels of the hepatitis B virus in her blood, she should see a doctor who specializes in treating liver disease. The doctor will decide whether the woman should start taking medicine when it is safe during the pregnancy (usually in the last three months). Every at-risk child should be vaccinated right after they are born.

FUTURE TREATMENT

At this time, hepatitis B is incurable, but there is ongoing intense research to find a cure for this disease. Currently available medications do not inhibit or eradicate covalently closed circular DNA (cccDNA), which is seen in the nucleus of infected liver cells in people with hepatitis B. There are many potential preventive molecules—including cccDNA inhibitors, immune modulators, capsid inhibitors, small interfering RNA, and hepatitis B surface antigen inhibitors—in developmental stages. As with hepatitis C, we hope to find a cure for hepatitis B in the near future, using a combination of molecules.

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CHAPTER 5

Understanding Hepatitis C

Approximately 2.4 million adults in the United States live with chronic hepatitis C. According to CDC estimates, 50,300 adults in the United States were infected with hepatitis C in 2018. Worldwide, it is estimated that 120 to 200 million people live with hepatitis C. Approximately 400,000 people worldwide die from hepatitis C–related liver disease or cancer every year. Unlike hepatitis B, hepatitis C is an RNA virus. The structure of the hepatitis C virus is shown in figure 5.1.

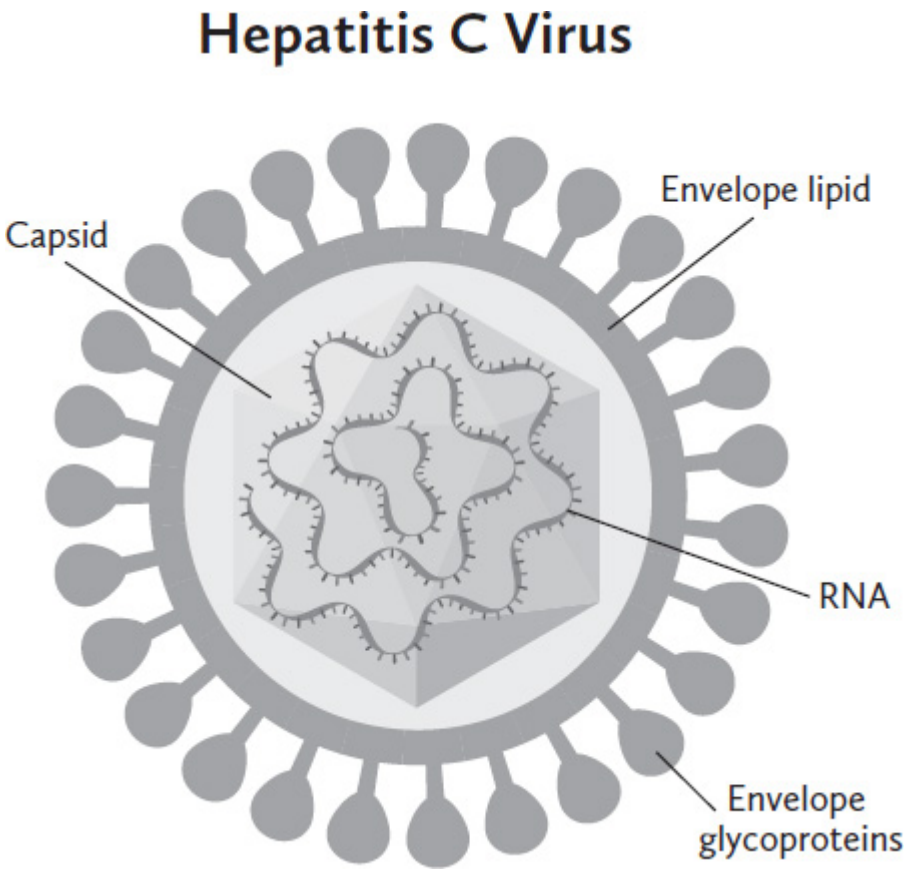

FIGURE 5.1. The structure of the hepatitis C virus

Hepatitis C, caused by the hepatitis C virus, can be either a short-lasting (acute) or long-lasting (chronic) illness. On average, it takes 45 days from the beginning of the infection

for symptoms to start to appear, but this time period can range from 15 days to 6 months.

Acute hepatitis C infection: When someone first becomes infected with hepatitis C, they have an acute infection. These infections usually last six months or less.

Chronic hepatitis C infection: In these types of infections, the hepatitis C virus stays active for more than six months.

About 30–50 percent of the people who have an acute hepatitis C infection will be cured without any treatment or long-term problems. Almost 50–70 percent of the people who have hepatitis C, however, will develop a long-lasting (chronic) infection. Chronic hepatitis C can cause long-term health problems, such as liver cirrhosis, liver cancer, and death.

There are several different types of hepatitis C viruses, which can be grouped into various categories (genotypes). Hepatitis C has genotypes 1 to 6 and many more subtypes within those. In the United States, about 70 percent of the people with hepatitis C have genotype 1.

SYMPTOMS

Most people (about 80–90 percent) who have acute hepatitis C infections do not have any symptoms. About 10–20 percent of the people who have acute hepatitis C will experience some of the following symptoms:

- Fatigue
- Loss of taste
- Loss of appetite
- Nausea or vomiting
- Yellow-colored skin or eyes
- Dark-colored urine
- Light-colored stools

People who have chronic hepatitis C rarely have symptoms, but if they do, they may feel tired or have discomfort in their

upper right belly.

HOW HEPATITIS C IS SPREAD

The hepatitis C virus spreads when blood or blood products from a person infected with the hepatitis C virus enter the body of someone who is not infected with the virus. This can happen when a person:

1. Shares intravenous needles or other drug equipment with an infected person
2. Gets a blood transfusion from an infected person
3. Gets an organ from an infected donor
4. Has sex with an infected person
5. Is accidentally exposed to the hepatitis C virus by a needlestick or spill
6. Gets a tattoo with equipment that is not clean
7. Shares toothbrushes or shaving razors with an infected person

In addition, a mother who has hepatitis C can pass the infection to her baby during birth.

The most common way of spreading hepatitis C is by people sharing syringes or needles to inject drugs. Less common ways are through sexual contact, accidentally getting stuck by a needle, a blood transfusion with infected blood, or an infected mother passing the virus to her baby at birth.

Before the discovery of hepatitis C in 1989, little was known about the infection, which was most commonly spread by transfusions with infected blood products and could cause chronic liver disease.

The discovery marked a major breakthrough in understanding transfusion-related hepatitis, resulting in the routine screening of blood products for hepatitis C. Thanks to these more-thorough screening procedures and safer practices among users, the number of new hepatitis infections has gone down in the United States, from about 230,000 per year in 1989 to 50,300 (estimated) in 2018.

Some people who are at a higher risk of becoming infected with hepatitis C include:

- People who use intravenous drugs
- People who were born between 1945 and 1965
- People who received a blood transfusion before 1989
- People who have HIV
- Men who have sex with men
- People who receive hemodialysis
- People who have hemophilia
- People who have multiple sexual partners
- People who are in prison
- People who inhale drugs
- Sexual partners of those infected with both hepatitis C and HIV

Most daily activities are safe and carry no risk of a hepatitis C infection.

- Sharing food or drinks
- Living in the same household
- Kissing, hugging, shaking hands
- Close, nonsexual body contact

DIAGNOSING HEPATITIS C

To determine if you have a hepatitis C infection, a doctor will do some of the blood tests listed in chapter 2, including checking your levels of liver enzymes. But, because many people who have a hepatitis C infection have normal levels of liver enzymes and have no symptoms, the doctor will test for several different things in your blood to be entirely certain whether you are infected (table 5.1). People who currently have hepatitis C will always have some hepatitis C RNA in their blood, so it's important to have the full set of tests to know whether you have a current or past infection. All of the results of these tests give your doctor a complete picture of your infection, including if the infection is acute or chronic.

Hepatitis C Antibodies

A person who has or ever has had a hepatitis C infection will have hepatitis C antibodies in their blood. Rarely, a person who has never had hepatitis C will have hepatitis C antibodies

in their blood (false positive antibodies). These occur more commonly in *immune-mediated diseases* (diseases related to the immune system), such as rheumatoid arthritis, lupus, and autoimmune liver diseases. In general, the hepatitis C antibody test is accurate, and 80 percent of those not previously treated whose blood contains detectable amounts of these antibodies have an ongoing hepatitis C infection.

TABLE 5.1. Tests for a hepatitis C infection

Test	If present, the results mean
Hepatitis C antibody test	the person has an active infection or has had a hepatitis C infection before
Hepatitis C RNA by PCR	the person has an active infection
Hepatitis C genotype and subtype	an indication of what type of hepatitis C infection the person has (types 1 to 6)

Hepatitis C RNA PCR test

To find out whether a person has an active hepatitis C infection, a blood test called an HCV RNA test is used. This test could detect small amounts of the virus circulating in the blood. This procedure could be done as a qualitative measurement (with a “yes” or “no” result) or as a quantitative test (to determine the amount of virus present). Qualitative tests are rarely used these days.

The quantitative PCR test measures the amount of hepatitis C genetic material (RNA) in the blood. The quantitative PCR result is described in international units (IU) per milliliter (ml) of blood. This test is used to determine whether a person has a current hepatitis C infection, as well as to show whether a hepatitis C treatment is working sufficiently. The test is not used to check whether you have a severe infection. In other words, a higher quantitative number does not necessarily mean that the infection is very serious or is getting worse.

The doctor will use other blood tests, an ultrasound of the liver, and additional tests to determine the amount of damage to the liver and figure out the best treatment plan.

People who have hepatitis C should also be tested for:

1. Hepatitis A
2. Hepatitis B
3. HIV
4. Other liver diseases

Since hepatitis C is common, and the way the disease shows up may vary in children and in people with an HIV infection, it is described in more detail in the next section.

ACUTE HEPATITIS C

Acute hepatitis C is a short-term illness that occurs within the first six months after exposure to the hepatitis C virus. The hepatitis C virus is the cause of 15 percent of all acute hepatitis cases reported in the United States. The number of new hepatitis C infections had decreased significantly over the past three decades in the United States, but, more recently, an increase has occurred, which has been attributed to the opioid epidemic.

Acute hepatitis C infection may occur from 2 to 12 weeks after the time of exposure (on average, 7 weeks), and illness from the infection may last for 2–12 weeks. Acute hepatitis C can be mild—only about 10–20 percent of the people who have the infection will develop symptoms. Very rarely, the acute infection can be severe and prolonged (lasting for weeks to months), accompanied by jaundice or liver failure.

About 30 percent (or higher, if jaundice develops) of the people who have acute hepatitis C are cured spontaneously. These people will have hepatitis C antibodies in their blood for the rest of their life, but they will have no hepatitis C virus in their body. Nonetheless, the presence of antibodies does not protect these people from a future reinfection by the hepatitis C virus.

There are no blood tests that can distinguish between a person who has an acute hepatitis C infection and someone who has had the infection for a long time (chronic infection). A physician may suspect a person has an acute hepatitis C infection under the following circumstances:

- The person has had an identifiable exposure to the virus, followed by an increase in liver enzymes or the presence of symptoms.
- The person has previously had consistently normal liver enzymes, later followed by a marked increase in liver enzymes and the presence of symptoms.
- The person had an earlier negative hepatitis C RNA test result, but a second test result is positive.

The only way for a physician to conclusively diagnose an acute hepatitis C infection is to record the development of antibodies (called seroconversion) in an individual who previously lacked those antibodies. This process happens most frequently when a needlestick occurs that exposes a person to the hepatitis C virus and the individual is monitored for a certain length of time, or in studies that look at high-risk individuals who test negative for a hepatitis C infection. Testing for hepatitis C antibodies, however, is not a reliable way to confirm an acute hepatitis C infection, because in as many as 30 percent of the people, the production of antibodies may be delayed when symptoms appear.

CHRONIC HEPATITIS C

Once chronic hepatitis C develops, the likelihood that the person will spontaneously clear the virus is less than 10 percent. People with chronic hepatitis C rarely have any symptoms when the disease is mild. People in the advanced stages of liver disease are the ones who develop symptoms—such as jaundice, fluid in the abdomen, swelling in the legs, or confusion—which is an important reason for individuals who have chronic hepatitis C to seek help before these conditions occur.

Because people who have hepatitis C often do not have symptoms, many of them learn they have liver disease as a result of routine blood tests. After diagnosing hepatitis C in an individual, the physician will assess the severity of the liver disease (described in chapter 2) by a combination of blood tests, FibroScan, or (rarely) a liver biopsy. Today, a liver

biopsy is performed only when other non-invasive tests are inconclusive or when another accompanying liver disease is suspected.

Stages of Liver Scarring (Fibrosis)

Your doctor may describe the severity of scarring in terms of *stages*. Stage 0 is when there is no liver scarring. A commonly used scoring system (Metavir) describes liver scarring (fibrosis) as minimal or mild (early, or stage 1), moderate (intermediate, or stage 2), severe (advanced, or stage 3), or established (stage 4) cirrhosis. Scoring systems are applicable to almost all liver diseases and are not unique for hepatitis C.

Progression to Cirrhosis in Chronic Hepatitis C

Approximately 20–30 percent of the people who have hepatitis C will develop cirrhosis within 10 to 20 years after they become infected, and around 30 percent may develop cirrhosis after 40–50 years. It is important to remember, however, that 30–40 percent of the people who have hepatitis C may never develop any serious liver damage.

Alcohol is perhaps the most important risk factor in predicting a progression to cirrhosis, and individuals who have hepatitis C should abstain from drinking alcohol. Other risk factors for developing cirrhosis are acquiring a hepatitis C infection through a blood transfusion and contracting hepatitis C after the age of 50. HIV coinfection also makes hepatitis C–induced liver disease worse. No convincing evidence suggests that the amount of hepatitis C virus in the blood (the viral load) and the virus's genetic subtype (genotype) predict the progression of this disease.

Some Strategies for Preventing the Progression of Hepatitis C or Other Liver Diseases

1. Avoid drinking alcohol completely.
2. Receive vaccinations for hepatitis A and hepatitis B.
3. Maintain good general health, weight, and lifestyle.
4. Control your cholesterol and triglyceride levels, high blood pressure (*hypertension*), and diabetes.
5. Stop smoking.

6. Seek treatment for a hepatitis C infection. A cure will reduce the risks of progression to cirrhosis and the development of liver cancer.

COINFECTION WITH HIV AND HEPATITIS C

Because hepatitis C and HIV are blood-borne infections, it is common for individuals to be infected with both the hepatitis C virus and HIV. Worldwide, approximately 40 million people have HIV and, of those, between 4 and 5 million also have hepatitis C. In the United States, between 25 and 33 percent of those who have HIV—approximately 150,000 to 300,000 people—also have hepatitis C.

With the availability of effective HIV treatments, such as highly active anti-retroviral therapy (HAART), hepatitis C–related liver disease has emerged as a major cause of death among people who have HIV. The 10-year survival rate for people receiving HAART is nearly 90 percent, reinforcing the importance of treating hepatitis C in those who have HIV.

Among people who have HIV and use intravenous drugs, between 60 and 90 percent also have hepatitis C. In contrast, intravenous drug use was reported by between 15 and 30 percent of the people who only had HIV. Among people who contracted HIV through contaminated blood products, approximately 50–70 percent have hepatitis C. The risk of transmission from each needlestick exposure is 10 times higher for hepatitis C than for HIV.

The rate of a hepatitis C infection is low (7–14 percent) in people who become infected with HIV through sexual behaviors. This low prevalence of hepatitis C among sexual partners of people who have HIV indicates a lesser transmission rate of hepatitis C through sexual exposure. Nonetheless, to further prevent the spread of HIV and hepatitis C, people infected with both diseases should use condoms during sexual intercourse.

- All HIV-infected individuals should be tested for hepatitis C with a hepatitis C antibody test.

- Individuals at high risk of a hepatitis C infection should routinely undergo a PCR test to detect hepatitis C RNA, even if hepatitis C antibodies are not present.

Effect of an HIV Infection on Hepatitis C

For many people, an HIV infection worsens hepatitis C–induced liver disease, especially in those who have low CD4 (T cells, or white blood cells that fight infection) counts. For people who have acute hepatitis C, an HIV infection decreases the likelihood of spontaneous clearance of the hepatitis C virus from 15 to 30 percent down to 5 to 10 percent. And for those who have a chronic hepatitis C infection, HIV infection causes higher hepatitis C viral counts and a faster progression to liver disease. Many studies have shown that the risk of developing cirrhosis is twice as high for individuals who have both diseases. Also, there is a much shorter length of time for developing cirrhosis in people who have both diseases than in those who only have hepatitis C (7 years versus 23 years). Similarly, the risk of death from liver disease is higher in coinfected individuals.

People who have HIV are surviving longer because of HAART, and thus a significant number of people who have HIV are now dying of complications from advanced liver disease, including liver cancer. Once cirrhosis occurs, coinfected people have a six times higher risk of developing complications from cirrhosis—abdominal swelling (*ascites*), mental confusion (*hepatic encephalopathy*), and bleeding from blood vessels (*variceal bleeding*)—compared with people who only have hepatitis C. Therefore, it is extremely important for coinfected people to receive treatment for their hepatitis C infection. Although an HIV infection adversely affects the natural progression of hepatitis C disease, the presence of a hepatitis C infection does not seem to affect the progress of HIV disease.

The following are important considerations for those who have both HIV and a hepatitis C infection:

1. People who have acute hepatitis C and HIV are less likely to get better on their own than those who don’t

have HIV.

2. People who have chronic hepatitis C and HIV are more likely to have high amounts of the hepatitis C virus in their blood and more serious damage to their liver.
3. Some studies have shown that people with both infections are much more likely to have cirrhosis of the liver, as well as to develop cirrhosis much faster.
4. People who have both HIV and hepatitis C infections are more likely to develop liver cancer than people who only have a hepatitis C infection.
5. People who have both HIV and hepatitis C infections and then develop cirrhosis (late-stage liver disease) have a much higher risk of other, very serious problems with their liver such as swelling and bleeding.

Treatment of Hepatitis C in People Who Have HIV

The cure rates for hepatitis C in people who have HIV are similar to those in individuals without HIV. Therefore, all people who have HIV should consider hepatitis C treatment, which is similar for those with and without HIV.

In general, anti-retroviral medications should not be interrupted to start treatment for hepatitis C. Those newly diagnosed with HIV and not yet on HIV medications preferably should start HIV medications four to six weeks before beginning treatment for the hepatitis C virus.

- People who have hepatitis C and HIV should not drink alcohol. The disease can progress more rapidly in individuals who consume alcohol.
- People with both hepatitis C and HIV should be treated for hepatitis C.
- If a person is newly found to be infected with both HIV and hepatitis C, they should talk to their doctor about the best time to start treatment for each infection, the best medicines to treat each infection, and the possible side effects of each medication.

The only consideration when selecting a medication for hepatitis C is *drug-drug interactions* (negative interactions between drugs). HIV medications may need to be switched occasionally to reduce these interactions. Your physician will make this determination. If a change is necessary, it is wise to

wait for four to six weeks before starting treatment for hepatitis C.

- All people who have HIV and hepatitis C should consider HIV treatment, irrespective of their CD4 counts.
- A physician should look at possible drug interactions with HIV medications when treatment for hepatitis C is initiated.
- People who are newly diagnosed with HIV and hepatitis C preferably should begin HIV treatment four to six weeks before starting treatment for hepatitis C. Similarly, if HIV medications need to be changed because of potential drug-drug interactions, it is preferable to wait for four to six weeks after the switch before starting hepatitis C treatment.

Advanced Liver Disease in People Who Have HIV

People who have advanced (decompensated) cirrhosis and HIV should seek the expertise of a liver specialist. Treatment of hepatitis C may carry major risks for these individuals, and they may not tolerate hepatitis C treatment. Some people may require a liver transplant before their hepatitis C is treated. Survival rates after a transplant are similar to those for individuals who only have hepatitis C.

People who have both HIV and hepatitis C are more likely to develop liver cancer than those with only hepatitis C. Screening for liver cancer is important for people with HIV who are coinfected with either hepatitis B or hepatitis C.

HEPATITIS C IN CHILDREN

Many aspects of hepatitis C are different for children than for adults, including the method of transmission, the natural history of the disease, and subsequent complications. Only a small proportion of people with chronic hepatitis C are children. Approximately 240,000 children in the United States have hepatitis C antibodies, but only from 68,000 to fewer than 100,000 are infected with the virus (as confirmed by a hepatitis C RNA test).

The advent of blood screening for hepatitis C in 1990 had a significant impact on the rate of infection in children, as well as for the general population. Children who had hemophilia and received multiple transfusions of blood or blood products before 1990 had infection rates ranging between 50 and 95 percent. Among children who received multiple blood transfusions before 1990, either for cancers or during surgery for congenital heart disease, 10–20 percent were infected with hepatitis C. Children who received hemodialysis treatment before 1990 also had a hepatitis C infection rate of 10–20 percent.

Hepatitis C does not spread from child to child. The American Academy of Pediatrics recommends that children who have hepatitis C do not need to have any restrictions on attending school or daycare and participating in sports, including sports with body contact.

In low-income countries, a significant number of children become infected through unsafe blood products and contaminated needles (when reused), syringes (when reused), and medical instruments. Unfortunately, this source of transmission will remain a major pathway for infection in low-income countries.

Transmission from Mothers to Babies

Hepatitis C transmission from a mother to her baby during pregnancy or delivery, although rare, currently remains the main method by which children become infected with hepatitis C. About 1 percent (ranging from 0.1 to 2.4 percent) of pregnant women are infected with hepatitis C, and only 4–7 percent of pregnant women who have an active hepatitis C infection give it to their babies. The transmission rates are higher when mothers are also infected with HIV. If a mother has both HIV and hepatitis C infections, the rate of transmission of the hepatitis C virus to the infant is two to four times higher.

The effect of other factors—including severe liver disease in the mother, amniocentesis, the type of delivery, and complications during birth—on mother-to-infant transmissions

remains largely unknown. Suggestions to physicians include avoiding the use of internal fetal scalp monitors and breaking the mother's water too early (more than six hours) before delivery. There are no specific recommendations on the method (cesarean versus vaginal) or timing of delivery to prevent the transmission of a hepatitis C infection. Nonetheless, women should not have a cesarean section merely to prevent passing either or both of the HIV and hepatitis C viruses to their babies.

Also, breastfeeding does not increase the risk of transmission, unless the mother's nipples are bleeding.

Testing all pregnant women for hepatitis C is recommended, instead of merely risk-based screening. These women should also be tested for hepatitis B and HIV. Treating hepatitis C during pregnancy is not recommended.

Natural Progression of the Disease in Children

As in adults, an acute infection in children may be asymptomatic. Most children who have chronic hepatitis C do not exhibit any physical or cognitive (mental) symptoms until they develop advanced liver disease.

The natural history of hepatitis C acquired from mothers remains poorly defined. Infection occurs when the baby's immune system is not completely developed. For a short amount of time, some infants may have the virus in their blood without developing a hepatitis C infection. Other infants may have an acute, self-limiting infection that is noticeable. Children who acquire hepatitis C from their mother have a rate of spontaneous clearance of the virus as high as 50 percent.

The natural progression of a hepatitis C infection in children depends on how the child got the infection. In children who became infected through a blood transfusion, the underlying disease—such as hemophilia or cancer—may predict how hepatitis C progresses. For example, in children who have thalassemia (an inherited disorder where the body does not make enough hemoglobin and therefore has fewer healthy red blood cells than normal), an iron overload in their blood may cause liver disease (including cirrhosis). When they

become infected with hepatitis C, their disease may progress faster.

The risk of serious liver injury appears to be lower for children who have hepatitis C than for adults with that disease. Although cirrhosis can occur in children, it happens less frequently than in adults, and cirrhosis that requires a liver transplant is extremely rare.

HOW CAN WE PREVENT HEPATITIS C INFECTIONS?

Management after Accidental Exposure to Hepatitis C

Accidental exposure typically happens to healthcare workers, mainly by needlestick injuries, and carries a less than 2 percent risk of hepatitis C transmission. Dealing with this type of exposure is difficult because of no clear guidelines and a lack of data.

There is no evidence to suggest that antiviral treatment immediately after exposure (without any evidence of transmission) is beneficial. Most physicians agree that it is best to continue monitoring the exposed person by testing for hepatitis C RNA for three to six months after exposure.

Approximately one-half of individuals exposed in this manner may clear the virus spontaneously, especially if they develop symptoms. Once the infection is confirmed with a PCR test, however, it is wise to consider immediate antiviral therapy.

Prevention of Hepatitis C in Children

- Mother-to-infant transmission is the most common way for children to become infected with hepatitis C in developed countries. More research is needed to identify factors that affect transmission of the hepatitis C virus during pregnancy and delivery and help develop effective ways to prevent transmission.
- It is very important to identify infected children by screening babies born to mothers who have hepatitis C.

Preventing hepatitis C infections in adolescents requires educating them about high-risk behaviors, such as consuming alcohol and injecting drugs.

TREATMENT OF HEPATITIS C

Hepatitis C can be cured—in other words, the person will not have any more virus in their blood if the treatment is successful. There are several medicines, called antivirals, available to treat hepatitis C that fight the virus and help clear it permanently. All of the medicines that are now in use are very effective (95–100 percent cure rates) in curing hepatitis C infections, which can then help prevent liver disease from getting worse.

Tests Done Before Starting Treatment

Before beginning treatment for hepatitis C, a doctor will do a number of tests, including blood tests, an ultrasound of the liver, and (perhaps) tests to understand the severity of scarring (fibrosis).

> In the past, there were many different medicines to treat hepatitis C. They had serious side effects, had to be injected, and had to be taken for a long time. Because of more research, since 2014 new and improved medications have been made. These new medicines are even more effective (more than 95 percent cure rates) at treating the virus and have much less serious side effects.

One common test is to find out what genotype of the hepatitis C virus a person has. Knowing this information can help in deciding what the best medication is for the treatment, how much medicine should be taken, and how long it should be used. This has become less important, however, with the more effective treatments that are currently available.

In addition, everyone with hepatitis C needs to be tested for hepatitis B. If the person had a previous exposure to hepatitis B, there is a very small chance of reactivating the hepatitis B virus during hepatitis C treatment.

Most Commonly Used Medications

Several medicines are used to treat hepatitis C (table 5.2). The two most common ones are:

1. Sofosbuvir/velpatasvir (Epclusa)
2. Glecaprevir/pibrentasvir (Mavyret)

Those who were not cured using these medications (less than 5 percent) could be treated with a three-drug combination of sofosbuvir/velpatasvir/voxilaprevir (Vosevi) for 12 weeks, with an expected cure rate of 97 percent.

All of these medicines are very effective at treating hepatitis C and cure between 98 and 100 percent of the people infected by this virus. The length of treatment varies from 8 to 12 weeks.

TABLE 5.2. Medicines to treat hepatitis C

Medicine	Dose and how long to take it	Best for
Sofosbuvir/velpatasvir (Epclusa)	1 pill daily, taken for 12 weeks	• people with any genotype • people older than 3 years old • people who have an organ transplant
Glecaprevir/pibrentasvir (Mavyret)	3 pills daily, taken for 8 weeks	• people with any genotype • people older than 12 years old • people who have an organ transplant • people who have kidney failure
Sofosbuvir/ledipasvir (Harvoni)	1 pill daily, taken for 8–12 weeks, depending on the amount of virus in the blood and other medicines the person has tried	• genotypes 1, 4, 5, 6 • people older than 3 years old • people who have an organ transplant
Sofosbuvir/velpatasvir/voxilaprevir (Vosevi)	1 pill daily, taken for 12 weeks	• adults who haven't had success with other treatments

Note: Those with advanced (decompensated) cirrhosis should consult a liver specialist before beginning any treatments for hepatitis C.

Interaction with Other Medications

Drug-drug interactions can occur, and there are some medicines that should be avoided for optimal treatment results. Therefore, you must definitely give your doctor a complete list of your medications, including over-the-counter supplements. Common interactions with hepatitis C medications are shown in tables 5.3 and 5.4.

TABLE 5.3. Medications to avoid during treatment with Harvoni, Epclusa, or Vosevi

Acid medications (acid is important for drug absorption): • separate using antacids and taking acid medications by 4 hours • H2-receptor blockers—use with caution at lower doses • omeprazole—use with caution, and take no more than 20 mg
Anti-convulsants (medications to control seizures)—co-administration is not recommended: • carbamazepine • phenytoin • phenobarbital • oxcarbazepine
Anti-mycobacterials (medications to treat tuberculosis)—co-administration is not recommended: • rifabutin • rifampin • rifapentine
Anti-cancer medication—not recommended: • topotecan
Blood thinners: • dabigatran etexilate—monitor when used with Vosevi
Heart medications: • amiodarone should be avoided—could result in death • digoxin—levels need to be monitored • statins (lipid-lowering medications)—check with your doctor
Herbal supplements: • St. John's wort (*Hypericum perforatum*)—avoid
HIV medications (protease inhibitor)—check with your doctor about drug-drug

interactions:

- efavirenz, tipranavir/ritonavir—not recommended
- tenofovir—use with caution

Note: This is not a complete list. Check with your doctor or pharmacist before starting these medicines.

TABLE 5.4. Medications to avoid during treatment with Mavyret

Acid medications:

- no restrictions

Anti-mycobacterials (medications to treat tuberculosis):

- rifampin—avoid

Anticonvulsants (medications to control seizures):

- carbamazepine—avoid

Blood thinners (check with your doctor or pharmacist):

- dabigatran etexilate may need a dose modification

Heart medications:

- digoxin—levels need to be monitored
- statins (lipid-lowering medications)—check with your doctor

Herbal suppplements:

- St. John's wort (*Hypericum perforatum*)—avoid

HIV medications (protease inhibitors)—check with your doctor about drug-drug interactions:

- atazanavir—avoid
- darunavir, lopinavir, ritonavir, efavirenz—not recommended

Immunosuppressants:

- avoid in cyclosporine-based immunosuppression

Oral contraceptives:

- medication containing ethinyl estradiol—avoid

Note: This is not a complete list. Check with your doctor or pharmacist before starting these medicines.

Common Side Effects

The hepatitis C medications in table 5.2 are very well tolerated, and side effects are minimal (table 5.5). Most of

these side effects are very mild, and the majority of people do not experience any of them. Less than 1 percent of those taking hepatitis C medicines discontinue their treatment because of these side effects.

TABLE 5.5. Common side effects

Sofosbuvir/velpatasvir (Epclusa)	Glecaprevir/pibrentasvir (Mavyret)
• Headache • Tiredness • Nausea • Lack of energy • Insomnia	• Headache • Tiredness • Nausea • Diarrhea

Note: Side effects of sofosbuvir/ledipasvir (Harvoni) and sofosbvir/velpatasvir/voxilaprevir (Vosevi) are similar to those of sofosburvir/velpatasvir (Epclusa). Diarrhea may occur with Vosevi and Harvoni.

Monitoring During and After Treatment

Your doctor will periodically see you and monitor your treatment progress. Those with cirrhosis may require closer monitoring.

If, 12 weeks after the treatment is discontinued, a person has undetectable levels of the hepatitis C virus in their blood, that person is cured. The antibodies will stay in a person's blood for the rest of their life, but this does not mean the person has an active infection.

- A cured person can be reinfected with hepatitis C, so it's important to avoid behaviors that may be risky.

People who are cured of hepatitis C will see improvements in the damage that had been done to their liver, such as scarring (fibrosis) and cirrhosis. A cure will also lower their risk of developing liver cancer. For people who have a lot of scarring and advanced cirrhosis, it's important to keep seeing their doctor regularly, both to check on the progress of their liver disease and to look for signs of possible cancer.

Treatment of Acute Hepatitis C

As previously mentioned, approximately 30 percent of the

individuals who have an acute hepatitis C infection will spontaneously clear the virus and require no treatment. Spontaneous viral clearance rates of 44–67 percent have been reported in those who develop jaundice. In contrast to treatments for chronic hepatitis C, there have been no large clinical trials with newer medications to guide the treatment of people who have an acute hepatitis C infection. Nevertheless, the limited data available lead to the conclusion that, by receiving 8–12 weeks of treatment with the newer oral medications, 98–100 percent of patients with acute hepatitis C could be cured.

- Between 10 and 20 percent of the people who have acute hepatitis C develop symptoms, so acute hepatitis C can often be overlooked.
- People who have symptoms are more likely to spontaneously clear the virus, so they can wait to make a decision about starting antiviral therapy for three months from the time when symptoms appear.
- An 8–12 week treatment with oral medications could cure almost all patients with acute hepatitis C.

Treatment of Hepatitis C in Children

Not all medications approved for adults (see table 5.2) can be used in children.

- The combination of sofosbuvir and velpatasvir (Epclusa) is approved for children older than 3 years, for all genotypes.
- The combination of glecaprevir and pibrentasvir (Mavyret) is approved for children older than 12 years, for all genotypes.
- The combination of sofosbuvir and ledipasvir (Harvoni) is approved for children older than 3 years with genotypes 1, 4, 5, and 6.

For children who are younger than 3 years old, the current strategy is to defer treatment until they reach that age.

FURTHER READING

Hepatitis C. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/hepatitis-c/.
Hepatitis C. Centers for Disease Control and Prevention. https://www.cdc.gov/hepatitis/hcv/index.htm.
Hepatitis C information center. American Liver Foundation. https://liverfoundation.org/for-patients/about-the-liver/diseases-of-the-liver/hepatitis-c/.
Hepatitis C. National Institute of Diabetes and Digestive and Kidney Diseases. https://www.niddk.nih.gov/health-information/liver-disease/viral-hepatitis/hepatitis-c/.

CHAPTER 6

Alcohol and the Liver

Alcoholism is a worldwide problem. Estimates of the global burden of alcoholism are shown below:

- 3.3 million deaths from alcoholism per year
- 5.9 percent of all deaths (7.6 percent male, 4.0 percent female)
- the third leading preventable cause of death in high-income countries
- 5.1 percent of the global burden of disease is attributable to alcohol-related diseases

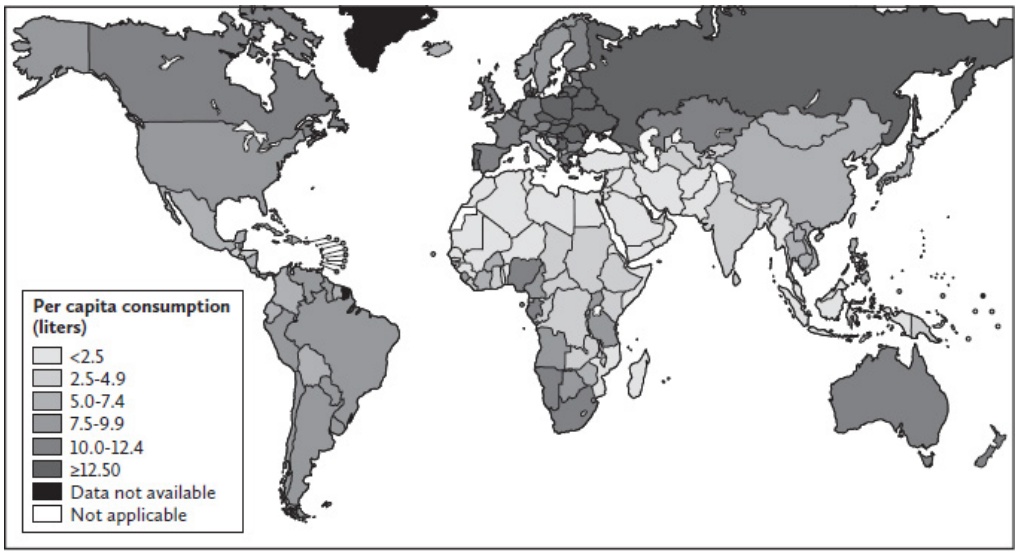

FIGURE 6.1. Total alcohol per capita consumption (15+ years), in liters of pure alcohol, in 2010. *Source*: World Health Organization

TOP FIVE RISK FACTORS FOR DISEASE, DISABILITY, AND DEATH

Daily drinking and binge drinking are increasing worldwide. This is seen in high-income and middle-income countries across the globe. In addition to its direct impact on health, excessive alcohol consumption has a negative impact at

multiple levels, including family life, disabilities, and traffic accidents.

Although the focus of this chapter is on liver disease, increased alcohol consumption can cause damage to many other parts of the body:

- Inflammation of the pancreas (pancreatitis)
- Depression
- Seizures
- Cancers of the mouth, throat, esophagus, colon, pancreas, liver, and breast
- Intentional and unintentional injuries, including traffic accidents
- Heart disease
- Pregnancy complications (fetal alcohol syndrome, pre-term birth complications)
- Pneumonia and tuberculosis

One of the liver's main jobs is to break down toxins and remove them from the body. Alcohol is one of those toxins. In general, if a healthy person consumes a reasonable amount of alcohol, their liver can get rid of the alcohol without it causing harm to their liver. A reasonable (moderate) amount of alcohol for the average adult is:

- One drink per day for women
- Two drinks per day for men

The risk of alcoholic liver disease increases with increased alcohol intake:

- An increased risk occurs when a person's pure alcohol intake is more than 1.1 fluid ounces (30 grams) per day
- In the United States, approximately 45 percent of all deaths from liver disease are related to alcohol

In terms of damage to the liver, the type of alcohol (beer, wine, liquor) or its quality (cheap versus high-end) doesn't make as much of a difference as the amount of alcohol in the drink and how often a person consumes alcohol. Many

consider beer and wine to be less toxic than whiskey, brandy, or rum, but this supposition is false. The more a person drinks, and the more often they drink, the greater the damage they do to their liver. The amount of alcohol in the beverage is very important. One drink is roughly equal to 0.5 fluid ounces (14 grams) of pure alcohol (figure 6.2).

The safe amount of alcohol an individual could consume daily is shown in table 6.1.

FIGURE 6.2. One drink = approximately 0.5 fluid ounces (14 grams) of pure alcohol

TABLE 6.1. How much alcohol is safe?

Type of person	Amount
Healthy adult men	maximum: 2 drinks a day
Healthy adult women	maximum: 1 drink a day
People who have liver diseases	none
People who had a liver transplant	none

Note: One drink is defined as equal to the following:

beer: 12 fluid ounces (355 milliliters), or 1 can/bottle

wine: 5 fluid ounces (148 milliliters), or 1 glass

80-proof liquor: 1.5 fluid ounces (44 milliliters), or 1 cocktail or drink

THE EFFECTS OF ALCOHOL

On the Liver

When a person consumes alcohol, enzymes (alcohol

dehydrogenase) in the liver cells convert the alcohol to acetaldehyde. Chronic drinking can create (*induce*) other enzymes that add to this conversion. Acetaldehyde is then changed (*metabolized*) to acetate in specialized subunits (the *mitochondria*) within liver cells. This process can result in the formation of molecules that are known as reactive oxygen species (ROS), which can damage liver cells. Acetaldehyde, directly or through other enzymes, can cause the liver to produce fatty acids, which then accumulate in the liver over a period of time and create *alcoholic fatty liver*. In the early stages of alcoholic liver disease, the only abnormality seen in the liver is an increased amount of fat (*fatty liver*).

Increases in acetaldehyde, acetate, ROS, and other chemicals that are produced by excessive drinking may trigger a reaction in the immune system, causing an inflammation of the liver. This stage is called *alcoholic hepatitis*. This is a serious condition that may cause a yellow discoloration of the eyes (jaundice), fatigue, and liver failure.

Alcoholic hepatitis may result in the onset of jaundice and liver failure after years of alcoholism. Although women are prone to alcohol-induced liver disease, alcoholic hepatitis is seen mostly in middle-aged men. The usual symptoms of alcoholic hepatitis are loss of appetite, jaundice, fever, pain in the upper right belly, abdominal swelling, muscle weakness, or confusion. In many people, this is a life-threatening condition. A doctor can easily recognize this condition, based on blood tests and a physical examination. A liver biopsy is rarely necessary. Using simple blood tests (serum bilirubin and prothrombin time), the doctor can also estimate the severity of this risk and decide on potential treatment options (discussed later in this chapter).

Inflammation of the liver also activates the type of cells (*stellate cells*) that cause collagen (scar tissue) to be formed in the liver. Too much scar tissue leads to cirrhosis. If a liver biopsy is done for people who show signs of alcoholic hepatitis, 50 percent of them will have cirrhosis.

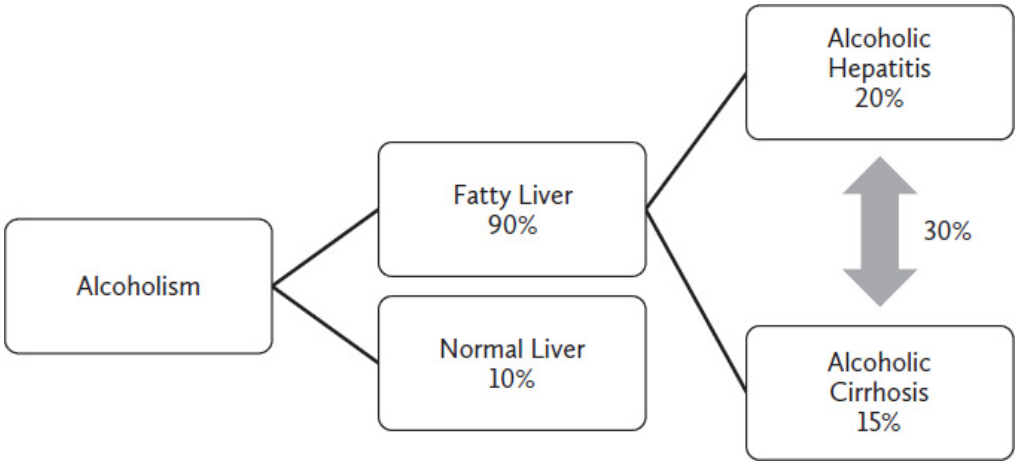

FIGURE 6.3. Alcoholic liver disease

Many factors determine whether a person is going to develop liver disease. The most important element is the amount of alcohol consumed. Other factors that increase a person's risk of developing liver disease are:

- Having a family history of alcoholic liver disease or other genetic traits
- Being a woman
- Being overweight
- Being Asian, African American, or Hispanic
- Eating poorly
- Having other liver diseases

About 10–20 percent of the people who drink heavily will develop liver disease. It is important to recognize that some people are genetically susceptible to developing alcohol-induced liver disease, but there are no easy ways or tests to identify such individuals.

Alcoholic liver disease covers a spectrum, starting with fatty liver on one end and cirrhosis and cancer at the other end. The progression is:

1. Alcoholic fatty liver
2. Alcoholic hepatitis
3. Alcoholic cirrhosis

The effects of these three stages of fatty liver disease are

shown in table 6.2.

Some people may start with alcoholic fatty liver disease, then progress to alcoholic hepatitis, and end up with cirrhosis. But other people may develop alcoholic hepatitis without having any symptoms, or develop cirrhosis without going through the alcoholic hepatitis stage.

TABLE 6.2. Stages of alcoholic liver diseases

Stage	What happens
Alcoholic fatty liver	drinking too much alcohol results in fat buildup in the liver cells and damages the liver the damage can be reversed when the person stops drinking alcohol
Alcoholic hepatitis	alcohol and chemical byproducts may trigger an immune-system response, causing inflammation of the liver; symptoms may appear acutely, but some people may not have any symptoms common symptoms are: • fevers • tiredness • nausea and vomiting • poor appetite • discomfort in the upper right belly • swelling of the abdomen • memory problems and confusion
Alcoholic cirrhosis	scar tissue replaces healthy liver tissue, and the liver becomes small and shrunken, which may cause: • jaundice • swelling of the abdomen • memory problems and confusion • bleeding from the stomach • wasting away of muscles • liver cancer

In People Who Have Liver Disease

For people who have any liver disease, particularly those who have hepatitis C, drinking alcohol, even in moderate amounts, can have damaging effects:

- Making the liver damage worse and causing more-serious damage, including cirrhosis, to happen faster

- Making the hepatitis infection worse by increasing the amount of the virus in the blood
- Increasing the risk of liver cancer

Alcoholism may prevent spontaneous clearance of the virus after a hepatitis C infection, leading to chronic infection and liver disease. Experimental studies show that alcohol increases the replication of the hepatitis C virus. Most studies show increased hepatitis C RNA levels in alcoholics, compared with non-alcoholics. Even a moderate amount of alcohol (one or two drinks a day, or a total of seven drinks a week) has a significant impact on hepatitis C RNA levels and the liver's progress toward cirrhosis. Overwhelming evidence suggests that in the presence of hepatitis C, even small amounts of alcohol may increase the progression of liver fibrosis and the development of cirrhosis. These studies clearly suggest that for the liver, hepatitis C and alcohol are a harmful combination. To prevent the rapid development of liver disease and improve the cure rate, two of the most important actions are to abstain from alcohol and get treatment for hepatitis C.

People who heavily drink alcohol and have a hepatitis C infection have a much higher risk of developing cirrhosis and liver cancer.

On Other Liver Diseases

The effect of alcohol on other liver diseases is not well studied. In many people with non-alcoholic fatty liver, drinking alcohol may make their disease worse. This is also likely to be true for all other liver diseases. Significant alcohol consumption also carries a serious risk for the development of liver cancer.

People with any liver disease should avoid drinking alcohol regularly. Ideally, they should abstain from alcohol.

PREVENTING ALCOHOLIC LIVER DISEASE

The best way to prevent alcoholic liver disease is not to drink alcohol on a regular basis and not to exceed the recommended limits. Other factors that may help reduce risks or complications are:

- Maintain a healthy weight—and lifestyle—with exercise
- Stop smoking, which will also reduce the probability of heart disease and cancers
- Go to a doctor for routine checkups and get blood tests regularly
- Get the vaccines for hepatitis A and B

The most important factor in preventing alcoholic liver disease is to minimize alcohol consumption, including binge drinking.

TREATMENT OF ALCOHOLIC LIVER DISEASE

Those with evidence of liver disease should avoid alcohol completely. The only way to do this is to abruptly stop drinking alcohol. A slow weaning process simply does not work. Some people may need medications to reduce their alcohol withdrawal symptoms, and almost all of them would benefit from alcohol rehabilitation. Counseling could be done in an outpatient or in-patient setting. Outpatient counseling could be either individual sessions or group therapy. Unfortunately, the success rate of complete abstinence from alcohol is less than 40 percent, even among those who have severe liver disease. Nonetheless, the following factors will help improve this success rate:

- Acknowledgment of the problem (most people are reluctant to accept the fact that they are alcoholics)
- Willingness to seek help (most people believe they do not need help)
- Management of underlying depression (this problem is often undiagnosed)
- Good social and family support (many alcoholics have burnt their bridges)

- Follow-ups with the doctors treating the condition (compliance is usually poor)

> Complete abstinence from alcohol is the only proven treatment for alcoholic liver disease.

Alcoholic Hepatitis

Alcoholic hepatitis is a serious disease, with very high death rates, especially in those who develop jaundice. Abstinence from alcohol is a must. Other treatments for this condition are mostly supportive ones:

- Good nutrition (multiple meals and snacks), especially foods high in protein (at least 1.5 grams/kilogram, or 0.75 grams/pound) and high in calories (35–40 kilocalories/kilogram, or 18–20 kilocalories/pound)
- Nutritional supplements
  - Vitamin supplements—B1 (thiamine), B6 (pyridoxine), and B9 (folate)
  - Mineral supplements—phosphate and magnesium
- Routine checks for infection
- Tests using cultures of body fluids and sputum (mucus, or phlegm, from the lungs) if an infection suspected

For those with severe alcoholic hepatitis, a trial treatment with steroids (40 mg of prednisolone daily, for 1 week) is recommended. This treatment should be discontinued after one week if the response is unsatisfactory. (Your doctor can assess the result by blood tests, using a scoring system called Lille scores.) If there is an improvement, treatment should be continued for four weeks.

Based on the current evidence, the optimal treatment of alcoholic hepatitis includes:

1. Supportive care and abstinence from alcohol for people with mild to moderate hepatitis
2. Supportive care, abstinence from alcohol, and a trial treatment with prednisolone for people with severe

alcoholic hepatitis
3. A liver transplant as an option (although very controversial) if the above treatments fail

Alcoholic Cirrhosis

Many people will already have cirrhosis when they are diagnosed with alcoholic liver disease. Approximately one in four individuals (25 percent) will develop a complication of cirrhosis within a year after the diagnosis, and one in two (50 percent) within five years. The risk is higher in those who do not abstain from alcohol. If a person continues to drink after developing a complication, 7 in 10 (70 percent) will die within five years. Those with cirrhosis will need periodic screening for complications from this condition, including liver cancer.

Combating Alcoholism at the Societal Level

A multipronged approach is needed to combat alcoholism at the societal level, both from the community and at all legislative levels.

Awareness and early diagnosis are important. Once diagnosed, there should be multiple kinds of interventions, including education and the treatment of underlying disorders, such as depression.

Legislation and the enforcement of various rules and laws regarding alcohol have also been shown to reduce alcoholism in many countries around the world. These include:

- Greater taxation (to substantially increase the cost of alcoholic drinks)
- Effective enforcement of "no driving under the influence" (DUI) laws
- Control of opening times for liquor stores and bars
- A ban on alcohol-related advertisements
- Education for children on responsible drinking

FURTHER READING

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CHAPTER 7

Non-Alcoholic Fatty Liver Disease

Fat can accumulate in the liver for many reasons, but two common causes of fatty liver are alcoholism and metabolic syndrome (a set of conditions that occur together, including increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal cholesterol or triglyceride levels). Other causes are shown below.

Common causes of fatty liver:

- Alcohol
- Non-alcoholic fatty liver disease (NAFLD)

Other causes of fatty liver:

- Hepatitis C
- Wilson disease
- Lipodystrophy (loss of adipose, or fat, tissue)
- Abetalipoproteinemia (a very rare genetic disorder that causes interference in the normal intestinal absorption of fats—including fat-soluble vitamins—and in fat mobilization by the liver)
- Starvation
- Total parenteral nutrition (intravenous feeding)
- Medications
- Amiodarone
- Methotrexate
- Tamoxifen
- Steroids

Fatty liver is usually diagnosed by liver imaging (using ultrasound, a CT scan, or an MRI). FibroScan (a specialized ultrasound) and MR elastography (an MRI-based technique) can diagnose as well as quantify the amount of fat in the liver.

By definition, a fatty liver contains more than 5 percent fat. Based on the amount of fat in the liver, the severity of the

condition could be graded as follows.

Grade	Amount of Fat
0	< 5%
1	5% to 33%
2	34% to 66%
3	≥ 67%

NON-ALCOHOLIC FATTY LIVER DISEASE

The focus of this chapter is on non-alcoholic fatty liver disease (NAFLD)—its causes, associated conditions, natural progression, and long-term outcomes.

How Common Is NAFLD?

This disease is very common worldwide and is seen in one out of four adults. Approximately 70 million Americans are thought to have NAFLD. There are geographical differences in how widespread NAFLD is:

- Highest in the Middle East (32 percent) and South America (30 percent)
- Midrange in North America and Europe (24 percent) and in Asia (27 percent)
- Lowest in Africa (13.5 percent)

NAFLD is more commonly seen in men and older people. It is less common in blacks, compared with whites and Hispanics. The amount of people with NAFLD has been greater in high-income countries, but this number is rapidly shifting, and many middle-income countries are now catching up.

NAFLD is very common in diabetics and in people with high cholesterol and triglyceride levels. NAFLD is seen in 50 to 70 percent of those with diabetes, and 50 percent of those who go to clinics for disorders from lipids.

NAFLD is seen in children, too, and it is becoming an increasing problem with the obesity epidemic happening all over the world.

Who Develops Fatty Liver?

Lean people rarely have fatty liver, but they may develop this condition if they have pre-diabetes or diabetes. People with fatty liver have one or more of the following conditions:

1. Obesity
2. High cholesterol or triglyceride levels
3. Diabetes or pre-diabetes
4. Hypertension
5. Metabolic syndrome

Metabolic syndrome is diagnosed if three or more of the following five criteria are met:

1. Waist circumference over 40 inches (102 cm) in men or 35 inches (88 cm) in women
2. Blood pressure over 130/85 mmHg or taking medications for hypertension
3. Fasting triglyceride level over 150 mg/dl
4. Fasting HDL cholesterol level less than 40 mg/dl in men or less than 50 mg/dl in women
5. Fasting blood sugar over 100 mg/dl or taking medications for diabetes

Other Conditions Associated with NAFLD

There are a few other clinical conditions that are associated with NAFLD:

- Polycystic ovary syndrome, or PCOS (a hormone disorder)
- Other endocrine disorders:
  - Hypothyroidism (an underactive thyroid)
  - Hypogonadism (low levels of testosterone in men)
  - Hypopituitarism (an underactive pituitary gland)
- Sleep apnea
- Whipple surgery (removal of a part of the pancreas, usually because of pancreatic cancer)

Why Does Fat Accumulate in the Liver?

Liver is the processing center for fat (fatty acids, to be more precise). The accumulation of fat in the liver can result from an increased delivery of fatty acid or a decrease in its disposal. Fatty acids arrive in the liver from three sources: (1) stored fat (usually from the central part of abdomen, particularly in obese individuals), (2) daily fat intake, as well as fatty acids produced by bacterial flora in the digestive tract, (3) fatty acid produced in the liver of diabetics or pre-diabetics, due to *insulin resistance*. Of these three sources, the first and second contribute up to 75 percent of the fatty acids entering the liver, with more than two-thirds coming from stored fat under the skin and inside the abdomen (*visceral fat*).

Liver processes fat by burning it (oxidizing it via mitochondria inside the liver cells) or by exporting it as very low-density *lipoproteins* (complex particles that transport cholesterol and triglycerides). If the influx of fatty acids is greater than the liver's ability to burn or export them, the liver stores the extra fatty acids as lipid droplets (*triglycerides*) in the liver. Over a period of time, stored lipid droplets increase the size of the liver. This expansion sometimes causes discomfort in the upper right belly or a mild elevation in liver enzymes. But the majority of people with fatty liver will have no symptoms or no liver enzyme abnormalities. Fatty liver is usually identified incidentally, through an ultrasound done for other purposes.

Progression of NAFLD

Not all of the people with NAFLD will have progressive liver disease. About 5–10 percent develop an inflammation of liver, called non-alcoholic steatohepatitis (NASH). NASH is usually a progressive condition, resulting in scarring of the liver (fibrosis) and cirrhosis. Some individuals may develop complications of cirrhosis, including liver cancer.

For people with NASH, it may take 20–30 years for this disease to progress to cirrhosis. This time period may be even longer in those who have fatty liver without much inflammation. It is reassuring that only a minority of people

will develop progressive liver disease.

Only a small number of individuals with fatty liver will develop progressive liver disease, although—because of its greater prevalence worldwide—the death rate for people with this condition is expected to go up significantly (three to four times higher) across the globe in the next decade.

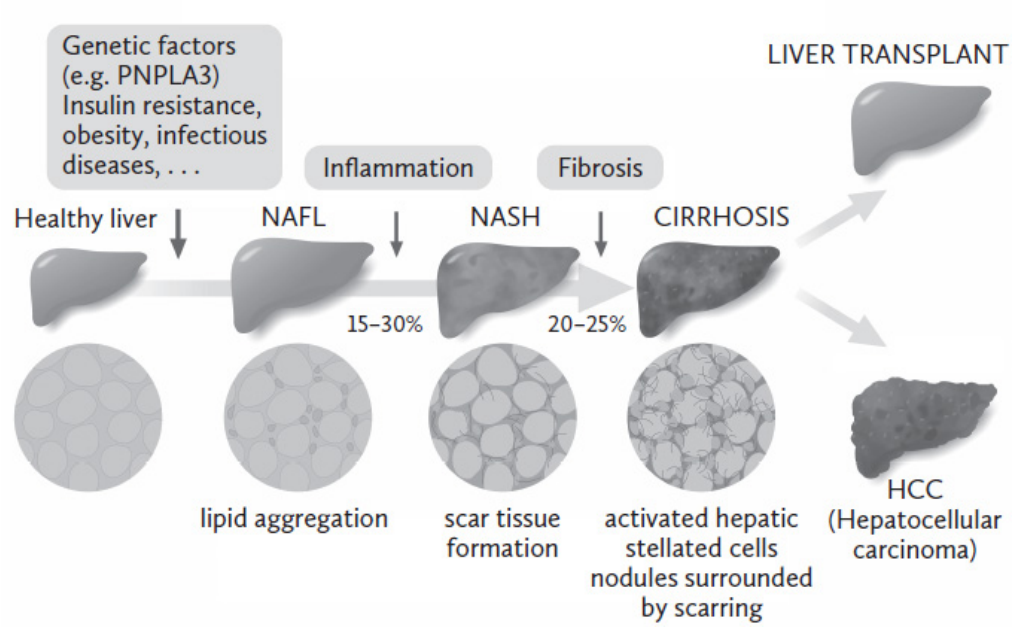

FIGURE 7.1. The NAFLD spectrum

Why Does the Disease Progress in Some and Not in Others?

There are no good explanations for why some people develop NASH and others do not. Similarly, we do not understand why some people end up with cirrhosis, while NASH has an indolent course in others.

Many speculations exist, including genetic factors; environmental factors; *co-morbid* risk factors (occurring at the same time), such as alcoholism or diabetes; and, perhaps, even characteristics of intestinal bacterial flora (the *microbiome*). Although our understanding of NASH is improving, we are not at a stage where we can predict the progression of this disease. Nevertheless, those with NASH plus type 2 diabetes seem to have a greater chance for the disease to get worse.

Does Fatty Liver Affect Life Expectancy?

People with fatty liver appear to be at greater risk of dying from heart disease, cancers, or liver disease. Having fatty liver makes a person 5 times more likely to die from heart disease, and 15 times more likely to die prematurely from all causes, when compared with those without fatty liver disease. Fatty liver could reduce a person's life expectancy by as much as five to eight years. Therefore, it is important to effectively manage the various conditions involved in metabolic syndrome, which otherwise could lead to the development of fatty liver.

Fatty liver alone does not increase the risk of death from liver disease, but people with NASH have a greater risk of dying from cirrhosis (12 times higher) or liver cancer (5 times higher), compared with those without fatty liver.

HOW IS NASH DIAGNOSED?

Fatty liver disease can be diagnosed with imaging tests, and NASH is suspected when the liver enzymes are significantly elevated in the presence of fatty liver. A liver biopsy is needed to confirm the diagnosis, rule out other causes of liver disease, and help determine the severity of liver scarring (fibrosis).

Since the amount of fibrosis could be assessed non-invasively (by FibroScan, MR elastography, or a combination of blood tests and imaging) with 80–90 percent accuracy, a liver biopsy should only be performed under the following conditions:

1. *When a diagnosis is uncertain*: there are no known risk factors, but fatty liver and/or abnormal levels of liver enzymes are present.
2. *When there is more than one potential cause for liver disease*: for instance, if tests show elevated iron saturation or the presence of auto-antibodies.
3. *To determine the severity of fibrosis in those who are likely to have advanced liver disease*: useful for predictive purposes, clinical trials, or a choice of other therapeutic options

MANAGEMENT OF NAFLD

There are no approved medications for fatty liver or NASH. The most important aspect of treatment for these conditions is optimal management of the affected person's weight and any co-morbid conditions, such as diabetes, hyperlipidemia (high cholesterol), and hypertension. Those who have risk factors for coronary artery disease may also benefit from additional preventive actions, including undergoing tests to screen for *occult* (not immediately apparent) diseases and no longer smoking (if applicable). Alcohol consumption should be reduced to a minimum (not more than one drink per day, and, ideally, only infrequently).

Lifestyle modification (discussed in the next section) is the mainstay of a treatment strategy for NAFLD. Currently there are no approved medications for this condition, but many clinical trials are in progress for dealing with fatty liver, NASH, and cirrhosis. Another option that could be considered is *bariatric* (weight-loss) surgery, as long as that individual has multiple other conditions that may benefit from this type of surgery. A liver transplant is a possibility for people with advanced cirrhosis and other complications.

Lifestyle Modification

This includes diet control and regular exercise. According to the World Health Organization, exercise should include 45 minutes of vigorous exercise (enough to raise your heart rate), four to five days per week. The important aspect of diet control is to reduce your intake of calories (discussed in the next section). Unfortunately, less than 10 percent of adults follow this lifestyle modification.

An improvement in various disease conditions—fatty liver, liver inflammation, and liver scarring—is dependent on the degree of your weight loss.

Lifestyle modification is also an essential part of a management strategy to reduce other metabolic complications.

Liver biopsy improvements, based on weight loss:

- More than 3–5 percent reduces fatty liver (steatosis)
- Over 7–9 percent reduces inflammation
- At 10 percent or more, reduces scarring (fibrosis)

Dietary Advice for Those with Fatty Liver

The two most common risk factors for NAFLD are excess caloric intake and reduced physical activity. Consequently, lifestyle modification is critical in managing fatty liver disease, as well as preventing its progression to NASH and cirrhosis.

The basic strategy is to lose weight. Both dieting and exercise are equally important to promote weight loss and *improve* (reduce) insulin resistance. The goal is to lose 10 percent of your baseline weight. For example, if your initial weight is 200 pounds, you should try to lose 20 pounds. The normal recommendation is to lose no more than one to two pounds per week for the first six months. In people with fatty liver who are modestly obese, vigorous exercise provides benefits, even when there is no weight loss, possibly because stored excess fat may be replaced with lean muscle mass.

There are many other ways to achieve weight loss. A general approach is to decrease the amount of calories in your meals by making different food choices. A reasonable diet should be high in fiber; low in saturated fats; and, preferably, contain a combination of plant and animal proteins. Most importantly, this diet should be followed on a long-term basis. In other words, you should:

1. Choose more foods with a higher fiber and water content, such as fruits and vegetables
2. Consume fewer fatty and sugary foods
3. Reduce the portion size, which is critical

Excess calories could come from many sources, but added sugars, especially in sweetened beverages, are a problem for both adults and children throughout the world. People who consume sugary beverages, ice cream, and other sweets tend to

gain weight easily, as all of these items contain easily absorbable sugars. While fructose (a type of sugar) is harmful in sweetened beverages, fructose in fresh fruit may have a beneficial effect. Another source of excess calories is a diet rich in saturated fat and cholesterol. These elements may play a major role in hardening of the blood vessels, and heart attacks are a leading cause of death in people with NAFLD. Saturated fats are present in animal-based foods, including meat, dairy products, and eggs, as well as in palm and coconut oils. While saturated fats are harmful, omega-3 fatty acids may have protective benefits.

A common and controversial topic is whether the kinds of food you eat—and the proportion of carbohydrates, protein, and fat in that food—make a real difference. There are different theories and speculations, but no consensus. It is generally agreed that processed carbohydrates from refined flours are more harmful than carbohydrates derived from unrefined plant-based foods like oatmeal, sweet potatoes, and lentils. Similarly, unsaturated fats from nuts, seeds, and fish rich in omega-3 fatty acids are better than saturated fats from meat, butter, cheese, and eggs.

There is evidence to suggest that people who eat more whole grains have a lower risk of cardiovascular disease, obesity (especially central-body obesity), and diabetes. A diet rich in whole grains may also reduce NAFLD. Potential explanations for this include a lowered caloric intake and, possibly, a modification in gut bacteria (the latter has been implicated in causing NAFLD). The ability to help control a person's blood-sugar level with different foods, especially with an oat-based diet, has been shown to be beneficial in reducing obesity and abdominal fat, and in improving *lipid profiles* (measurements of the healthy and unhealthy fats in the blood).

A Mediterranean-type diet is less likely to cause insulin resistance and NAFLD. This type of diet is typically low in saturated fats and animal protein, and high in monounsaturated fatty acids (for example, olive oil), with an adequate balance between omega-3 and omega-6 fatty acids. It is mostly a plant-based diet, with lots of vegetables, fruits, legumes (such as

peas and beans), whole grains, nuts, and seeds. A Mediterranean diet helps prevent coronary artery disease and thus provides an additional benefit for people with NAFLD.

Dietary Supplements

In a clinical trial for people with NASH, vitamin E, at a dose of 800 IU per day, was shown to decrease fat in the liver. Higher doses of vitamin E, however, may increase the risk of prostate cancer and perhaps heighten the likelihood of dying for people with heart diseases. Vitamin E may also interact with other medications. Therefore, lower doses of vitamin E (200–400 IU) are preferable, although the overall benefit of lower doses is unproven. Vitamin E does not improve scar tissue in the liver and is only recommended for adults with NASH who do not have diabetes or cirrhosis.

Summary of Dietary Recommendations

Plant-based foods—such as vegetables, fruits, legumes, whole grains, nuts, and seeds—are healthier than foods with refined grains and added sugars.

- Have the bulk of your diet come from plant-based foods
- Plant-based diets may also reduce cholesterol levels and, theoretically, *polyphenols* (organic compounds) from plant-based foods may reduce oxidative stress (a chemical imbalance in the body), inflammation, and insulin resistance
- Plant-based diets are beneficial because they are high in fiber and contain fewer refined sugars
- Limit (as much as possible) the consumption of added sugars from processed foods and sweetened beverages
- Decrease the amount of saturated fats and transfats in the foods you eat, and increase your amount of omega-3 fatty acids
- Reduce the quantity of fast foods, bakery goods, and sweets in your diet.
- Exercise for 45 minutes a day, four to five days a week
- Reduce your weight by at least 10 percent from how much you weighed at the time NAFLD was diagnosed

- Consider bariatric surgery in the presence of morbid obesity (a body mass index greater than 40) and other conditions, such as high blood pressure, diabetes, sleep apnea, and the like

MEDICATIONS

Only a small number of individuals with NAFLD will develop progressive liver disease. Approximately 25 percent of the people with NAFLD who have liver inflammation (NASH) at the time of their diagnosis may also have advanced scarring of their liver. Advanced scarring is associated with an increased risk of death. Based on prediction models, the number of people with NASH is expected to increase by more than 50 percent in the United States and elsewhere by 2030. The prevalence of decompensated cirrhosis (complications from a previously stable liver condition) and cancer related to NAFLD is also expected to increase globally.

Currently, the US Food and Drug Administration (FDA) has not approved any treatment options to improve scarring (fibrosis) caused by NAFLD. A number of compounds targeting multiple pathways involved in the progression of NAFLD are currently in different phases of clinical trials. Many of these medications that showed promise in the early stages of such trials were found to be ineffective in phase-3 trials.

Use of a combination of drugs is currently being explored in multiple ongoing studies. Developing a combination therapeutic strategy to tackle NASH ideally should involve a drug that targets the metabolic components that cause fatty liver, as well as other agents that reduce inflammation and scarring. One major challenge in the treatment trials is identifying reliable biomarkers—without needing multiple liver biopsies—to measure improvement in the amount of scarring, within a defined time period, in a disease with a long natural history.

TABLE 7.1. Current status of pharmacotherapy on liver scarring

No proven benefit	Possible benefit	Probable benefit

vitamin E	pentoxifylline	obeticholic acid
metformin	pioglitazone	
ursodeoxycholic acid	cenicriviroc	
simtuzumab	elafibranor	
selonsertib	liraglutide	
	emricasan	

Until we identify an effective medication or a combination of medications, the mainstay in the treatment of fatty liver is weight loss through moderate-intensity exercise, along with a low-calorie diet. Bariatric surgery is an option for obese patients who do not respond well to traditional lifestyle modifications. A critical need is to develop effective medications to improve or slow down scarring of the liver, given the magnitude of its clinical implications.

- Fatty liver (NAFLD) is seen in one in four adults in the United States.
- NASH is less common, but it is a progressive disease.
- Deaths in people with NAFLD are mostly from cardiovascular events, cancer, and liver disease, in that order.
- There are no FDA-approved medications for NAFLD, but clinical trials are in progress.
- Bariatric surgery is an option for people whose lifestyle modifications fail.
- For individuals with liver cancer and cirrhosis with complications, a liver transplant is an option.

FURTHER READING

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CHAPTER 8

Other Causes of Liver Diseases

Although viral hepatitis (hepatitis C and hepatitis B), excess alcohol consumption, and metabolic syndrome from non-alcoholic fatty liver disease are the most common causes of chronic liver diseases that result in cirrhosis, there are many other causes. These will be discussed very briefly in this chapter.

There are a number of other causes of liver diseases, including:

- Autoimmune liver diseases
  - Autoimmune hepatitis (AIH)
  - Primary biliary cholangitis (PBC)
  - Primary sclerosing cholangitis (PSC)
  - Overlap syndrome (a combination of more than one type of autoimmune disease)
- Genetic disorders
  - Hemochromatosis
  - Wilson disease
  - Alpha-1 antitrypsin deficiency
- Drug-induced liver injuries (DILIs)
  - Acute (any drug could cause it)
  - Chronic (only common drugs are listed here)
    - Amiodarone
    - Methotrexate
    - Minocycline
    - Nitrofurantoin

AUTOIMMUNE HEPATITIS (AIH)

People with autoimmune hepatitis have elevated levels of liver enzymes (mostly AST and ALT). This condition is predominantly seen in middle-aged women, but it could develop at any age and in both sexes. The common symptoms

are fatigue, joint pain, loss of appetite, and (in severe cases) yellow discoloration of the eyes (jaundice). Those with autoimmune hepatitis may also have other autoimmune conditions, such as thyroid disorders, or have a family history of other autoimmune diseases. AIH can develop suddenly or occur over a lengthy period of time. Also, a person's liver enzyme elevations could be intermittent. Rarely, AIH can lead to liver failure over a short period of time.

AIH is often suspected when there are no other obvious causes of liver diseases. Blood tests usually show the presence of auto-antibodies—such as anti-smooth muscle antibodies (ASMA), anti-nuclear antibodies (ANA), or, in young people, anti–liver-kidney microsomal antibodies (anti-LKM). Autoimmune hepatitis could be subtyped (types 1 to 3), based on the presence of these antibodies. In addition, *immunoglobulins* (a type of protein) may also be elevated in the blood. It is important to note, however, that false positive antibodies are common in the presence of viral hepatitis or non-alcoholic fatty liver disease, and sometimes they are even seen in the absence of any disease. Some medications, such as minocycline or nitrofurantoin, can induce autoimmune-like hepatitis.

If autoimmune hepatitis is suspected, you should consult a liver specialist, since this is a lifelong disease. Therefore, it is important to have a firm diagnosis before initiating treatment. Most liver specialists could make a diagnosis of autoimmune hepatitis based on blood tests and a liver biopsy. With borderline findings from these procedures, however, a specialist may use previously published criteria (table 8.1).

TABLE 8.1. Simplified criteria to make a diagnosis of autoimmune hepatitis (AIH)

Criteria	Points
IgG > 16 g /L	1
IgG > 18 g /L	2
ANA, ASMA, or anti-LKM > 1:40	1
ANA, ASMA, or anti-LKM > 1:80 or SLA/LP* positive	2

Histology compatible with AIH	1
Histology typical of AIH	2
Absence of viral hepatitis	2

Note: If the score is more than 5, the condition is probably autoimmune hepatitis. If the score is more than 6, the condition is definitely autoimmune hepatitis.

*SLA/LP = soluble liver antigen / liver pancreas

Treatment

The treatment for autoimmune hepatitis is very effective, and more than 90 percent of the people with this condition will go into remission by taking steroids (prednisone or prednisolone). Liver enzymes will return to normal when the disease is in remission. To reduce the side effects of steroids, these drugs are often combined with another medication, called azathioprine. The purpose of the treatment for AIH is to suppress the immune system and thereby reduce liver damage caused by an overactive immune system. In most people, the disease could be controlled with doses of prednisone (less than 10 mg daily) and azathioprine (100 mg daily). Those who do not tolerate or respond to azathioprine have other options. People who have significant side effects from prednisone could use a different type of steroid called budesonide (6–9 mg daily) to reduce the side effects of prednisone.

The failure rate of an azathioprine and prednisone combination is less than 10 percent. For those who do not tolerate or respond to azathioprine, AIH could be managed with other medications, such as mycophenolate mofetil (MMF), tacrolimus, or cyclosporine. MMF is the best studied second-line treatment for autoimmune hepatitis, but it carries the potential risk of birth defects and should be used cautiously in women of childbearing age. Tacrolimus (commonly prescribed after an organ transplant) is another second-line option.

The treatment for AIH is usually lifelong for 70–80 percent of the people with this disease. The prednisone dose is minimized or eliminated for many people with AIH within three years. The usual practice is to also attempt to wean a

person off azathioprine after three years. This could be done if their levels of liver enzymes and immunoglobulins are normal for three years, or, preferably, if a liver biopsy does not show any ongoing inflammation of the liver. In 20–30 percent of people with AIH, their liver enzymes will remain normal, but 70–80 percent of these individuals will relapse, so their treatment will need to be restarted. Many liver specialists may once more attempt to wean patients off the medications after another three years of treatment. If this fails, the treatment is continued for life.

Prognosis

The prognosis for individuals with autoimmune hepatitis is excellent. The majority will have a normal life expectancy and an excellent quality of life, but they will need lifelong follow-ups, since the disease may relapse, even during treatment. Those who are on a long-term treatment plan with azathioprine may need periodic skin examinations (for skin cancer) and should follow common, age-appropriate forms of surveillance for breast, colon, and prostate cancer. Individuals who are on steroids should have periodic bone density measurements (to check for bone thinning).

Very rarely, people who are diagnosed with advanced cirrhosis, or those with severe autoimmune hepatitis and liver failure, may need a liver transplant. The outcomes of liver transplants are excellent.

PRIMARY BILIARY CHOLANGITIS (PBC)

Primary biliary cholangitis is a rare disease. Approximately 95 percent of the cases of PBC are seen in middle-aged women. Those with this condition are mostly diagnosed during an investigation of elevated liver enzyme levels found on routine blood tests. People with PBC predominantly have elevated ALP levels, with relatively normal or mildly elevated AST and ALT levels.

When symptoms are present, the most common one is itching. Other symptoms may include fatigue and joint pain. Like people with AIH, other autoimmune disorders are

common in individuals who have PBC or have family members with this condition.

The characteristic blood test abnormality in diagnosing PBC is the presence of anti-mitochondrial antibodies (AMA), which are seen in up to 95 percent of people who have PBC. Immunoglobulins, especially IgM, may be elevated. A diagnosis of PBC can be made if two out of three of the following criteria are met:

1. An elevated alkaline phosphatase (ALP) level
2. A positive anti-mitochondrial antibody (AMA) test
3. Characteristic liver biopsy findings, showing inflammation of tiny bile ducts

A liver biopsy is not essential for a firm diagnosis of PBC. The procedure is often done, however, to determine the severity of scarring (fibrosis) or to confirm suspected PBC when the diagnosis is in doubt. About 5 percent of the people with this condition may not have AMA in their blood. For those individuals, a diagnosis is made on the basis of a liver biopsy.

Treatment

Progress has been made recently in the management of PBC. Previously, PBC was considered to be a progressive liver disease, but our understanding of the disease's progression has now improved. Although there is no cure for this condition, it could be controlled in 60–70 percent of the people with PBC, either with ursodeoxycholic acid (UDCA, or ursodiol) alone, or in combination with obeticholic acid (OCA) or fenofibrate. The goal of this treatment is to normalize the ALP level, or at least bring it down to less than 1.6 times the upper limit of the normal range. When this target blood level is reached, the disease does not appear to progress further, or to only do so very slowly.

The treatment for PBC is lifelong. Ursodeoxycholic acid has minimal side effects. Some individuals may experience abdominal discomfort, and this could be managed in most people by adjusting the dose. Obeticholic acid is expensive,

and up to 20 percent of those taking this drug may experience itching as a side effect.

Prognosis

People with advanced cirrhosis that is secondary to PBC need to be monitored for complications of hypertension in the portal veins (*varices*) and liver cancer. A bone density test is important, especially since the disease is predominantly seen in post-menopausal women. If jaundice is present, affected individuals should take fat-soluble vitamin supplements. A liver transplant can cure those with PBC and other complications. Post–liver transplant recurrences of PBC are very uncommon, and survival after a transplant is excellent.

PRIMARY SCLEROSING CHOLANGITIS (PSC)

Primary sclerosing cholangitis (PSC) is a rare condition, seen mostly in young to middle-aged men. This disease is caused by inflammation of the large and medium-sized bile ducts. In a few cases it only involves the small bile ducts. Just as in PBC, the predominant blood test abnormality in PSC is elevated levels of ALP. About 80 percent of the people with PSC will have a history of either ulcerative colitis (an inflammatory colon disease) or Crohn's disease (an inflammatory disease of the small and large intestines). A diagnosis of PSC is made on the basis of cholangiography, used to examine the bile ducts: either by magnetic resonance cholangiography, or MRC (a special type of MRI), or by endoscopic retrograde cholangiography, or ERC (using X-rays and a long, flexible, lighted tube called an endoscope). Although auto-antibodies are seen in blood tests of people with PSC, these auto-antibodies are not useful in diagnosing the disease. PSC typically has a "beaded appearance"—irregular narrowing and widening (*dilatation*) at multiple areas in the bile ducts.

Usually, PSC is suspected if routine blood tests show an elevated ALP level in a person with a history of ulcerative colitis or Crohn's disease. About 10–15 percent of those with PSC may have intermittent pain in their upper right belly, with

or without a fever. Itching is another symptom associated with PSC.

Treatment

There is no effective treatment for PSC. Ursodeoxycholic acid, although frequently prescribed, does not appear to change the progression of the disease. Sometimes the bile ducts may be clogged by inflammatory *strictures* (narrowings), caused by scar tissue. These strictures could be dilated with a balloon, guided by an endoscope, during ERC. This could relieve jaundice or itching and may delay the disease's progression.

Prognosis

In the majority of people with primary sclerosing cholangitis, the disease will progress slowly, and many individuals may require a liver transplant within 20 years after being diagnosed with PSC. One of the serious complications of PSC is cancer of the bile duct or gallbladder. People with PSC should be monitored for these cancers, which may occur in 10–15 percent of the individuals who are affected by PSC during their lifetime. Those with ulcerative colitis or Crohn's disease also need to be monitored for colon cancer.

OVERLAP SYNDROME

Sometimes people with predominant features of autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), or primary sclerosing cholangitis (PSC) may have "overlapping" biochemical, immunological, histological (microscopic), or cholangiographic components of more than one disease. This condition is called overlap syndrome, and it is seen in up to 10 percent of the people with AIH. The main characteristics of autoimmune hepatitis, primary biliary cholangitis, or primary sclerosing cholangitis are shown in table 8.2.

Liver specialists suspect overlap syndrome when the clinical or biochemical abnormalities are not typical of one disease alone, or when the treatment response is suboptimal. Although AIH, PBC, and PSC may overlap with each other, the overlap of PBC with AIH is more meaningful, since AIH

is easily controllable with medications. An overlap between PSC and AIH is often seen in children.

A PBC-AIH overlap can be difficult to diagnose at times. Various criteria for determining this overlap have been proposed. One such set of standards is known as the Paris criteria (table 8.3).

PBC-AIH overlap syndrome is suspected when at least two of the three accepted criteria for PBC, along with an interface with hepatitis plus one of the two other features of AIH, are present. If an overlap syndrome between PBC and AIH is suspected, the initial treatment is based on which disease predominates. Depending on the response, the treatment for the other condition may be added. Many people may end up taking a combination of azathioprine and UDCA.

An overlap syndrome between PSC and AIH is suspected (mostly in children and young adults) when the following components are present:

- Clinical, biochemical, and histologic features of AIH, with atypically elevated ALP levels
- A negative anti-mitochondrial antibody (AMA) test
- Cholangiographic features of PSC seen during an ERC or MRCP procedure
- Failure to normalize liver enzymes with *immunosuppression* (the use of drugs to suppress the immune system)

TABLE 8.2. Main characteristics of autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis

Autoimmune Hepatitis (AIH)		
ASMA (~80%) ANA (~80%) anti-LKM 1 (~5%) anti-SLA/LP* (~20%) IgG elevated	• interface with hepatitis; lymphoplasmacytic (lymphocyte and plasma) infiltrates	• all ages—bimodal peak • women 4:1 • acute or chronic • responds well to immunosuppression
Primary Biliary Cholangitis (PBC)		
	• florid ductal (bile duct)	• middle-aged people

AMA (90%) ANA (20% to 50%) IgM elevated	injury; lymphocytic infiltrates	• women 9:1 • florid ductal injury • responds well to UDCA or OCA
Primary Sclerosing Cholangitis (PSC)		
ANA, ASMA, and pANCA† may be seen and Ig may be elevated	• periductal fibrosis (bile duct–scarring) • diagnosis by cholangiogram	• usually young to middle-aged people • men 2:1 • variable response to UDCA

*SLA/LP = soluble liver antigen / liver pancreas

†pANCA = anti-neutrophil cytoplasmic antibody that targets a specific protein called myeloperoxidase

TABLE 8.3. Paris criteria for PBC-AIH overlap

PBC criteria*	**AIH criteria***
ALP ≥ 2 times upper limit of normal (ULN) or GGT ≥ 5 ULN	ALT ≥ 5 ULN
Positive AMA 1:40	IgG ≥ 2 ULN or positive ASMA
Liver histology: florid bile duct lesion	Liver histology: moderate or severe periportal (around the portal vein) or periseptal (around the septum) lymphocytic piecemeal necrosis (cell death)

Sources: Chazouillères O et al. Hepatology. 1998 Aug;28(2):296–301; Kuiper EM et al. Clin Gastroenterol Hepatol. 2010 Jun;8(6):530–534.

Note: A sensitivity of 92 percent and a specificity of 97 percent are seen for a diagnosis of overlap syndrome made using the Paris criteria, with clinical judgment serving as the gold standard.

*At least two of the three accepted criteria of PBC, along with an interface with hepatitis plus one or two AIH criteria, must be present.

The treatment for PSC-AIH overlap syndrome is with immunosuppression plus UDCA, or an immunosuppressive treatment alone.

Sometimes AIH occurs with elevated levels of ALP or bilirubin, without PBC or PSC overlap syndromes. This could be due to a negative AMA test for PBC or small duct PSC, as long as medication-induced cholestasis (a reduced or blocked flow of bile) is ruled out.

HEMOCHROMATOSIS

This is a common genetic disorder, affecting roughly 1 in 500 individuals, that is mainly seen in white people. Hemochromatosis is the result of excess iron accumulation in multiple organs, including the liver, heart, pancreas, skin, thyroid, and joints. The excess iron causes damage to the cells; then scarring in the affected organ; and, finally, organ failure.

Our bodies tightly regulate iron absorption from the intestine to maintain optimal iron storage. The body does not have a way to excrete excess iron. Therefore, if the mechanism that controls iron absorption fails, iron will continue to be absorbed from the intestine, irrespective of the amount of iron that is already stored elsewhere in the body. This occurs even with a normal intake of iron.

There are different genetic mutations (types 1–4) that cause hemochromatosis, but the most common mutation (type 1) results from a change in the homeostatic iron regulator (*HFE*) gene.

Hemochromatosis is usually seen in middle-aged men, as women are protected from this condition through menstrual blood loss. For that reason, hemochromatosis in women develops in old age, unless they had a hysterectomy when they were young. It takes many years for iron storage to reach a sufficient level to cause damage to the organs. Today, hemochromatosis is often diagnosed during routine blood tests, when an individual's liver enzymes are found to be elevated. Unfortunately, this diagnosis is often missed, and many people with this test result are instead diagnosed with cirrhosis or liver cancer, since there are usually no symptoms during the early stages of hemochromatosis. Liver cancer is a common—and serious—complication of this disease.

The main characteristics of hemochromatosis are as follows:

1. It is a common genetic disorder in the white population (a majority of individuals inherited it as an autosomal recessive condition, meaning both parents need to

contribute one copy of the gene).
2. It results in an excess of stored iron, which causes damage to multiple organs, including the liver, heart, pancreas, thyroid, and joints.
3. In its beginning stages, affected individuals will have no symptoms. The early symptoms are fatigue and joint pain.
4. It is usually diagnosed when cirrhosis is also present.
5. A person's skin may become tanned (darkened) in later stages, and that individual may develop diabetes. This condition is therefore often referred to as "bronze diabetes."
6. Blood tests may show an elevated level of liver enzymes, greater iron saturation (more than 45 percent saturation by iron carrying a protein called transferrin), and a higher amount of stored iron (serum ferritin) in the liver.
7. Gene testing (a blood test for the *HFE* mutation) will confirm the diagnosis in 90 percent of the affected people. Less-common genetic mutation tests are not easily available.
8. An MRI of the liver (to measure iron storage), and a liver biopsy (to measure iron levels), are also helpful in making a firm diagnosis.

Treatment

Although this condition is often missed in people, treatment is relatively easy in the early stages of hemochromatosis. The treatment consists of repeatedly drawing blood (*phlebotomies*). This is usually done once a week at first, removing roughly a pint of blood. The frequency of this procedure is decreased as the body's iron stores are reduced to within normal limits, which may take up to 50–100 phlebotomies.

When red blood cells are removed, the body will produce more red blood cells, which then utilize the stored iron, and thus slowly deplete the excess iron stores. Once iron stores reach a normal level (assessed by measuring iron saturation and the amount of serum ferritin in the blood), the frequency of phlebotomies could be reduced to three or four times per year.

In addition to phlebotomies, individuals with hemochromatosis should not take iron supplements or vitamin C. Moreover, they should not drink alcohol. Those with hemochromatosis should also undergo periodic screening for liver cancer.

- An affected person's immediate family members should be screened for hemochromatosis.
- Those with hemochromatosis should undergo liver cancer surveillance, as liver cancer is a common complication of this condition.

Prognosis

Only those people who also have complications from cirrhosis or liver cancer will need a liver transplant.

WILSON DISEASE

Unlike hemochromatosis, which is fairly common, Wilson disease is a rare autosomal recessive disease that causes an excess accumulation of copper, primarily in the liver or certain areas of the brain, resulting in tissue damage. Wilson disease, which usually occurs in young people, causes both liver disease and neurological disorders.

Wilson disease is caused by mutations of the gene (*ATP7B* gene) responsible for the liver's normal excretion of copper into bile. This mutation causes copper to accumulate in the liver, brain, cornea of the eye, and other organs. Organ damage is predominantly seen in the liver and brain, although joints and the kidneys may also be involved. Some individuals may develop anemia from red blood cells breaking down (hemolysis). Neurological complications include tremors, speech problems, or personality disorders (people with this latter symptom could be admitted to psychiatry wards). Wilson disease could easily be missed during its early stages, unless a doctor strongly suspects its presence through clinical observation.

As with most liver diseases, there are no symptoms in the early stages of Wilson disease. Symptoms related to liver

disease appear only in the presence of liver failure or cirrhosis. If Wilson disease is suspected, your doctor will perform the following tests:

- A serum ceruloplasmin test to measure the amount of the protein (ceruloplasmin) that stores copper in the liver and carries it from the liver into the blood (the level of ceruloplasmin may be reduced)
- A 24-hour measurement to detect copper in the urine
- An eye examination for abnormalities (Kayser-Fleischer rings) due to copper accumulating in the cornea

A diagnosis of Wilson disease is confirmed by a liver biopsy and measurement of the amount of copper in the liver.

Treatment

The purpose of the treatment for Wilson disease is to remove copper from the body. Three medications are commonly used: trientine, penicillamine, and oral zinc supplements. Trientine is the preferred drug to remove copper, because it has fewer side effects. Orally ingested zinc competes with copper and slows down its absorption in the body. Hence oral zinc supplements are used in combination with either trientine or penicillamine.

The treatment for Wilson disease is lifelong. Close monitoring is needed to be sure the treatment is being followed (a major problem in young people), as well as to look for side effects. Individuals with Wilson disease should undergo periodic surveillance for liver cancer.

People who have Wilson disease should minimize their consumption of foods with a higher copper content, including shellfish, liver, nuts, dried fruits, chocolate, and mushrooms.

Prognosis

A liver transplant can cure people with acute liver failure or those with complications from cirrhosis.

ALPHA-1 ANTITRYPSIN DEFICIENCY

Alpha-1 antitrypsin deficiency is very rare disorder that may cause liver or lung damage (often both), due to an inadequate amount of the alpha-1 antitrypsin (AAT) enzyme. This deficiency is caused by the mutation of a gene called *SERPINA 1*. To get the disease, a person has to inherit two copies of the mutated gene, one from each parent. The normal genotype is referred to as MM, and the abnormal one as ZZ.

AAT protects lung cells (alveoli) from damage caused by an enzyme (elastase) released by white blood cells in response to an infection. A low level of this enzyme causes emphysema. In liver cells, the accumulation of a variant of AAT causes liver damage, resulting in cirrhosis and liver cancer. Rarely, a person's skin may also be involved.

Alpha-1 antitrypsin deficiency is suspected if an individual has a family history of emphysema without any known risk factors, or in the presence of both emphysema and liver disease. AAT is often diagnosed during an investigation of abnormal liver enzymes or emphysema. In the affected person, chest X-rays may indicate emphysema, and blood tests may show low alpha-1 antitrypsin levels. ATT is confirmed by genotyping or a liver biopsy (if there is evidence of liver disease).

Treatment

There is no treatment for liver disease that is secondary to AAT deficiency. Those with emphysema and a severe AAT deficiency may benefit from an infusion of human alpha-1 antitrypsin, pooled from multiple donors. Since the mechanism of liver damage is different, this treatment does not benefit those with liver disease. As in most liver diseases, people with an AAT deficiency should not drink alcohol, and they should have periodic, non-invasive tests to assess liver scarring.

Prognosis

In people with complications of cirrhosis or liver cancer, a liver transplant is an option to cure those conditions.

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CHAPTER 9

Complications of Liver Disease

This chapter will discuss complications of liver disease, under three subsections:

1. Acute liver failure
2. Chronic liver failure (decompensated cirrhosis)
3. The impact of liver disease on organs other than the liver

ACUTE LIVER FAILURE

Liver failure occurs when the liver cannot perform some of its functions. Most often, liver failure develops gradually, over many years. In acute liver failure, however, the liver loses its functions quickly, usually within six months, but sometimes over a period of several days.

Acute liver failure is a rare condition, but it can be associated with a fatal outcome. Approximately 2,000 cases of acute liver failure are reported in the United States every year. This condition is more common in countries that have high rates of hepatitis A, B, and E infections.

People who experience acute liver failure can have any of the following symptoms:

- Mental changes (hepatic encephalopathy), including irritability and confusion, caused by the liver's inability to eliminate ammonia and other toxins in the blood
- Easily bruised parts of the body or bleeding from the gums, caused by the decreased production of blood-clotting factors
- Yellow discoloration of the eyes or skin (jaundice)

Causes

The causes and outcomes of acute liver failure may vary, depending on the subtype. Some of the possible factors are listed in table 9.1.

Acute liver failure is commonly caused by medications, such as acetaminophen. In the United States, acetaminophen (generally referred to by its brand name, Tylenol) is becoming the most common cause of liver failure. This condition usually occurs when a large amount of acetaminophen is consumed, either intentionally or inadvertently. People who use medications that contain both acetaminophen and narcotic drugs (such as codeine) to control pain may underestimate the amount of acetaminophen they use. The FDA is attempting to reduce this risk by banning pain medications that are co-formulated with acetaminophen. Keep in mind that acetaminophen is more likely to cause liver failure in people who drink alcohol excessively. Moreover, some people may underestimate the amount of acetaminophen they consume when they are under the influence of alcohol. Acute liver failure can also occur in people who have other liver diseases and take more than the recommended dose of acetaminophen. Therefore, everyone—whether they are healthy or have liver disease—should avoid taking more than 2,000 milligrams (four 500 mg tablets or capsules) of acetaminophen in one day.

TABLE 9.1. Possible causes of acute liver failure

Tylenol (acetaminophen)
other medications or herbal preparations
hepatitis B
autoimmune hepatitis
hepatitis A
ischemic hepatitis
Budd-Chiari syndrome (obstruction of hepatic vein blood flow)
Wilson disease

In addition to acetaminophen, many other medications—including nonsteroidal anti-inflammatory drugs (ibuprofen and similar drugs), antibiotics, anti-seizure drugs, and anti-tuberculosis medicines—can cause acute liver failure.

Viral hepatitis (hepatitis A, B, or E) or autoimmune hepatitis can also bring on acute liver failure, but hepatitis C usually does not. Nonetheless, because hepatitis A or B is more likely to cause acute liver failure in someone who already has a hepatitis C infection, individuals with hepatitis C should be vaccinated for hepatitis A and B.

Acute liver failure could also be brought about by an inadequate blood supply to the liver (ischemic hepatitis). This condition is more common in elderly individuals and people who have heart conditions. After any major surgery, liver failure may suddenly develop in the immediate post-operative period, a condition most commonly caused by the rapid worsening of a previously unidentified chronic liver disease. Acute liver failure after surgery, however, can also be caused by insufficient blood flow to the liver, or by a toxic reaction to anesthetic agents or antibiotics.

For approximately 20 percent of individuals with acute liver failure, its cause is unknown. A physician may perform a liver biopsy if the reason for the acute failure cannot be identified. Most people who have acute liver failure, however, will not require a liver biopsy.

Acute liver failure is an urgent condition that leads to the failure of other organs (multi-organ failure). Early recognition of the reason why this failure occurred may help in its successful treatment. Therefore, for the best outcome, it is important to seek help from a medical center that has plenty of experience in treating liver disease.

Treatment

Treatment for acute liver failure is based on the cause of the disease. There are no specific treatments if the reason for the condition is not listed in table 9.2.

Early treatment using N-acetylcysteine (NAC) has been shown to improve a person's chances of recovery without a liver transplant. If poisoning from eating death-cap mushrooms (*Amanita phalloides*) is suspected, the recommended treatment is a combination of intravenous penicillin and silibinin, given together. A liver transplant is the only treatment option for most people who have acute liver failure caused by Wilson disease. Although treatment with penicillamine, trientine, or zinc is not effective in many instances, these medications could occasionally be beneficial. Early diagnosis of acute liver failure may avoid a liver transplant for many people who have autoimmune hepatitis. Most physicians will start a trial treatment of intravenous steroids before proceeding with a liver transplant. Antiviral treatments are not helpful for the management of acute liver failure caused by viral hepatitis.

TABLE 9.2. Potential treatment for acute liver failure

Cause	Treatment
Acetaminophen	N-acetylcysteine (NAC) administered intravenously or by mouth
Mushroom poisoning	combination of penicillin and silibinin administered intravenously
Wilson disease	trientine or pencillamine in combination with zinc could be tried while awaiting a liver transplant
Autoimmune hepatitis	steroids administered intravenously
Budd-Chiari syndrome	blood thinners and sometimes TIPS (a type of shunt) to open up blocked hepatic veins

In cases of acute Budd-Chiari syndrome (caused by blood clots blocking the hepatic veins, which carry blood from the liver to the heart), medications that can dissolve the blood clots (thrombolytic therapy) or the placement of *stents* (small metal tubes) to open the clogged veins may relieve liver congestion and reverse acute liver failure. Pregnancy-associated acute liver failure usually goes away after the baby is born.

Prognosis

The survival rate for individuals who have acute liver failure can be influenced by its cause. People whose acute liver failure is caused by acetaminophen use or hepatitis A have a better chance of survival than those for whom the cause is unknown (presumably a viral condition) or results from other medications. Individuals who have both Wilson disease and acute liver failure are less likely to survive without a liver transplant. When a person experiences acute liver failure, the decision about whether a liver transplant is necessary has to be made quickly.

The complications of acute liver failure include the following:

1. Hepatic encephalopathy
2. Swelling in the brain
3. Metabolic complications, including hypoglycemia (low blood sugar), acidosis (too much acid in the body), and alkalosis (too much bicarbonate [alkali] or not enough acid in the blood)
4. Gastrointestinal bleeding
5. Bacterial infections
6. Clotting abnormalities
7. Respiratory failure
8. Circulatory complications
9. Kidney failure

People with acute liver failure are best treated in medical centers that are equipped for liver transplants. It is much better to transfer a patient to a liver transplant facility before that individual goes into a coma. Helicopter transport is preferable to traveling in a pressurized aircraft or by automobile. The United Network for Organ Sharing's current rules permit people who have acute liver failure to be listed as "status 1," ensuring that they have the highest priority on the waiting list for a transplant.

Liver Transplants

Before the advent of liver transplants, the survival rate for people with acute liver failure was between 10 and 20 percent. Transplantation has improved the survival rate considerably and is now the gold standard for treatment.

CHRONIC LIVER FAILURE

Most people who have liver disease do not have any symptoms until their liver has been damaged for a long time. When a person with liver disease starts to feel very tired, or their skin turns yellow, that means their liver damage has gotten worse, and they have cirrhosis. Individuals with either of these signs should see their doctor right away.

Some of the symptoms that a person with late-stage liver disease may have are listed in table 9.3. But these signs could also happen because of other conditions—not just liver disease—so it's important to see a doctor to rule out any other medical problems.

TABLE 9.3. Symptoms of late-stage liver disease

Symptoms
• severe fatigue
• short-term memory problems
• yellowing skin (jaundice)
• impotence in men
• enlarged breasts in men (gynecomastia)
• swelling of the abdomen or legs
• vomiting blood or passing black stools
Signs
• spider-like collections of blood vessels (spider nevi) on the face, arms, or chest
• loss of armpit or pubic hair
• redness (erythema) in the palms
• decrease in size of the testicles
• prominent veins on the abdominal wall
• fluid in the belly (ascites)
• flapping tremors (asterixis)
• wasting away of muscles

Cirrhosis is a serious result of liver disease, no matter what the cause. When a person develops cirrhosis after long-term liver damage, their liver cannot do its work normally. If the

cirrhosis is found early on, and the cause is treated, then the damage will stop and, in some people, their liver can reverse the damage.

Some of the serious problems that can happen when a person develops cirrhosis are:

- Fluid buildup, which causes
  - Swelling in the abdomen (ascites)
  - Swelling in the legs (edema)
  - Swelling in different parts of the body (anasarca)
- Bacterial infections
  - In the fluid that builds up in the abdomen (spontaneous bacterial peritonitis)
  - In the urinary system (kidneys, bladder, urethra)
  - In the respiratory tract (sinuses, nose, airway, lungs)
- Internal bleeding in the digestive system
  - From larger veins in the esophagus (esophageal varices)
  - From large veins in the stomach (gastric varices)
  - From large veins in the large or small intestine (ectopic varices)
- A change in a person's mental state (hepatic encephalopathy):
  - Altered sleep patterns
  - Short-term memory problems
  - Confusion
  - Coma (rare)
- Liver cancer
- Wasting away of muscles

Most of these conditions are caused by higher blood pressure in the blood vessel that carries blood from the intestines, pancreas, and spleen to the liver (the portal vein). To understand the causes of these major problems and the ways in which a doctor will manage them to help a person feel better, it's important to know more about the liver and how it works.

Changes in the Liver's Blood Flow

The liver gets blood from two different blood vessels:

1. The *hepatic artery*, which brings oxygen-rich blood from the heart to the liver
2. The *portal vein*, which brings blood from the intestine, pancreas, and spleen to the liver

The portal vein supplies most of the blood to the liver (approximately 70 percent). The liver processes the important nutrients in blood coming from the intestine, gets rid of some of the toxins carried from the intestine, and processes the medicines that the intestine absorbed. The remaining 30 percent of the liver's blood supply comes from the hepatic artery. The liver is unique because of this dual blood supply, which provides an advantage if the portal blood flow is blocked (by a blood clot, tumor, or scarring due to cirrhosis), because the hepatic artery can compensate, to some extent, by increasing the blood flow to the liver. If the hepatic artery is blocked, however, the portal vein cannot bring additional blood to the liver.

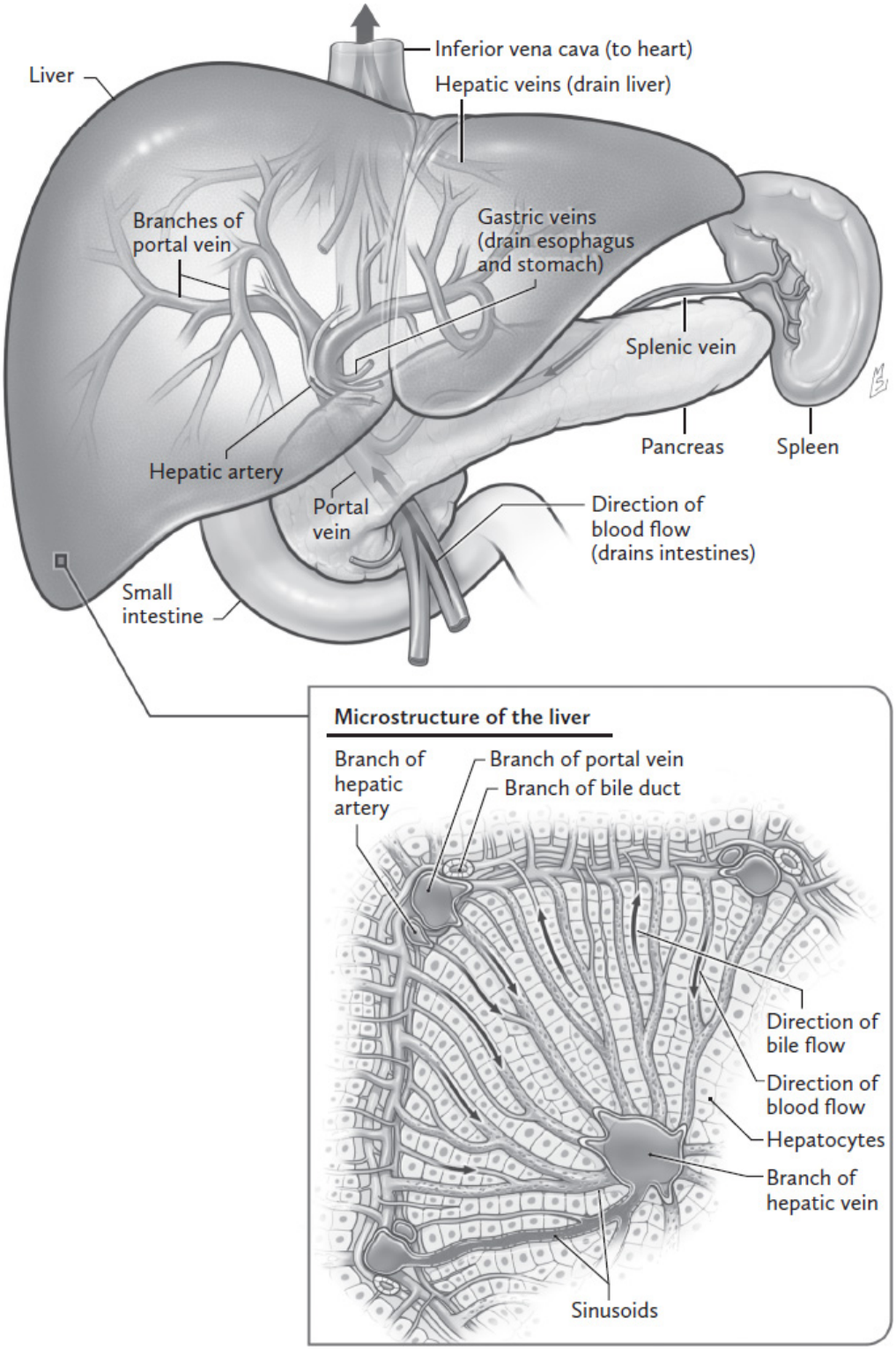

FIGURE 9.1. Liver anatomy, showing blood vessels and bile ducts

Under healthy conditions, the liver can accommodate significant increases in blood flow—for example, after eating—without raising the pressure in the portal vein. The portal vein branches into smaller veins, which then become small channels, called *sinusoids*. The sinusoids bathe the liver cells

(*hepatocytes*), and then drain into small veins (branches of the hepatic veins). These small veins join to become three relatively large hepatic veins (the right, middle, and left hepatic veins). Blood in the hepatic veins drains into the *inferior vena cava*, the large vein that empties the blood from the lower part of the body into the right-hand side of the heart.

Normal pressure in the portal vein is less than 5–12 mm Hg (millimeters of mercury), and the pressure difference between the portal vein and the inferior vena cava (the *porto-venous gradient*) is less than 5 mm Hg. In a healthy individual, this pressure difference remains more or less constant. In a healthy liver, large increases in blood flow can be easily accommodated without an increase in portal vein pressure.

For people who have cirrhosis, this blood flow can become clogged because of scar tissue, nodules, and blood clots in the small branches of the portal vein. In addition, people with cirrhosis undergo changes in their nervous system and their hormones, which also hinder blood flow in the liver. When these problems are combined, they lead to an increase in pressure in the portal vein (portal hypertension).

Although other factors can cause portal hypertension, cirrhosis is the most common factor. Portal hypertension is diagnosed when the porto-venous gradient is more than 5 mm Hg, but the complications of portal hypertension usually appear when the pressure exceeds 10 mm Hg. There are no reliable, non-invasive ways to measure portal vein pressure. A direct means is to insert a needle into the liver and push the needle into the portal vein, but this method is rarely used. The portal vein pressure usually is measured indirectly, by placing a catheter (a thin, hollow tube), with a balloon at its tip, into the hepatic vein. The catheter is inserted into a neck vein and then guided into the hepatic vein. Pressure readings are taken with the balloon both inflated (hepatic vein wedge pressure, which is a reflection of portal vein pressure) and deflated (hepatic vein free pressure). The difference between the wedge pressure and the free pressure (the hepatic vein wedge pressure gradient) is an approximation of the porto-venous gradient.

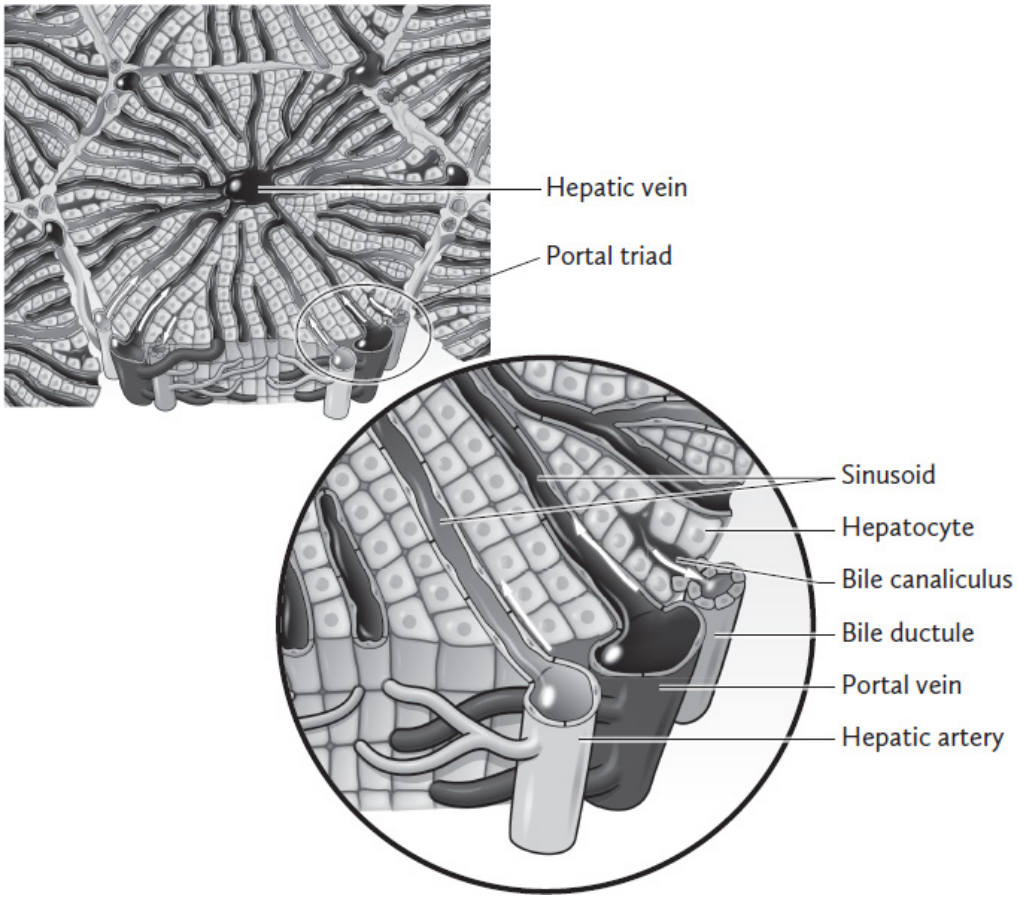

FIGURE 9.2. The relationship between blood vessels, liver cells, and bile ducts

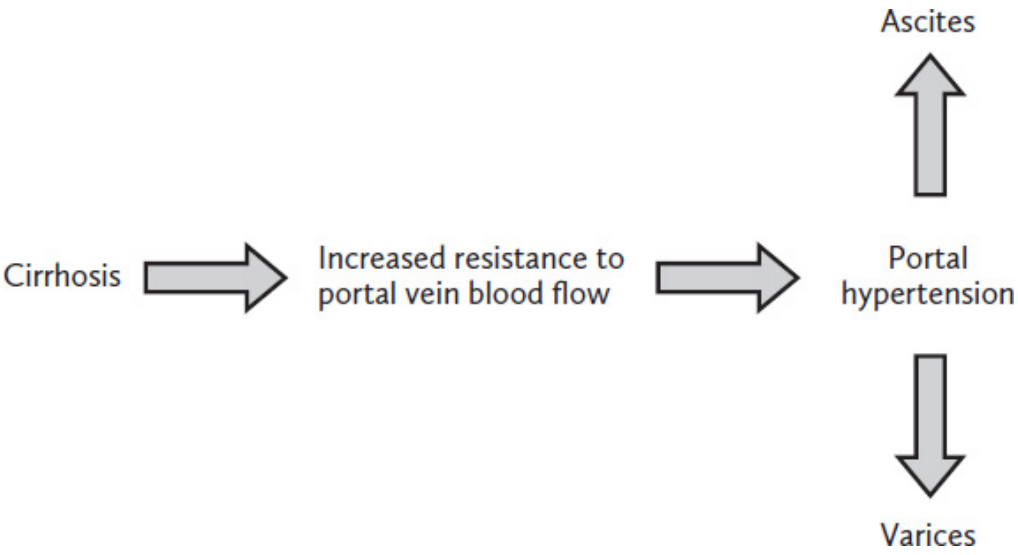

FIGURE 9.3. Cirrhosis of the liver can lead to high blood pressure in the portal vein

Fluid Buildup

One major problem that happens in people who have cirrhosis is a buildup of fluid in the belly (ascites) and legs (edema). Individuals who have ascites initially may not have any

discomfort, other than from the cosmetic appearance caused by a large belly. As ascites gets worse, people may feel significant discomfort and pain, and they may have difficulty breathing.

To help control the buildup of fluid in the belly, the first step a doctor will probably suggest is that an individual should reduce the amount of salt in their diet. People who have this type of fluid buildup should not consume more than 2,000 mg of sodium per day, so paying attention to how much salt is in your food is very important. A good way to control your sodium intake is to eat fewer processed foods and more fresh foods. Getting the advice of a registered dietician or a nutritionist can be helpful in making the healthiest diet choices.

If cutting down the amount of salt in a person's diet doesn't help reduce fluid buildup, a doctor may prescribe medicines (called *diuretics*) to help that individual produce more urine. The doctor may suggest taking both furosemide and spironolactone, so they can work together. Furosemide is fast acting and may cause a loss of potassium. Spironolactone is slow acting and uses a different mechanism, thereby conserving potassium. Taking a combination of the two medications helps keep the potassium levels steady and avoids the need for potassium supplements. Depending on how a person reacts to the medicines, their doctor may adjust the amount they need to take. It is very important to take these medicines according to the doctor's instructions, because serious problems—like kidney failure—can occur.

Another way a doctor may try to get rid of excess fluid in the belly is to remove the fluid by placing a needle in the belly (a process called paracentesis). First, the doctor will use an ultrasound to figure out the correct place to insert the needle. Before taking out a lot of fluid, the doctor will give that individual some intravenous albumin (a protein made by the liver). This infusion of albumin is important for maintaining blood flow to the kidneys and allowing the kidneys to work properly.

People undergoing paracentesis should ask their doctor if they should get albumin before any fluid is taken out, because some physicians may not do this. An albumin infusion is given to prevent kidney damage.

When a person's liver disease continues to get worse, controlling the amount of sodium and taking diuretics will often not help in reducing the amount of fluid built up in their belly. For these individuals, getting a new liver through a transplant from an organ donor may be the best way to treat their condition. If a person cannot have a liver transplant, a doctor may try to place a small tube in their liver to connect the portal vein to the hepatic vein. This should help drain some of the extra blood from the portal vein and allow that blood to go back to the heart. This procedure is called a transjugular intrahepatic portosystemic shunt (TIPS). It may be of benefit to people who have fluid buildup in their belly, but it has some very serious risks, including an ammonia buildup that can cause mental confusion (hepatic encephalopathy).

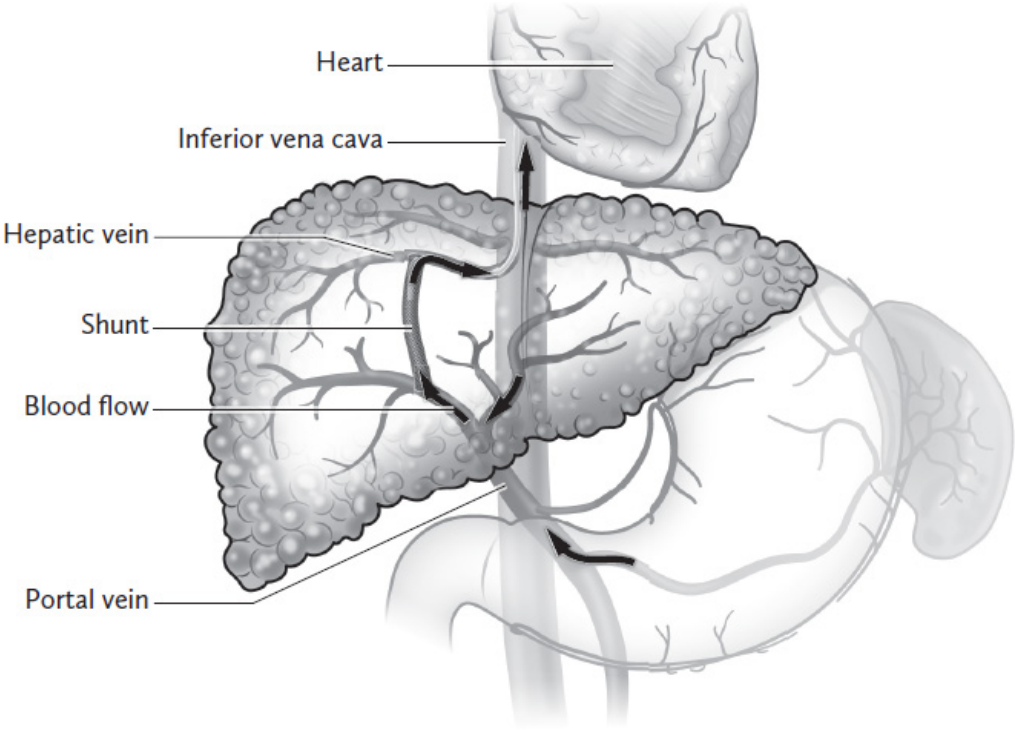

FIGURE 9.4. A transjugular intrahepatic portosystemic shunt (TIPS or TIPSS)

Infections

A person who has fluid buildup in their belly may also get

infections caused by bacteria in that fluid. This serious problem is called spontaneous bacterial peritonitis. These infections can be deadly in almost 30 percent of the people who have fluid buildup. Anyone who has fluid buildup in their body and has a fever, pain in their belly, or mental confusion should see their doctor right away.

The doctor will check the fluid for possible infections by inserting a needle into the belly, removing some of the fluid, and counting the number of white blood cells (the blood cells the body uses to fight infections). The doctor may prescribe antibiotics to help treat the infection. People who have gotten these types of infections once are very likely to get them again. Thus, to prevent any future infections, they may need to take antibiotics for the rest of their lives.

Bleeding

When the blood pressure in the portal vein increases, the body tries to lower that pressure by opening up new blood vessels to help take blood away from the liver. Over time and with greater pressure, these smaller blood vessels get larger to handle more blood flowing to them. As the pressure increases, they can burst and bleed (figure 9.5). These larger blood vessels (*varices*) can burst in the esophagus (the tube from the throat to the stomach), stomach, or other organs in the body (such as the large or small intestines or the rectum). Swollen blood vessels in the esophagus (esophageal varices) are a common source of this bleeding.

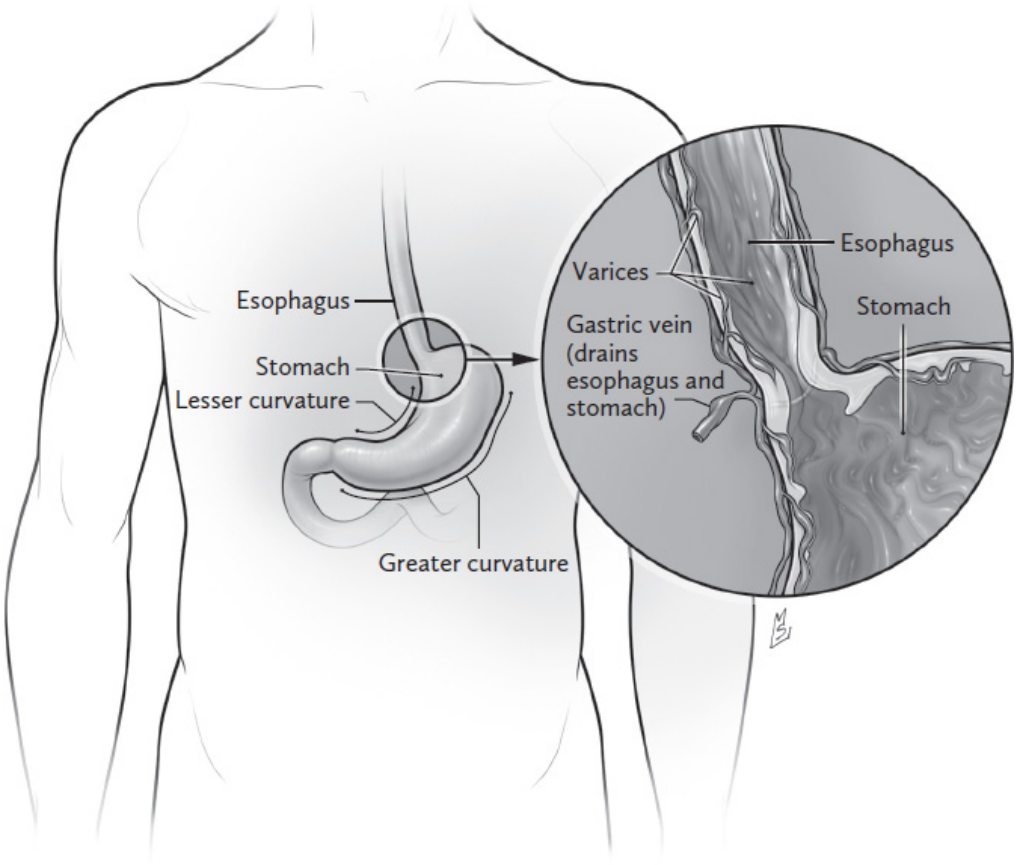

FIGURE 9.5. Bleeding in the blood vessels in the esophagus, as viewed from inside the esophagus

Preventing First-Time Bleeding

A doctor can check whether an individual risks having a burst blood vessel by inserting a tube in the person's throat and looking into their stomach and esophagus with a video camera. This procedure is called an *endoscopy*. Based on the size of the veins, their color, and other characteristics, the doctor can tell whether that individual has a risk of bleeding. If so, the doctor will help lower that risk by using various treatment options (table 9.4).

If the person has a high probability of bleeding, the doctor may prescribe medicines (propranolol, nadolol, or carvedilol) to help lower that risk. These drugs do not reduce the risk of bleeding completely, but they can reduce it by about 60 percent. The doctor will probably begin with a small dose and then increase it slowly. People who have a risk of bleeding from the stomach or esophagus must take these medicines for

the rest of their lives, or until they have a liver transplant.

TABLE 9.4. Treatment options for variceal bleeding

Treatment	Reason to apply treatment
Using medicines (either propranolol, nadolol, or carvedilol)	prevent bleeding by lowering blood pressure in the veins
Using a rubber band (banding)	prevent a blood vessel from bursting or stop a bleeding blood vessel
Using a metal tube (TIPS)	stop bleeding and prevent future bleeding by lowering the pressure in the portal vein by taking blood from the portal vein to the hepatic vein
Using a balloon (balloon tamponade)	stop bleeding in a blood vessel
Injecting glue	stop bleeding from gastric varices

Another way the doctor may try to lower a person's risk of bleeding is to use a rubber band to stop the blood flowing to the affected blood vessel (variceal banding). During an endoscopy, the doctor can suck the enlarged blood vessel into the endoscope, use a small device (like a cap) attached to the endoscope, and put a rubber band over the blood vessel. This procedure is relatively simple, with only very few (and rare) risks, including bleeding and narrowing of the esophagus. The doctor may need to repeat this procedure up to two to four times over a period of three months before the vein disappears.

To help lower the risk of bleeding, the doctor may suggest that a person should take both medicines plus have the banding procedure. If the individual cannot safely take these medicines, the doctor may only do the banding procedure. In general, banding is superior to medications in reducing the risk of bleeding. Banding is an invasive procedure, however, so a doctor may present both options to the patient and base the treatment on that individual's preference.

Sudden Bleeding

Each time a blood vessel bursts, that person has a 20–40 percent risk of dying. About one-third of all deaths in

individuals who have cirrhosis are caused by burst varices. Those who have blood vessels burst in their stomach have the highest risk of dying (greater than 50 percent).

After the first blood vessel bursts, a person's chances of survival depend on the stage of liver disease. Often, an individual who has cirrhosis will only find out they have this liver disease after they have bleeding in their stomach or esophagus. The signs of bleeding are:

1. Throwing up blood
2. Having red or black stools
3. Experiencing significant dizziness

If a person has any of these symptoms, they should go to a hospital right away. Getting help early can improve that individual's chances of recovering.

In the emergency room, the doctor may check to see how much blood the person has lost, give them replacement blood, administer antibiotics to prevent any bacterial infection, check for blood clots in the portal vein, and prescribe medicines to help lower the pressure in their blood vessels and stop the bleeding.

After stabilizing the person, the doctor will locate where the bleeding is by performing an endoscopy and then try to stop the bleeding by putting bands on the affected blood vessels. If the bleeding doesn't cease, the doctor may use a special balloon to compress the blood vessels (a process called balloon tamponade). Most bleeding will be stopped using these steps. If none of these methods work, the doctor (usually an interventional radiologist) may try to insert a small metal tube (stent) into the portal vein, to drain blood from this vein into the hepatic vein and lower the blood pressure in the portal vein (a TIPS procedure).

How to Prevent Repeat Bleeding

Once a person has a burst blood vessel, they are much more likely to have this happen in the future. If that individual survives after the first time such bleeding occurs, they have a

very high risk of having additional bleeding in the following two years, especially during the first six weeks after the initial bleeding.

Their doctor will again suggest using medicines and the banding procedure—methods used to stop the first bleeding episode. The doctor is more likely to use both of these treatments together, because the combination works better than either one by itself.

When medicines and banding do not help prevent repeated bleeding, the doctor may suggest using a TIPS procedure, which works well to prevent the bleeding from happening again. This procedure, however, risks having the tube become narrowed or blocked. For the best results, the physician has to periodically check the stent to ensure that there is no blockage, but this monitoring is expensive.

For people who have late-stage liver disease, these treatment options will not help their liver get better or help them survive. The best treatment for these individuals is to have a liver transplant.

Changes in a Person's Mental State

As cirrhosis and liver disease progress, people may develop memory problems and, later, mental confusion. These symptoms, known as hepatic encephalopathy, occur when toxins are not eliminated from the body by the liver.

A healthy liver processes ammonia and other toxins that get into the blood from the intestine. When a person has cirrhosis, this may not take place, because their liver is not working properly. Instead, blood is being diverted through other veins and bypasses the liver. When this happens, these toxins may reach the brain, causing a variety of symptoms, including sleep disturbances, memory problems, confusion, and, in extreme cases, coma.

These symptoms are often brought on by constipation or a high-protein diet. Although eating a normal amount of protein is encouraged, people who have advanced cirrhosis should avoid high-protein diets and should make every effort to

increase their fiber intake, which may help them avoid constipation. Individuals who have advanced cirrhosis are encouraged to eat plenty of vegetables. Also, a physician may prescribe a medicine called lactulose, a syrup that causes an increase in bowel movements and changes the bowel's pH and its microorganisms (bacterial flora), thereby reducing the amount of ammonia that is formed and then absorbed.

If lactulose does not work in relieving hepatic encephalopathy, the physician may prescribe antibiotics, such as rifaximin (Xifaxan) or, rarely, metronidazole. Rifaxamin, a non-absorbable antibiotic, is preferred because of its *efficacy* (effectiveness) and its relatively fewer side effects. The only disadvantage is its higher cost, compared with other antibiotics. When none of these approaches are successful, the physician may recommend a protein-restricted diet.

Bleeding, infections, abnormalities in *electrolytes* (minerals in blood and other bodily fluids), or kidney failure often cause hepatic encephalopathy.

Liver Cancer and Other Complications

Cirrhosis can cause other problems, such as liver cancer, osteoporosis, and, in advanced cases, vitamin and mineral deficiencies. People who have late-stage cirrhosis are often malnourished.

Liver cancer is one of the most dreaded complications of cirrhosis and is often found in advanced stages of this disease, when the options to treat the cancer are few. Liver cancer is one of the most common forms of cancer, causing about 10 percent of all adult deaths. (Liver cancer is discussed in more detail in chapter 10.)

People who have cirrhosis should be screened for liver cancer every six months. Early stages of liver cancer can be treated very effectively.

IMPACT OF LIVER DISEASE ON ORGANS OTHER THAN THE LIVER

Liver disease may also affect other organs. A few of these

non-liver conditions are specific to individuals with viral hepatitis (hepatitis C and hepatitis B). Additionally, advanced cirrhosis could affect the lungs, heart, kidneys, brain and nervous system, bones, and muscles.

Approximately 5 percent of the people who have hepatitis C may develop diseases in organs other than the liver (table 9.5). People with hepatitis B may also be affected by 1–10 percent of the conditions listed in table 9.5. The problems that affect other organs are believed to be caused by excessive stimulation of the immune system from a chronic hepatitis C or hepatitis B infection, rather than by the hepatitis C or B virus. Keep in mind that most of these conditions can arise without having a hepatitis C or B infection. They can also randomly occur in people with hepatitis C or hepatitis B.

TABLE 9.5. Conditions possibly associated with hepatitis C or a hepatitis C infection

Strong association (mostly with hepatitis C):

- a combination of cryoglobulinemia and leukocytoclastic vasculitis (a thickening of blood proteins and inflammation of blood vessels)
- membranoproliferative glomerulonephritis (an inflammation of the filters, called glomeruli, in the kidney)
- sialadenitis (an immune disorder that destroys tear glands and salivary glands)

Probable association (mostly with hepatitis C):

- porphyria cutanea tarda (a skin condition in which blisters appear in exposed parts of the skin)

Suspected association (hepatitis C and, to a lesser extent, hepatitis B):

- autoimmune thyroid disease (thyroiditis)
- idiopathic thrombocytopenia (a blood disorder from low platelet counts)
- Behçet's disease (an inflammation affecting many parts of the body)
- cancer of the lymphatic system (non-Hodgkin's lymphoma)
- mucosa-associated lymphoid tissue (MALT) lymphoma (cancer of the mucus lining of the stomach and other mucous membranes, including those of organs such as the salivary glands, thyroid, and lungs)
- lichen planus (a skin condition in which bumps appear on the skin; it can involve the oral mucosa, genitals, and nails)
- Hyde's prurigo nodularis (presence of multiple skin nodules and intense itching)
- Mooren's corneal ulcer (a painful ulceration of the cornea; a rare condition)
- idiopathic pulmonary fibrosis (lung-tissue scarring without a known cause)
- diabetes
- CREST syndrome (a multi-symptom form of scleroderma, which is a hardening and thickening of connective tissues)

Some of the conditions described in table 9.5 probably are caused by an abnormal over-production of B-cells (a type of white blood cell), such as membranoproliferative glomerulonephritis, lymphoma, cryoglobulinemia, leukocytoclastic vasculitis, and MALT lymphoma. Others are autoimmune diseases, such as Behçet's disease, Hyde's prurigo nodularis, Mooren's corneal ulcer, and lichen planus. Sialadenitis, thyroiditis, idiopathic thrombocytopenia, and other conditions (such as porphyria cutanea tarda) remain poorly explained. Many of these disorders improve after treatment for hepatitis C or hepatitis B, although some remain unchanged. The internet has a wealth of information about and pictures of these conditions, but a few common ones are briefly discussed here.

Essential Mixed Cryoglobulinemia

The most common (and proven) condition that occurs in association with a hepatitis C infection is mixed cryoglobulinemia. A person affected with this disease has proteins (called cryoglobulins) in the blood that thicken only at cold temperatures. Approximately 5–8 percent of the people with this disorder will develop B-cell lymphoma (malignant tumors of the lymph system). Rarely, cryoglobulinemia will involve more than one organ, and this condition may be life threatening, especially with severe inflammation of blood vessel walls (vasculitis). In other rare instances, cryoglobulinemia may involve fluid leakage into the covering of the heart (pericardial effusion) or the covering of the lungs (pleural effusion). The treatment will be effective to some extent when the precipitating cause (hepatitis C) is cured, but this response is not universal.

Membranoproliferative Glomerulonephritis

People with both membranous and membranoproliferative glomerulonephritis, a type of kidney disease in which the filters in the kidney (called glomeruli) are inflamed, are more likely to have a hepatitis C or hepatitis B infection than individuals who have other types of kidney disease. Membranoproliferative glomerulonephritis, which can occur

with or without cryoglobulinemia also being present, may not be associated with either a hepatitis B or hepatitis C infection. If membranoproliferative glomerulonephritis is suspected, a physician will perform a kidney biopsy. Individuals who have glomerulonephritis may not have other symptoms of chronic liver disease. In those who also have hepatitis B, children are the ones more likely to be affected.

People with membranoproliferative glomerulonephritis usually have a large amount of protein in their urine, blood in their urine, swelling in their legs, and mild to moderate kidney damage. Approximately 60 to 70 percent of the individuals with this condition may have detectable cryoglobulins in their blood. Studies show that treatment of a hepatitis C or hepatitis B infection may improve membranoproliferative glomerulonephritis. In children with a kidney disease associated with hepatitis B, 30 to 60 percent of them will improve without any treatment (spontaneous remission). In adults with hepatitis B and kidney disease, 30 percent may develop kidney failure, and up to 10 percent may require dialysis or a kidney transplant.

Polyarteritis Nodosa

Polyarteritis nodosa, a type of immune-mediated inflammation of the small and large blood vessels, could be caused by hepatitis B and is usually seen after a person's recent exposure to hepatitis B. Up to 50 percent of the people with acute polyarteritis nodosa may have a hepatitis B infection. Those with acute polyarteritis nodosa may have symptoms such as high fever, anemia, joint pain, blood in the urine, chest pain, high blood pressure, nervous system problems, or bleeding from the gastrointestinal tract, depending on the extent to which the blood vessels are involved. Unless treated, 30 percent of those with this disease could die within five years.

Sialadenitis

Sialadenitis, or inflammation of the salivary glands, could be caused by many conditions. It can occur with a hepatitis C infection. Sialadenitis is also frequently seen with cryoglobulinemia. Although Sjögren's syndrome involves a

similar inflammation of the salivary glands, these are two separate diseases. Sialadenitis that occurs with a hepatitis C infection is considered to be part of the hepatitis C–related over-production of *lymphocytes* (white blood cells). The presence of this condition may increase a person's risk of B-cell non-Hodgkin's lymphoma.

Porphyria Cutanea Tarda

Porphyria cutanea tarda is a general term used for a skin condition caused by deposits of a chemical (porphyrin) in the skin, making the skin sensitive to sunlight. It can be a genetic (inherited) disorder or an acquired condition. Porphyrins are created during the production of heme (a component of hemoglobin that carries oxygen in red blood cells). Porphyria cutanea tarda results from a deficiency in an enzyme called uroporphyrinogen decarboxylase, leading to an over-production of porphyrins.

A person with this disease typically has increased skin fragility and develops fluid-filled sacs or lesions (called vesicles and bullae) on areas of the skin that are frequently exposed to the sun (usually the back of the hands or the forearms), which leads to skin discoloration or scarring from the formation of small white bumps (called milia). Different forms of this skin condition include thick hair growth on the face and body, dark spots, and thickened skin that develops over a period of time. Typically, the disease affects middle-aged men who drink alcohol excessively and have symptoms of liver disease and iron overload. This condition is also associated with hepatitis C and, to a lesser extent, with a hepatitis B infection.

Although porphyria cutanea tarda can occur in people who do not have viral hepatitis, individuals with this skin condition frequently also have hepatitis C or hepatitis B. Despite this strong association, the exact mechanism by which viral hepatitis causes porphyria cutanea tarda remains unclear. The conventional treatment for porphyria cutanea tarda is to repeatedly remove blood, thus reducing the amount of iron in the body to the point of a mild iron deficiency. In addition, everyone who has porphyria cutanea tarda should avoid

drinking alcohol and not take estrogen supplements (either hormone replacement pills or contraceptive pills).

Lichen Planus

Lichen planus is a benign disease, characterized by itchy bumps on the skin. These bumps may be violet in color and can appear on the wrists, ankles, and genitals, as well as in the mouth. This condition is believed to be caused by the over-production of T-cell lymphocytes. The prevalence of hepatitis C in people who have lichen planus varies considerably from one geographic area to another, and the evidence linking hepatitis B with lichen planus is even weaker.

Autoimmune Thyroid Disease

There may be an association between autoimmune thyroid disease and a hepatitis C infection. Autoimmune thyroid disease is also seen in people with autoimmune hepatitis and primary biliary cholangitis. Studies have documented a high prevalence of thyroid antibodies in individuals who have a chronic hepatitis C infection. Both underactive thyroid (hypothyroidism) and overactive thyroid (hyperthyroidism) conditions have been observed in people with hepatitis C who are treated with alpha-interferon.

Non-Hodgkin's Lymphoma

Several reports, particularly from studies in southern Europe, have suggested a relationship between a hepatitis C infection and non- Hodgkin's lymphoma. The association of non-Hodgkin's lymphoma with hepatitis B is inconsistent. The development of non-Hodgkin's lymphoma among people who had a hepatitis C infection was seen most frequently in connection with cryoglobulinemia.

Other Non-Liver Complications

Several other conditions—including idiopathic pulmonary fibrosis, cutaneous necrotizing vasculitis (an inflammation of the small blood vessels), Mooren's corneal ulcer, idiopathic thrombocytopenia, diabetes, Behçet's disease, and CREST syndrome—have been described in association with viral

hepatitis, but no studies have proven that viral hepatitis is the cause. An increasing number of studies have found a relationship between type 2 diabetes and a hepatitis C infection. Nonetheless, because both conditions are common, it is difficult to prove a cause-and-effect relationship.

IMPACT OF CIRRHOSIS ON OTHER MAJOR ORGANS

In people with cirrhosis, especially in the presence of increased portal vein pressure, other organs may also be affected. Some organs are involved with compensated cirrhosis (severe liver damage), and others with decompensated cirrhosis (liver failure). (Some of these complications have been discussed previously.)

Kidney Disease

The kidneys are frequently involved when a person has advanced cirrhosis.

Hepatopulmonary Syndrome and Portopulmonary Hypertension

Hepatopulmonary syndrome and portopulmonary hypertension are two conditions, specific to cirrhosis, that cause lung problems. These diseases are seen in less than 5 percent of the people with cirrhosis.

Hepatopulmonary syndrome is the result of blood bypassing the lungs or being shunted through the base of the lungs, causing low oxygen saturation in the blood. People with this condition have shortness of breath, which gets worse when they sit up. With a normal amount of air in a room, their blood oxygen level will be low. A liver transplant is a good treatment option for this condition.

In some individuals, pressure in their pulmonary artery (the blood vessel that drains blood into the lungs) may become high, causing pulmonary hypertension. This condition usually occurs in people with lung disease. Rarely, cirrhosis can cause a similar problem, which is known as portopulmonary

hypertension. This is a serious complication of cirrhosis and requires treatment from specialists with expertise in this condition. A liver transplant could cure a mild case of portopulmonary hypertension.

Heart Disease

A type of heart disease called cirrhotic cardiomyopathy may be seen in people with advanced cirrhosis who have high portal vein pressure. This condition causes the heart to pump blood less efficiently and leads to low blood pressure or heart failure. Cirrhotic cardiomyopathy is seen more often when a person with this disease is under stress. EKG abnormalities (particularly a prolonged QTc interval, when the heart rate is slower than normal) are common. No effective medical treatment exists for this condition, but a liver transplant can cure it.

FURTHER READING

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CHAPTER 10

Liver Cancer

Cancer of the liver cells, also known as hepatocellular carcinoma (HCC), is one of the most common cancers in the world. Worldwide, more than 800,000 people are diagnosed with liver cancer every year, and it causes more than 700,000 deaths a year. In the United States, 42,000 patients are diagnosed with liver cancer yearly, and around 30,000 people die from it every year. In the United States and parts of Europe, the number of liver cancer cases is increasing, because the number of people who have NASH cirrhosis is increasing.

Liver cancer is more common in men (two to four times higher) than in women. The risk of liver cancer increases with age.

In addition to HCC, there are other types of cancer that could start from the liver. These are rare (approximately 10–20 percent of all liver cancers) and include intrahepatic cholangiocarcinoma (cancer originating from bile ducts), and angiosarcoma or hemangiosarcoma (cancers originating from blood vessels). Cancers can also begin elsewhere and spread to the liver (metastatic liver cancer).

This chapter will focus mostly on HCC. Intrahepatic cholangiocarcinoma could also be managed similarly.

POSSIBLE CAUSES OF HCC

Compared with people who don't have any liver disease, individuals who have other types of liver disease are more likely to develop liver cancer, especially those who have had hepatitis B or hepatitis C (table 10.1)

TABLE 10.1. Causes of liver cancer

Common causes

- cirrhosis from any cause
- hepatitis B
- hepatitis C
- hemochromatosis

Other risk factors

- smoking
- alcoholism
- obesity
- diabetes
- aflatoxins
- anabolic steroids

For people who have hepatitis C or hepatitis B infections, drinking alcohol makes them more likely to develop cancer. Individuals who have cirrhosis, no matter what the cause, are also more likely to develop liver cancer. In addition, obesity has been shown to increase a person's chances of developing liver cancer. Other risk factors are diabetes and smoking.

Cirrhosis, irrespective of the cause, is a predisposing risk factor for the development of liver cancer. In a given population, this risk is three to four times higher for people who have cirrhosis than for those who have chronic hepatitis without cirrhosis. Among individuals who have a hepatitis C infection, 5 percent develop liver cancer during their lifetime. The risk appears to increase, however, with severe cirrhosis. Approximately 15 percent of the people who have cirrhosis and hepatitis C will develop liver cancer during their lifetime.

Another risk factor (not currently seen in high-income countries) that can cause liver cancer is cancer-causing toxins (*aflatoxins*). In certain regions of Southeast Asia and sub-Saharan Africa, exposure to aflatoxins is common. Two types of fungi found in poorly stored grains, nuts, and seeds produce these toxins. Chemicals such as vinyl chloride (used in the plastics industry) may cause angiosarcoma (cancer in the inner lining of the blood vessels) and increase the risk of HCC, but their use is strictly controlled.

Genetic disorders—such as alpha-1 antitrypsin deficiency, Wilson disease, hemochromatosis, glycogen storage disorders (glycogen is a complex form of sugar), and tryrosinemia (elevated blood levels of the amino acid tyrosine) are also risk

factors for HCC.

SYMPTOMS

Many people who have liver cancer have no symptoms, as symptoms are only seen in advanced stages of the disease. Most people with cirrhosis and HCC have symptoms that are related to cirrhosis.

Some of the symptoms that people can have with advanced cancer are:

- Weight loss
- Loss of appetite
- Nausea and vomiting
- Fatigue
- Yellowing skin
- Pain in the belly

SCREENING AND TESTING

The earlier a person knows they have liver cancer, the better their chances for treatment and a cure. Screening is a way of checking for cancer before a person may have any symptoms. Individuals who have any of the other conditions that make them more likely to develop cancer, especially people who have hepatitis B or cirrhosis from any cause, should see their doctor every six months to have a cancer screening. People who have ever had liver cancer before should also see their doctor for regular surveillance, because they are more likely to develop liver cancer again.

There is no reliable blood test for liver cancer. Instead, a doctor will check for liver cancer by doing the following actions:

- Checking the blood for higher than normal levels of alpha-fetoprotein (AFP)
- Doing an ultrasound scan
- Using computed tomography (CT) or magnetic resonance

imaging (MRI)
- Taking some liver tissue to check for cancer (a biopsy) if a diagnosis cannot be established through blood tests or imaging

Alpha-fetoprotein is a protein made in the liver. The levels of AFP in a healthy adult are usually very low. About two-thirds of the people who have liver cancer have higher than normal levels of AFP in their blood. If an individual has levels that are greater than 400 ng/ml (nanograms per milliliter), they are likely to have liver cancer. When a person's levels of AFP keep rising, it usually means that they probably have liver cancer. But it's important to know that this is not a foolproof test. Elevated levels may or may not mean that a person has liver cancer. Nonetheless, any individual who has higher than normal levels of AFP should also have an ultrasound. If the doctor is not sure whether a person has liver cancer based on the AFP blood test and an ultrasound, a CT scan or an MRI scan may also be done. Of the various imaging tests, CT and MRI scans are more accurate than an ultrasound examination, but the first two tests are more costly than an ultrasound.

In addition, a doctor may take a biopsy of the liver to test for liver cancer and do a CT scan of other parts of the body to make sure the cancer has not spread. The risk of transmitting liver cancer by means of the biopsy needle (cancer spreading along the skin track) is low.

Any person who has liver cancer should be tested for hepatitis B, hepatitis C, and checked for other possible causes, such as hemochromatosis.

Blood tests and an ultrasound (some medical centers also use CT or MRI scans) are two common ways of checking for liver cancer, but these techniques may not be able to find all liver cancers, especially if an individual has tumors that are small. But, if people make sure their doctor screens them every six months, they have a better chance of any cancer being discovered at an early stage. If a person has liver cancer, the size of the tumor, whether it has spread to any lymph nodes, and whether it has spread to other parts of the body will all help a doctor figure out what stage of cancer that person

has.

TREATMENT

The treatment options for liver cancer are:

- Surgery
  - Removing the tumor and the surrounding part of the affected liver
  - Getting a new liver through a transplant
- Local treatment (with needles)
  - Heating the cancer cells to destroy them (radiofrequency ablation or microwave ablation)
  - Injecting the tumor with alcohol (percutaneous ethanol injection)
  - Freezing the cancer cells to destroy them (cryotherapy)
- Local treatments using a catheter in the blood vessel that feeds the tumor
  - Blocking the tumor's blood supply and treating the tumor with anti-cancer drugs (embolization or transarterial chemoembolization, known as TACE)
  - Injecting the the tumor's blood supply with radioactive beads (transarterial embolization with beads of radiation, known as TARE)
- Radiation therapy
  - Destroying the tumor with external beam radiation therapy
  - Proton beam radiation therapy
- Chemotherapy
  - Using medications, including *immunotherapy* (activating the immune system to destroy tumors)

In the future, gene therapy may become applicable in the management of liver cancer.

The treatments for liver cancer and their results are shown in table 10.2.

When a person has liver cancer, a doctor will look at

several things to decide on the best treatment plan for that individual:

- The number of tumors, the size of the tumor(s), and where they are located, including whether they are close to any blood vessels
- Whether the liver cancer has spread to other parts of the body
- The stage of the liver disease, and whether the person has cirrhosis
- How bad the cirrhosis is, or whether the person has developed high pressure in the portal vein (by checking for varices via endoscopy)
- Whether the person has any other serious diseases
- Whether the person is healthy

There are more choices for the best way to treat liver cancer if the cancer is caught early, the tumors are small, and the cancer has not spread to other parts of the body. Many people, however, do not learn they have liver cancer until they experience symptoms, which usually means they have late-stage liver cancer. Individuals with late-stage liver cancer who also have symptoms usually only live for few months after they learn they have liver cancer.

TABLE 10.2. Treatments for liver cancer

Treatment	What is done	Results
Liver transplant	replaces the whole liver with a liver from an organ donor	five-year survival rate of 60% to 75%
Liver surgery	removes the tumor and parts of the liver that are affected by cancer	five-year survival rate of 35% to 42%, but the chances of having liver cancer again are high (50% to 85%)
Radiofrequency and microwave ablation	destroys the tumor by inserting a needle into the tumor and applying heat	five-year survival rate of 35% to 50%, but the chances of having liver cancer again are high (50% to 85%)

Percutaneous ethanol injection	destroys the tumor by injecting concentrated alcohol directly into the tumor (not frequently used)	five-year survival rate of 30% to 40%, but the chances of having liver cancer again are high (50% to 85%)
Cryosurgery	destroys the tumor by freezing the tumor (not commonly used)	limited data are available, but it may be similar to radiofrequency ablation
Transarterial radiotherapy	injects yttrium-90 into the tumor	used when no other treatments are possible
Chemotherapy	gives anti-cancer pills to keep the cancer from growing	used when no other treatments are possible
External beam radiation	destroys the tumor by radiation	limited data are available, but possibly it is effective in some
Proton beam radiation	uses very focused radiation, limiting possible damage to the surrounding organs	only very limited data are available

If the cancer is caught in the early stages and has not spread to other parts of the body, today there are many options to cure it (table 10.2). Recommendations about the best choice of treatment are listed in table 10.3. A doctor may use several different methods to treat the same person.

TABLE 10.3. Tumor size and treatment options for liver cancer

Tumor size	Treatment options
Small tumor(s) (usually less than 3 cm, or ~ 1.25 inches)	• liver transplant • liver resection • radiofrequency ablation • microwave ablation • alcohol injection • cryosurgery • transarterial chemoembolization
Tumor(s) (3 to 5 cm, or ~ 1.25 to 2 inches)	• liver transplant • liver resection • transarterial chemoembolization • transarterial radioembolization • external beam radiation

Large tumor(s) (5 cm or more, or ~ 2 inches or more)	• surgery (in the absence of cirrhosis) • transarterial chemoembolization • transarterial radiation (yttrium-90) • proton beam radiation
Tumor spreads outside the liver (metastases) or into a major hepatic blood vessel	• chemotherapy with or without immunotherapy

Removing the Tumor with Surgery

Liver cancer is caught early in only 20 percent of the people affected by it. For them, the tumor can be removed with surgery. This is the best treatment for people who do not have cirrhosis.

The chances of a person's survival after surgery are greatest in the following circumstances:

- The tumors are smaller than 2 inches (5 centimeters)
- A tumor is fibrolamellar (usually the type of cancer children have)
- A tumor is not on a blood vessel

But most individuals who have liver cancer also have cirrhosis (except people who have hepatitis B, or children with the fibrolamellar type of liver cancer). If a person has cirrhosis and their liver disease is mild, a doctor may try to remove the tumor with surgery. For individuals who do not have cirrhosis, the risk of dying from liver surgery (when it is performed by an experienced surgeon) is less than 3 percent, but that risk rises to about 8 percent in people who have cirrhosis.

On average, the chance of surviving for five years after surgery is about 35 percent, but that figure is higher if the person has small tumors. If an individual has this type of surgery and the liver cancer returns, that person may be considered for a liver transplant if they meet the transplant conditions.

Getting a New Liver through a Transplant

For people who have late-stage cirrhosis and liver cancer, the

best treatment is a liver transplant. The cure rate is high, and these individuals are less likely to get liver cancer again. Before a person can have a liver transplant, their doctor will figure out if they have a good chance for the transplant to be a success by looking at several conditions that have to be met (known as the Milan criteria):

- If the person has only one tumor, the tumor is smaller than 5 centimeters
- If the person has more than one tumor but fewer than three, all tumors are smaller than 3 centimeters
- The tumor has not spread to other parts of the body
- The tumor has not spread to a large blood vessel of the liver

People who meet these requirements have a 70–85 percent chance of living for five years after they are diagnosed with liver cancer (five-year survival rate). People who have larger tumors or more than three tumors may be able to get a liver transplant, but the results are usually not as good. There are criteria to shrink large tumors and then have a liver transplant if the tumors could be reduced enough in size to fulfill the Milan criteria.

The reasons why a person may not be suitable for surgery or a liver transplant are listed in table 10.4, along with other treatment choices. A doctor will look at the size of the tumor, its location, and how severe the liver disease is when deciding on what alternative treatments to use. Sometimes these treatments are intended as temporary solutions until a liver transplant can be done.

TABLE 10.4. Treatments for individuals who cannot have surgery

People who have one or more of the following conditions are not considered to be good candidates for tumor removal by surgery: • advanced cirrhosis • swelling in the belly • bleeding from blood vessels (varices) or the presence of large varices • mental confusion (hepatic encephalopathy) • tumors that have spread to other parts of the body • tumors that have spread to the liver's blood vessels • other serious heart or lung conditions

People who have one or more of the following conditions are not considered to be good candidates for a liver transplant:

- tumors outside the Milan criteria (cannot be shrunk to fulfill the criteria)
- tumors that have spread to other parts of the body
- tumors that have spread to the liver's blood vessels or the lymph nodes
- other serious heart or lung conditions
- other cancers
- age older than 70 years

Destroying the Tumor with Heat

There are two ways to destroy liver cancer cells with heat: using either radio waves or microwave energy.

Radiofrequency Ablation

If an individual has a small tumor, the cure rates after this type of treatment are similar to those for people who have liver surgery. The use of radiofrequency ablation has become popular and is now the preferred way to treat small tumors. A doctor can use this type of ablation to treat the liver cancer, or to keep the tumor from growing too quickly while the individual waits for a liver transplant. If the person's liver cancer returns after having this form of treatment, they could be considered for a liver transplant if they meet the transplant conditions.

Microwave Ablation

Microwave ablation uses heat from microwaves to destroy the liver cancer cells. This treatment is fast, can be used on several tumors at the same time, and can work for tumors that are larger than the ones that can respond to radiofrequency ablation. Many cancer centers now use microwave ablation instead of radiofrequency ablation to treat liver cancer.

Injecting the Tumor with Alcohol

In this form of treatment, a doctor injects alcohol into the tumor to destroy the liver cancer cells (percutaneous ethanol injection). This method works well for tumors that are smaller (less than 2 cm, or approximately 0.75 inches) and is not that expensive. For the best results, a doctor needs to repeat these injections over several intervals of time. The chances of

surviving for five years after this treatment are about 40 percent.

Cryotherapy

Unlike radiofrequency ablation or microwave ablation, where heat is used to destroy tumor cells, cryosurgery (also known as cryoablation) uses extreme cold to destroy tumor cells. Special catheters that can deliver liquid nitrogen or argon gas to the tumor produce this extreme cold. This technique, however, is not frequently employed.

Blocking the Tumor's Blood Supply with or without Chemotherapy

When using this treatment, a doctor will cut off the main blood supply to the liver cancer (*embolization*). Without its blood supply, the tumor will die. But because a tumor can get blood from many different blood vessels, the tumor may not be completely destroyed, so this treatment will not be successful.

Usually a doctor cuts off the blood supply and also injects the tumor with anti-cancer drugs (transarterial chemoembolization, or TACE). Unfortunately, some tumors receive blood from more than one arterial branch, or some cancer cells survive, leading to an inadequate treatment response or a recurrence of the tumor. This treatment does not cure a person's liver cancer, but is a way to slow down the the growth of the tumor. The chances of surviving five years after this treatment are only 6 percent, perhaps because TACE is used for people who have late-stage liver cancer.

Injecting the Tumor with Radioactive Beads

With this treatment, a doctor cuts off the main blood supply to the tumor and injects special radioactive beads to destroy the tumor cells (transarterial radiation therapy, or TARE). A doctor uses this treatment for people who have larger tumors. TARE is not considered to be a cure, but it helps prevent the tumor from growing too quickly. Some cancer centers prefer this option to TACE.

Destroying the Tumor with Proton Beam Radiation

Therapy

This treatment uses high doses of proton beam radiation from outside of the body to destroy the liver cancer cells. This type of radiation can target and destroy the tumor without causing damage to the surrounding organs. A doctor will use this treatment for people who have larger tumors. Proton beam radiation is more expensive and is available only in a limited number of cancer centers. It's not clear from research studies how well this treatment works.

Some centers also use external beam radiation therapy or stereotactic body radiation therapy as alternative to more conventional therapies.

Using Medications

There are many medicines that can be used to treat liver cancer (*chemotherapy*), especially in people with late-stage liver cancer for whom other treatments will not work. These medicines will keep the tumor from growing too quickly, but they do not cure liver cancer.

The medications can fall under following groups:

- Receptor tyrosine kinase inhibitors (TKIs block proteins that cause tumor growth)
  - Sorafenib
  - Lenvatinib
  - Regorafenib
  - Cabozantinib
  - Ramucirumab
- Checkpoint inhibitors (immunotherapy)
  - Nivolumab
  - Pembrolizumab
- Combination treatment (a TKI plus a checkpoint inhibitor, or one of these two inhibitors with other treatments, such as TACE or TARE)

The tumor responds in about a third of the people with combination treatments, and individuals who benefit from it will live longer. These treatments are not considered to be

curative.

People who take a TKI may have side effects, such as a rash (mostly on the hands and feet), fatigue, diarrhea, and high blood pressure. Immunotherapy may induce immune-mediated diseases, such as an elevation in liver enzymes, thyroid disease, or inflammation of the bowel (colitis).

Chemotherapy is rapidly evolving as a treatment for liver cancer, and more of these medications should be approved in the near future.

EARLY DETECTION AND PREVENTION

The best way to prevent liver cancer is to try to avoid the things that put people in greater danger of getting this disease. Universal vaccination for hepatitis B will reduce the risk of cancer worldwide. People who have a significant likelihood of contracting a hepatitis B infection because of certain behaviors should definitely get the vaccine for hepatitis B. There is some evidence that coffee consumption may reduce the cancer risk in people with cirrhosis (discussed in chapter 12). Treatment for hepatitis B and C will reduce the possibility of getting liver cancer. People with liver disease should minimize their alcohol intake and stop smoking. Body weight should be controlled if an individual is obese.

In order to have a major impact on reducing the death rate from liver cancer worldwide, an inexpensive yet sensitive diagnostic tool—and an equally effective treatment—would have to be made available. To date, no such test exists. Early detection of liver cancer, however, is possible with an ultrasound and an AFP measurement every six months for people who have a higher risk of developing cancer. Everyone with cirrhosis or hepatitis B (even those who do not have liver disease) should have regular screenings for liver cancer. Most people who have liver cancer go to their physician at an advanced stage of the disease, too late for any effective treatment. Screening for liver cancer could improve the cure rates by detecting small tumors earlier.

People who need to be screened for liver cancer every six months:

- Anyone with cirrhosis from any cause
- Anyone with hepatitis B

A TEAM APPROACH

People who have liver cancer may have the best results at a cancer center that uses a team approach. These centers have many different doctors who have special training in treating liver disease. These physicians will talk to a person about their condition and give that individual the best advice on how to treat it.

FURTHER READING

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CHAPTER 11

Liver Transplantation

A doctor may suggest a liver transplant when a person's liver disease has caused so much damage that their liver no longer is able to help keep them alive (*liver failure*) and other treatments will not work. During this surgery, the patient will get a new healthy liver from an individual who has recently died or part of a liver from someone who is still living. A liver transplant is successful for most people and will help them have longer, healthier lives.

COMMON REASONS TO NEED A LIVER TRANSPLANT

The reasons why a person may need a liver transplant are listed in table 11.1.

Every year, more people need liver transplants, but there are not enough healthy donor livers to meet this demand. Thus many individuals have to wait a long time before they can get a healthy liver, and about 10–20 percent of them will die before they are able to get a transplant.

Livers for transplants can come from people who have recently died, but often there are not enough designated organ donors to provide livers in this way. For this reason, doctors may suggest a transplant from a person who is living. In this type of surgery, a portion of that individual's healthy liver is given to the patient to replace their damaged liver. Because the liver can grow back in a few weeks, both the person who donates part of their liver and recipient of the transplant will have a healthy liver.

TABLE 11.1. Reasons for a liver transplant

1. Fluid in the abdomen (ascites) that does not respond to sodium restriction and diuretics

2. Infection of fluid in the abdomen (spontaneous bacterial peritonitis)
3. Confusion (hepatic encephalopathy)
4. Yellow discoloration of the eyes (persistent jaundice)
5. Presence of a small liver cancer
6. Kidney failure caused by liver disease (hepatorenal syndrome)
7. Bleeding from the stomach or esophagus despite a transjugular intrahepatic portosystemic shunt (TIPS)
8. Child-Pugh score Child C cirrhosis (unlikely to improve with treatment, with abstinence from alcohol, or with medications)
9. High MELD score (20 or more)

DECIDING WHO GETS A LIVER TRANSPLANT

Having one of the conditions listed in table 11.1 is just part of figuring out whether a person needs a liver transplant. A doctor will look at several things in deciding whether a transplant may be the best treatment choice for that individual and base their choice on the following questions:

1. Will the person get healthier from the liver transplant (both immediately and in the future)?
2. What kind of liver disease does the person have?
3. What stage of liver disease does the person have?
4. What kinds of symptoms does the person have? Does having those symptoms prevent the person from being healthy physically, mentally, and emotionally?
5. What is the person's chance of surviving the surgery (both immediately and in the future)?
6. What are the benefits to the person in having a transplant versus not having a transplant?
7. What are the disadvantages to the person in having a transplant versus not having a transplant?

Depending on the answers to all of these questions, if a

doctor decides that a liver transplant may be the right choice for that individual, the doctor will then help the person find a transplant team to talk to them about the next steps.

For example, an individual who has early-stage alcoholic cirrhosis and does not have any major problems or symptoms has the same odds of living for another five years, whether they have a transplant or not. So the cost of the liver transplant, the medicines a person needs to take after transplant surgery, and all the risks of having major surgery may not be right for them at that time. But, if their condition keeps getting worse over time, they can talk to their doctor again to help them decide about the possibility of having a transplant in the future.

THE TRANSPLANT EVALUATION PROCESS

A candidate for a transplant will first meet with a *transplant team*—a group of people who have special training in liver transplant surgery. The team members will talk to that individual to help decide whether to recommend a transplant. The transplant team is made up of a *hepatologist* (liver doctor), surgeon, social worker, psychologist, financial coordinator, and transplant coordinator. The evaluation process can last several hours, depending on the transplant center. During that time, the team will look in detail at a person's physical condition and conduct blood and other tests to check that individual's health and mental condition—as well as assess the patient's finances, insurance, and social support system—and discuss the best choices for that person, based on the team's experience and understanding of the latest research.

In evaluating a person for a possible liver transplant, the transplant team will consider the following:

1. Does the person have a disease or condition that will be helped with a liver transplant? If so, how soon does that individual need a liver transplant? Does the person have a late-stage disease that meets at least some of the conditions to have a liver transplant?
2. Does the person have any other diseases or conditions

that would prevent them from having a good result after a liver transplant?
3. Does the individual have people who can help take care of them and support them before and after the transplant surgery? Does that person have a past history of alcohol or recreational drug use? If so, is there a chance that the individual may start to drink alcohol and use drugs again?
4. Would it help if the person could have a transplant from a living donor, so they could get a transplant faster?

Reasons for a Transplant

The transplant team then thinks about the answers to each of those four questions and asks the following ones:

1. Does the person have a disease or condition that will be helped with a liver transplant?
2. If so, how soon does that individual need a liver transplant?
3. Does the person have a late-stage disease that meets at least some of the conditions to have a liver transplant?

If a person has any of the conditions listed in table 11.1, they may need a transplant. In addition, the decision of whether an individual would need a transplant should be based in their physical health and how long they may have left to live if they didn't get a transplant. Doctors use two different measurement systems to figure out the level (*stage*) of liver disease and a person's chances of dying from that disease: the Child-Pugh score, and the Model for End-Stage Liver Disease (MELD) sodium (MELD-Na) score. MELD-Na scores are used to prioritize organ allocation in the United States.

Child-Pugh Score

The Child-Pugh score (table 11.2) measures how serious a person's liver disease is and what their chances of surviving it are by looking at the results of blood tests, the levels of certain proteins in the blood, and that individual's symptoms. Each of these has a point value. To figure out a person's Child-Pugh

score, all of the points are added together. The total falls into one of three categories:

- *Child A*: A score of 5–6 points means the person has the least serious form of liver disease, with a very high chance of surviving after five years.
- *Child B*: A score of 7–9 points means the person has moderate liver disease, with a 75 percent chance of surviving after five years.
- *Child C*: A score of 10–15 points means the person has severe liver disease, with about a 50 percent chance of surviving after five years.

Model for End-Stage Liver Disease–Sodium Score

Doctors use the model for end-stage liver disease–sodium (MELD-Na) score to predict a person's risk of death if they have severe liver disease. The MELD-Na score is a number, based on the results of four different blood test results in people more than 12 years old (table 11.3).

A MELD-Na score can range from 6 (less sick) to 40 (extremely sick). A higher score means that the person's condition may be more serious and need a liver transplant. For example, if an individual has a score greater than 25, they will be put higher on the list to get a transplant, because they are more likely to die without a transplant than a person who has a score of less than 10. A pediatric end-stage liver disease (PELD) score is calculated for children younger than 12.

TABLE 11.2. Child-Pugh score calculation

Characteristic	1 Point	2 Points	3 Points
Encephalopathy	none	grades 1 to 2	grades 3 to 4
Fluid in the abdomen (ascites)	none	slight (or controlled by a diuretic)	at least moderate (despite a diuretic)
Bilirubin (mg/dl)	< 2	2 to 3	> 3
Albumin (g/dl)	> 3.5	2.8 to 3.5	< 2.8
International normalized ratio	< 1.7	1.7 to 2.3	> 2.3

(INR)

TABLE 11.3. Model for end-stage liver disease–sodium (MELD-Na) score

Blood tests as basis for the score
Serum bilirubin
International normalized ratio (INR)
Serum creatinine
Serum sodium (sodium values less than 125 mmol/L will be set to 125, and values greater than 137 mmol/L will be set to 137)

Note: MELD-Na is a mathematical score. It can be easily calculated for free on the Organ Procurement and Transplantation Network website, https://optn.transplant.hrsa.gov/resources/allocation-calculators/meld-calculator/.

The United Network for Organ Sharing (UNOS), the organization that manages the organ donation system in the United States, uses MELD-Na scores to help determine which people need a transplant the most and how soon they need it. An individual's score can go up or down, depending on their condition, so the transplant team will keep assessing that person's MELD-Na score periodically.

The only exception to this scoring system is people who are "status 1"—those whose livers have suddenly stopped working and are likely to die in a matter of days without a liver transplant.

A person's MELD-Na score is just one part of the decision about whether that individual will get a transplant—and how soon. The transplant team will look at many different factors, such as the potential recipient's age, how many donors and how many people needing a transplant live in a particular region, how geographically close the recipient is to the source of the donated liver, the blood type, and the donor's age. UNOS has developed new rules for making sure that donated livers are given fairly and equitably to the people who need them most.

Once the transplant team decides to put a person on the waiting list for a liver transplant, they will continue to check that individual's MELD score (or PELD score, for children) to see whether their condition is getting better, staying the same, or getting worse. If that person's MELD score changes to a

much lower number, they could be taken off the list.

Other Diseases

- Does a person have any other diseases or conditions that would prevent them from having a good result after a liver transplant?

The most important part of the process that the transplant team uses to evaluate a person who may need a liver transplant is to check whether that individual can handle the operation and have a healthy life afterward. Because transplantation involves major surgery, if the chances of a person dying from having this operation are higher than the worsening condition of their liver, then a liver transplant may not be the best decision. The transplant team will look at any other health problems that individual has, such as diabetes, heart disease, kidney disease, and cancer. Various reasons why a person may not have a good result after a liver transplant are listed in table 11.4, but these are just some of the things the transplant team will look at.

People who have kidney failure may need both a liver and a kidney transplant. A transplant doctor may decide to put some of these individuals on the lists for both liver and kidney transplants but, for others, decide to do a liver transplant first and, if necessary, perform a kidney transplant later. A person's age has less to do with the result of the operation than with their chance of living a healthy life in the long term. People who have diabetes or heart disease are about 40 percent more likely to die within five years after having a transplant than individuals who do not have these two conditions.

TABLE 11.4. Risk factors that predict a poor outcome after a liver transplant

1. Age older than 70 years
2. Uncontrolled diabetes with diabetes-related complications, such as generalized vascular disease
3. Severe obesity (body mass index more than 40)
4. Coronary heart disease
5. Kidney failure

6. Transplant while in the intensive care unit
7. MELD-Na scores more than 35
8. Poor performance status (measurements of how well the person is able to carry out ordinary daily activities)

Support System and History of Drug or Alcohol Use

- Does the individual have people who can help take care of them and support them before and after the transplant surgery? Does that person have a past habit of alcohol or recreational drug use? If so, is there a chance that individual may start to drink alcohol and use drugs again?

Often the hardest part of determining whether a transplant is the best choice for a person is checking on their social support system. Having someone else to help that person go to doctor appointments, take their medicines the right way, and assist them after the operation is very important in having a good result after the transplant. The transplant team's social worker and psychologist will talk to the patient about having this support and help the team make the best decision. After their evaluation, the whole transplant team discusses that individual's situation before making a decision.

A person who is placed on the list for a liver transplant must avoid all recreational drug use and alcohol consumption. If an individual has a problem with drug or alcohol addiction, most transplant centers will require that person to finish an approved rehabilitation program and have proof that they haven't drunk any alcohol or used recreational drugs for at least six months before they can be considered for a transplant. People who do not follow this restriction while on the waiting list for a liver transplant will be taken off the list. The transplant programs have strict rules in place to make the process of getting a liver transplant as fair as possible for everyone on the waiting list.

Living Donor Liver Transplants

- Would it help if the person could have a transplant from a living donor, so they could get a transplant faster?

Getting part of a liver from a donor who is alive has some advantages:

1. More potential living donors, to help more people needing a transplant
2. Less time spent waiting for a donor, especially for individuals who need a liver transplant right away
3. More time for the transplant team to help the person getting the transplant prepare for the procedure
4. Less time for the donated liver tissue to be without blood flow before it is put into the person receiving the transplant

The ability to get a liver transplant faster is helpful for people who don't have a high MELD-Na score but still need a liver transplant soon, such as those who have major complications from cirrhosis. Many individuals may able to have part of a liver donated from a family member or friend who is willing to do so. Thus the first step is talking to the transplant team about all of these possibilities.

The biggest problem with a liver donation from a living person is that the donor has a chance of getting sick and dying (roughly less than 1 in 400 people). For a healthy individual donating part of their liver, transplant surgery is a major operation that can be risky and does not directly help them in any way, other than getting a chance to help someone else. Any individual needing a transplant who is considering a discussion about this living donor option with the transplant team should first meet all the conditions for having a liver donated from a person who has recently died, as well as understand that the live person who is donating part of their liver has some major hazards to their health. The risks should be less than the benefits of having the operation. Moreover, the person who is donating a part of their liver should think very carefully about all of the risks to their health before they decide to proceed with this major operation. Making sure the donor stays healthy after the operation is extremely important.

TRANSPLANT SURGERY

Before the Transplant

The transplant team will base their decision about whether to place a person on the list for a liver transplant on the answers to all the questions the team has looked at. Once someone is in line for a transplant, the transplant team will do a lot of tests to better understand that person's health and make sure the individual is ready for this major operation. Some of the testing includes:

- Looking at how the lungs are working (lung function tests)
- Taking a chest X-ray
- Checking to see how the patient's heart is working (electrocardiogram)
- Taking a picture of the heart with ultrasound (echocardiogram) and a stress test (how the heart functions under stress)
- Doing blood tests
- Testing for HIV, hepatitis B, and other infections
- Taking an ultrasound picture of the blood vessels around the heart and neck (carotid arteries) if the doctor thinks the person has heart disease
- Taking a CT scan or an MRI to look at the blood vessels in and around the liver

During this evaluation, the patient will meet with all the members of the transplant team, including any specialist doctors. The team's psychologist and social worker will help that individual prepare for all of the things that are involved with having major surgery, as well as understand the liver transplant process. After the evaluation is finished, the entire transplant team will get together to talk about the evaluation results and decide for certain if a liver transplant is right for that patient.

After the Transplant

After a liver transplant operation, the patient may have many short-term and long-term problems. Liver surgeons are very experienced these days, and immediate surgical complications

have been reduced. It is a complex surgery, however, and may take three to six hours, even when done by an experienced team. The potential and immediate surgical complications are listed in table 11.5.

TABLE 11.5. Immediate complications of a liver transplant

Complications	Outcome
Complications from surgery	• blood loss is common and may require many units of blood or blood products • blockage of an artery in the lungs is extremely rare • blockage of a liver artery may require another surgery or radiological intervention (less than 2% to 3%) • a liver graft that is not working (less than 5%) usually requires a retransplant • a bile leak (up to 10%) is easily managed with a stent
Potential infections	• bacterial infections (of the chest, urinary tract, abdominal cavity, and wound) in the first few days • viral infection (opportunistic infections, such as cytomegalovirus) after the first 2 to 3 weeks • fungal (yeast) infections in the immediate post-operative period
Organ rejection	• minor rejection (~20% to 40%) is easily treated with medications, including steroids and, rarely, a monoclonal antibody
Death	• occurs in less than 5% of transplant recipients

Many of the short-term and long-term problems can be prevented if the patient learns a lot about the process, follows all the transplants team's instructions after the surgery (table 11.6), and gets tested regularly (table 11.7).

A person may choose to go back to their regular doctor after the transplant. Learning as much as possible about the process will help an individual know what they need to do after the surgery. Even if they see their regular doctor, it may be a good idea to keep in touch with the transplant team by phone. If the patient does not hear back, they should keep calling until they reach a transplant team doctor.

TABLE 11.6. How organ recipients can improve liver transplant outcomes

1. *Be well informed about a liver transplant*, including its risks and complications.

2. *Follow the transplant team's instructions*. Because the team manages many liver transplant patients, team members are likely to be a better source of information than many websites or other people's experiences. Major concerns regarding these instructions should be discussed with a transplant physician.
3. *Have blood tests done periodically, as recommended by the transplant team* (see table 11.7). Follow up on blood test results and make sure the team has seen the results. If possible, obtain a copy for your medical records. Learn what the blood tests mean. Call the transplant physician if there is a major change in your blood test results or you have any new symptoms. Sometimes the physician may not have received or seen the test results.
4. *Take medications as recommended*. Do not miss any doses, and do not self-treat.
5. *Maintain your health and manage any other health conditions*. Optimal health maintenance is essential for a better outcome. The long-term outcome depends on better management of other conditions or drug-related complications, such as diabetes, hypertension, obesity, high cholesterol, kidney failure, and cancers. Few people die from liver disease after the immediate post-operative period.

TABLE 11.7. How often should a liver transplant recipient get blood tests?

Time period after the transplant	How often to get tested?
0 to 3 months	1 to 2 times per week
3 to 6 months	every 1 to 2 weeks
6 to 12 months	every 2 to 4 weeks
1 to 5 years	every 4 to 6 weeks
after 5 years	every 3 months

Take Anti-Rejection Medications

When an individual has had a liver transplant, their body will treat the new liver as a foreign object. Their immune system will "attack" the new liver, making it less able to help the person recover from their liver disease. These anti-rejection (*immunosuppressive*) medicines will prevent the patient's immune system from doing that and will help their body not reject the new liver. A person has to take these medicines for the rest of their life. The most common medicines given to people who have had liver transplants are listed in table 11.8.

These medicines will help save a person's life. They are, however, associated with a few side effects. By making sure a person has healthy (*therapeutic*) levels of the medicines in their body, some of these side effects can be avoided. This is

why it's important to get regular blood tests and talk to a doctor about the results. For some of these medicines, the patient should have a blood test before taking the medication, to measure the appropriate amount (trough level) of that medicine correctly.

When taking these immunosuppressive medicines, it is very important to talk to your doctor or to a pharmacist about any other medications you are using, to make sure all the medicines will still work and will not cause serious drug-drug interactions. Some commonly used antibiotics can keep the anti-rejection drugs from working. Therefore, it is important to check with your pharmacist or your doctor before taking any new medicines.

TABLE 11.8. Common immunosuppressive agents taken after a liver transplant

Agent	Properties
Tacrolimus (Prograf), twice daily	A commonly used calcineurin (an enzyme that activates T cells) inhibitor. Blood levels should be maintained between 6 and 12 ng/ml (trough levels before taking the medicine in the morning), depending on the interval after the transplant and other immunosuppressive medications being used.
Cyclosporine (generic and Neoral), twice daily	A commonly used calcineurin inhibitor. Blood levels should be maintained between 100 and 200 ng/ml (trough levels before taking the medicine in the morning), depending on the interval after the transplant and other immunosuppressive medications being used.
Sirolimus, once daily	A relatively new drug approved for a kidney transplant, with no kidney toxicity. Blood levels should be maintained between 6 and 10 ng/ml.
Mycophenolate mofetil (Cellcept or Myfortic)	A drug used with tacrolimus, cyclosporine, or steroids. As a single agent, it is inadequate for immunosuppression, so it is used in combination with other drugs. Blood levels are not monitored.
Prednisone	A drug used only in the first few weeks after surgery, as most people are weaned off this drug by six months. It is used with other drugs in the immediate post-operative period.

Avoid Some Activities

Most people can lead a normal life after having a liver transplant. Nonetheless, to stay as healthy as possible, they

need to do certain things and avoid other actions:

- Right after having transplant surgery, stay away from crowded places, don't be near people who are sick, don't eat raw shellfish, and don't do any gardening.
- Do not have close contact with anyone who has recently had a live vaccine (such as an oral polio vaccine).
- Do not get any live vaccines. Talk to a doctor first about whether a vaccine is needed.
- Do not lift anything heavy for the first few months after surgery, and then gradually begin to exercise.
- Do not drink any alcohol.
- Do not take any new medicines, even if only for a short time. Check with a doctor first before taking any additional medications.
- Talk to a transplant doctor before changing anything about the anti-rejection medicines.

PROBLEMS AFTER SURGERY

Immediate Problems

The surgical team will closely check all people who have had a liver transplant to make sure any problems that happen right after surgery are taken care of immediately. Some of these issues can occur right after the operation, such as complications from the surgery itself and bacterial infections (see table 11.5).

Around two to four weeks after the transplant, people may get other infections, because their immune system is weak from the anti-rejection medicines. To prevent some of these infections, a doctor may give special antiviral medicines (valganciclovir or for 3 months), anti-fungal medications (fluconazole for 3 months), or antibiotics (a sulfamethoxazole/trimethoprim combination, commonly known under the brand name Bactrim, for up to 6 months).

Later Problems

Problems that can happen later are listed in table 11.9. The

immunosuppressive drugs, as well as other conditions the patient had before the surgery, can cause many of these problems. Being overweight, having high blood pressure, and having diabetes are the most common conditions an individual will have before the surgery that can cause more problems after the transplant. When a person with these conditions is taking immunosuppressive drugs, that individual is more likely to have serious heart problems. Transplant recipients should make sure they are following steps to stay healthy and control these conditions, to keep such problems from happening.

TABLE 11.9. Late complications of a liver transplant

Complication	Outcome
Hypertension	is common (20% to 30%) and may be related to tacrolimus or cyclosporine
Diabetes	may be related to tacrolimus or cyclosporine (10% to 15%)
Kidney failure	develops after five years in up to 20% of transplant recipients, probably because of tacrolimus, cyclosporine, diabetes, or hypertension
High cholesterol	may be related to medications (sirolimus is known to cause high cholesterol), obesity, or diabetes
Anemia	is common (30% to 40%); may be multifactorial and is usually mild
Osteoporosis	is common, especially with steroid use
Cancer	is common as skin cancer; other cancers include breast, colon, and prostate cancer
Lymphoproliferative disease	may be related to Epstein-Barr virus (the same virus that causes infectious mononucleosis); seen in less than 3% of transplant recipients
Obesity	is the most common problem
Bile duct problems	occur in up to 10% of transplant recipients
Recurrent disease	depends on the primary disease

A person who has had a transplant is more likely to get skin

cancer (basal and squamous cell cancer), and they should see a skin doctor (dermatologist) once a year to check for these possible forms of cancer. They also have a higher risk of having other types of cancers, such as breast, prostate, or colon cancer. People who have inflammatory bowel disease should have a colonoscopy every year to check for colon cancer.

The field of liver transplantation keeps changing as more research is done to improve the process. For example, liver transplant doctors are conducting ongoing research to find out if some people could stop taking immunosuppression medicines a few years after their liver transplant.

FURTHER READING

Liver Transplant. American Liver Foundation. https://liverfoundation.org/for-patients/about-the-liver/liver-transplant/.

Living donor liver transplant: An introduction for donors and recipients. American Liver Foundation. https://liverfoundation.org/living-donor-liver-transplant-an-introduction/.

Transplant living. United Network for Organ Sharing. https://transplantliving.org/.

Liver policy: Making liver distribution more fair and equitable. United Network for Organ Sharing. https://unos.org/policy/liver-distribution/.

European Association for the Study of the Liver. EASL clinical practice guidelines: Liver transplantation. J Hepatol. 2016 Feb;64(2):433–485. https://doi.org/10.1016/j.jhep.2015.10.006/. Epub 2015 Nov 17.

Martin P et al. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. Hepatology. 2014 Mar;59(3): 1144–65. https://doi.org/10.1002/hep.26972/.

CHAPTER 12

Liver Health

A liver that functions well is extremely important for our well-being. As discussed in earlier chapters, the liver has many important functions, including making essential proteins; processing fats and carbohydrates; creating and secreting bile to help the intestines absorb fats and fat-soluble vitamins; getting rid of potentially harmful chemicals the body produces; and getting rid of toxins, such as from drugs, alcohol, and environmental poisons.

The original concept of "liver health" perhaps came from traditional Chinese and Indian medicine, but the idea that a healthy liver is essential for the proper functioning of the human body was recognized all over the ancient world. Today's modern medicine accepts this widely held belief, but there are many fundamental differences in the interpretation of liver health. While many assume that liver health could be sustained by taking herbal or mineral supplements, the scientific evidence suggests that liver health can be maintained only by avoiding toxins (including unnecessary medications and excessive alcohol), preventing viral infections (by being vaccinated and not engaging in high-risk behaviors), and keeping an ideal body weight through good nutrition and exercise.

Despite the overwhelming absence of scientific evidence, the use of nutritional supplements and "liver-cleansing" methods are widely practiced all over the world. This chapter will examine these practices in more detail. Estimates indicate that 20 percent of the US population takes herbal preparations and spends approximately $50 billion on these unproven remedies. According to the Global Wellness Institute, approximately $360 billion is spent worldwide on traditional and complementary medicine.

COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) IN THE TREATMENT OF LIVER DISEASE

The National Center for Complementary and Alternative Medicine defines complementary and alternative medicine (CAM) as "a group of diverse medical and healthcare systems, practices, and products that are not presently considered to be part of conventional medicine." Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, herbs are classified as dietary supplements. Under the wording of this law, supplements are broadly defined as "anything that supplements the diet" and include vitamins, minerals, herbs, amino acids, enzymes, and herbal extracts. The FDA has little regulatory control over dietary supplements. Therefore, these products remain unregulated. Unlike drugs approved by the FDA, supplements can be sold without manufacturers or regulators demonstrating the clinical benefits of these items. Although marketers cannot make explicit health claims for a supplement (like "cures cancer"), they can promote its known effect on what the 1994 act calls the "structure and function" of the body (claims such as "protects against cell damage"), and they can give the product any name they like ("Liver Master," "Liver Health," "LiverWell," "LiverCleanse," "LiverDetox," "Anti-Alcohol Complex," and so on).

The use of herbal medicines can be traced as far back as 2100 BC in ancient China (the Xia dynasty) and India (the Vedic period). The utilization of herbal plants and alternative techniques (such as acupuncture) was originally confined to Asia and Africa but now has become universal. The current increase in the use of alternative medicine by people who have liver disease could be attributed partly to the failure of conventional treatments to cure some of the more common forms of liver disease, such as hepatitis B and non-alcoholic fatty liver disease. Another reason for the popularity of herbal preparations is the perception that they are "natural" and therefore are a safer form of therapy. The holistic and spiritual appeal of these substances also attracts people with chronic liver diseases to these forms of treatment.

Many herbal preparations for liver disease fall within "mainstream" homeopathic, traditional Chinese, and Ayurvedic medicine. A discussion of all such preparations is beyond the scope of this book, but this chapter focuses on some commonly used herbal medicines and supplements available in the United States. The loose classification of CAM supplements and techniques used in treating liver disease listed in table 12.1 is not complete by any standards, and it is increasing.

TABLE 12.1. Complementary and alternative medicines used in the treatment of liver disease

Supplements or medications		
Defined formulations	**Poorly defined formulations**	**Techniques**
silymarin	TJ-9	acupuncture
Phyllanthus amarus	compound 861	prayer
St. John's wort	Liv 52	spirituality
glycyrrhizin	CH-100	massage therapy
	homeopathy	hypnotherapy
	Ayurvedic medicine	energy therapy
	traditional Chinese medicine	

Herbal Products

In US surveys, more than one in three people (30 to 60 percent) who had liver disease said they were using naturopathic remedies. The most common item is milk thistle, followed by green tea, St. John's wort, and dandelion root. Many individuals ingest multiple preparations, and most people do not tell their physician they are taking herbal products. The use of herbal preparations and supplements is increasing in the United States and rest of the world.

A scientific review of herbal preparations is challenging, because many of them are not standardized and often contain concoctions of various extracts. These products are unregulated, so preparations marketed under the same or similar names might have completely different compositions.

Most of the herbal products available on the market have not been tested in clinical trials. Even when they are tested, the measures that are used (the end points) are often subjective ("feeling good," "having more energy," and so on) rather than reproducible data (such as clearance of a virus, improvement in liver biopsy findings, a decrease in the size of a tumor). In addition, the toxicity of herbal remedies—their harmful effects—is poorly reported or documented. Some herbal preparations may also contain subtherapeutic doses of conventional (*allopathic*) medications, which are deliberately mixed in, making matters worse as far as clinical tests are concerned. Some commonly used preparations are discussed in the following sections.

Milk Thistle (Silymarin)

Milk thistle is an extract from *Silybum marianum*, a plant grown commercially throughout the United States. The active component in milk thistle extract is silymarin, a mixture of plant compounds called flavonolignans (silydianin, silychristin, and silybin). Silybin (also known as silibinin) makes up 60 to 70 percent of silymarin and is its most biologically active ingredient, with the remaining 30 to 40 percent being chemically undefined.

Silybin is the major active ingredient of silymarin, and its pharmacological properties are well understood. In laboratory experiments, silybin shows antioxidant properties (that is, it prevents the formation of chemicals called free radicals, which damage cells) and appears to protect liver cells and reduce inflammation and scarring, with little or no toxicity. Nonetheless, the clinical trials of silybin were done with only small numbers of people, were poorly designed, and used variable and subjective measures of its effects.

Many clinical trials have been conducted to assess the efficacy of silymarin for treating acute viral hepatitis. These trials were not conducted according to the usual scientific standards. Moreover, in many of the trials, the cause of the person's acute hepatitis was poorly defined and the follow-up period was short. The results showed inconsistent benefits, with some demonstrating favorable effects in the treatment

groups and others not indicating any difference between the treated and untreated (*control*) groups. On the basis of current evidence, the use of silymarin for the treatment of acute viral hepatitis (A or B) cannot be justified. No good trials have been conducted on the use of silymarin for people who have a chronic hepatitis B infection. Silymarin has no role in treating hepatitis C.

Silymarin has also been tested in people with alcohol-related liver disease, primary biliary cholangitis and non-alcoholic fatty liver disease. Some of these studies showed an improvement in liver enzymes in the treatment group compared with the control group, but the results are inconsistent. No side effects related to silymarin were observed in clinical trials, suggesting that silymarin is safe even at higher than customary doses. Milk thistle does not cause any drug-drug interactions. There is no firm evidence, however, to suggest that it has any long-term benefits for people who have acute or chronic liver disease.

St. John's Wort

St. John's wort is a widely used herbal preparation with potentially serious herb-drug interactions with many medicines, including medications used for the treatment of hepatitis C and as *immunosuppressants* (drugs used to suppress the immune system) after an organ transplant. St. John's wort, an extract of the herb *Hypericum perforatum*, contains many pharmacologically active ingredients. The main ingredient is hyperforin, a substance that may have some beneficial properties for people who experience moderate or severe depression. There is no evidence, however, that St. John's wort is comparable or superior to commonly used antidepressants. Many people take this preparation, perhaps for its mood-elevating effect. Nonetheless, St. John's wort has many possible adverse effects because of the potential herb-drug interaction with commonly used medications.

St. John's wort induces the production of enzymes that clear some commonly used medications from the body. This results in reduced blood levels of these medications and makes them ineffective or less effective. If you are taking St. John's wort, please ask your physician whether it is safe to do so.

Glycyrrhizin

Glycyrrhizin, containing chemicals called sulfated saponins and lectins, is derived from licorice root. It has been used for more than 20 years in Japan to treat chronic hepatitis. The standardized glycyrrhizin-containing *aqueous* (liquid) extract, called Stronger Neo-Minophagen C (SNMC), has been tested in many people who have liver disease. Clinical trials have shown improvement in liver enzyme levels in people with chronic hepatitis who took SNMC. In a long-term study, SNMC reduced the development of liver cancer in people who had a hepatitis C infection, but low potassium levels and hypertension were observed in 10 and 3 percent, respectively, of those treated with SNMC. These effects are thought to be related to its hormonal properties (resembling the effect of hormones called mineralocorticoids), and caution needs to be exercised when using this compound for people who have preexisting portal hypertension, as it may worsen peripheral edema (swelling in the legs) and cause electrolyte abnormalities. It is safer to avoid this herbal product for those reasons.

Phyllanthus amarus

The herb *Phyllanthus amarus*, known as "bahupatra" in India, contains compounds called hypophyllanthins and polyphenols and is said to have antiviral properties. Despite claims in some clinical studies of the clearance of hepatitis B surface antigens, there is no firm evidence that this substance is beneficial.

TJ-9 ("Xiao Chai Hu Tang" or "Sho-saiko-to")

The Chinese herbal medicine known as TJ-9 is widely used in Japan for the treatment of liver disorders. It is a dried mixture of seven herbs (from the roots of *Scutellaria*, *Glycyrrhiza*, *Bupleurum*, and ginseng (*Panax*); *Pinella* tubers; jujube fruit;

and ginger root). The major alkaloids from *Scutellaria*, called baicalin and baicalein, are strong antioxidants and are known to inhibit cell multiplication and induce the death of liver cancer cells. Despite its wide use, there are few clinical trials with TJ-9. The potential benefit of this compound in preventing liver cancer was also tested in a five-year study of 260 people who had cirrhosis. The rates of liver cancer development were similar in the treatment and control groups, but there was a trend favoring the treatment group for people who did not have hepatitis B. There was no difference in survival rates between the treatment and control groups, suggesting that the benefits of this compound, if any, are marginal.

Compound 861

Compound 861, which comes from China, is an aqueous extract of many herbs. In laboratory experiments, it has been shown to reduce scarring of the liver. There are no well-conducted studies, however, to confirm that this is an effective compound.

Liv 52

The Ayurvedic drug known as Liv 52, widely used in India, is an extract of several plants. As with many other herbs, there are animal experiments showing potential benefits from its use. Some studies on people who had acute hepatitis reported an improvement in their liver enzymes, but these studies had no control group. Thus it is difficult to draw any conclusions, especially since spontaneous improvement in liver enzyme levels is common in acute hepatitis. A two-year clinical trial, consisting of 188 people who had alcohol-related liver disease, failed to show any survival benefit for people with cirrhosis, and the death rate was higher in the treatment group for people who had more-advanced liver disease (81 percent versus 40 percent in the control group). Because of its potential toxicity, people with liver disease should not use this drug.

Other Drugs and Herbal Products

CH-100 is a Chinese herb that has been used for the treatment

of hepatitis C, but no consistent beneficial effects have been identified so far. Many other compounds are used by people who have liver disease, including picroliv, thymosin, bing gan ling, kurorinone, Iscador Qu, and *Acanthopanax senticosus*. The active ingredients in these substances are mostly unknown, and there are no good clinical trials showing any benefits from using these products. In general, these compounds should be avoided.

OTHER TREATMENT OPTIONS

Homeopathy

Homeopathy is based on the belief that very tiny quantities of natural ingredients—such as sulfur, snake venom, duck liver, squid ink, mercury, arsenic, and a host of other naturally occurring compounds—may cure illnesses. Modern homeopathic mixtures are sometimes diluted a million times or more, often so many times that no active ingredients may be left in them. Homeopathy was first introduced in the United States in 1825, and its use has recently increased, with homeopathic medicine sales rising substantially in this country. Many people use homeopathic medications, but no good clinical trials of these medications have been conducted.

Acupuncture

A survey conducted among people who had hepatitis C indicated that 1 in 10 had received acupuncture as an alternative attempt at therapy. Acupuncture has been studied in people who have hepatitis B and as an adjunctive (secondary) treatment for pain following liver cancer surgery. There is no evidence of a liver disease–related benefit from acupuncture, and there is a potential risk of contracting blood-borne infections if sterile techniques are not employed.

Coffee, Green Tea, Iron Supplements, and Vitamins

Coffee

There is some evidence to suggest that drinking two or more cups of coffee a day may prevent the development and

progression of liver cancer. There may be other beneficial effects (improvement in liver enzymes, slower progression of fibrosis) for other liver diseases, including fatty liver disease.

Caffeine (in coffee and tea) is a naturally occurring methylxanthine, and in laboratory experiments it has been shown to prevent the multiplication of cancer cells. Several studies have confirmed the benefit of coffee in cancer reduction. This benefit was seen in both men and women, regardless of the cause of liver disease—even in those who drank alcohol regularly. A low consumption of coffee was associated with a 30 percent reduction in liver cancer risk, and high consumption was associated with a 60 percent reduction. Based on these studies, it is reasonable to conclude that coffee drinking is beneficial for people with liver disease.

> There is evidence to suggest that coffee consumption is beneficial for people with liver disease, and the regular consumption of two or more cups of coffee may reduce the risk of liver cancer.

Green Tea

Although green tea consumption is common, liver injury due to green tea or its extracts is uncommon. One problem with green tea, however, is that there are hundreds of different types of green tea available around the world. It is therefore not known whether any specific type of green tea (or its impurities) is the culprit in rare cases where it causes liver damage. Green tea consumption is increasing in western countries for its medicinal properties, including its alleged weight-loss characteristics. Clinical trials have not shown any liver benefits from drinking green tea for weight-loss purposes, but these studies also have not indicated any adverse effects, suggesting that liver injury is very uncommon. Green tea extracts, widely available in the United States, are derived from the leaves of *Camellia sinesis* plants.

There are multiple types of green tea, and many of them may vary from batch to batch, with some impurities. The exact cause of liver damage from green tea is unclear, for the same reasons. Many green tea products have been shown to contain

a number of unknown herbs or other commonly used medicines, such as anti-inflammatory agents, steroids, sildenafil (Viagra), and so on. These ingredients are never documented on the package.

Iron Supplements or an Iron-Rich Diet

Adequate iron intake is important to maintain normal levels of hemoglobin (the chemical that carries oxygen in red blood cells), and iron deficiency will lead to anemia. Iron absorption is controlled in the small intestine, but the long-term ingestion of excess iron (in food or as supplements) may lead to "iron overload," which may then cause damage to liver cells.

People who have liver disease should avoid iron supplements if they do not have an iron deficiency. Please ask your doctor about the safety of using iron supplements if you have been told you need to take them.

Vitamins

Higher doses (above clinically recommended doses) of vitamin A, niacin (vitamin B3), vitamin C, and vitamin D can result in liver damage. Niacin and vitamin A can cause serious liver damage and should not be taken without consulting a doctor. Abnormalities from a vitamin C overdose are usually transient.

It is safe to take vitamin D if blood tests show low levels of it, as vitamin D has many beneficial effects, including maintaining bone density. Low bone density (osteopenia and osteoporosis) is common in people who have cirrhosis. Low vitamin D levels are also common in the general population, as well as in individuals with liver disease. Excess vitamin D levels may be harmful, however, and people should avoid an excess intake of vitamin D.

Potential Liver Toxicity from Herbal and Dietary Supplements

In the United States, findings suggest that 20 percent of drug-induced liver injury is due to dietary supplements. In literature from elsewhere in the world, this ranges from 2 to 70 percent,

with the wide variation mostly due to reporting bias. The list of liver-damaging supplements in table 12.2 is not complete, but it can be used as a guide.

The major causes of liver injury in the United States are anabolic steroids (used as body-building supplements), green tea extracts, and nutritional supplements that contain multiple ingredients.

In addition to being damaging to the liver, many herbal preparations may interfere with the elimination of other commonly used medications (table 12.3). This interference can cause either low or high blood levels of other medications.

Please let your doctor know that you are using any of these preparations if you are also taking other medications. Avoid them during hepatitis C treatment.

TABLE 12.2. Supplements with a potential for causing liver damage

Indication for use	Supplements
Joint problems	flavocoxid (Limbrel), Schiff Move Free products, glucosamine (only weak evidence)
Pain control	black cohosh, comfrey
Weight loss	conjugated linoleic acid, ephedra (ma huang), germander, green tea, Herbalife products, Hydroxycut products, usnic acid
Gastrointestinal problems	OxyElitePro® (for weight loss), aloe vera, chaparral, greater celandine
Psychological problems	kava-kava, skullcap, valerian
Other indications	noni, pennyroyal, Liv 52

TABLE 12.3. Herbal preparations and other substances that may increase or decrease other medication levels

danshen	germander	papaya
devil's claw	gingko biloba	pyrrolizidines
dong quai	ginseng	Sho-saiko-to
echinacea	glycyrrhizin	St. John's wort
feverfew	grapefruit juice	tamarind
garlic	kava-kava	

Summary on Supplements

Herbal preparations are widely used by people who have liver diseases, despite the absence of scientific evidence regarding their benefits. Some herbal preparations have been shown to improve liver enzyme levels but not have any positive impact on viral counts, liver biopsy results, or the incidence of liver cancer. In addition, some herbal preparations are associated with toxic effects or with herb-drug interactions (such as St. John's wort), while others, like milk thistle (silymarin) and TJ-9, are relatively safe.

There is increasing evidence that two or more cups of coffee a day may be beneficial for people who have chronic liver disease. Iron supplements should be used only if an individual has an iron deficiency. Similarly, vitamin A or niacin supplementation (outside a multivitamin pill) should be under the supervision of a doctor. People should consult with their physician before they decide to use any herbal preparations.

Anyone who is planning to use an herbal preparation may also benefit from visiting the LiverTox website (see "Further Reading"), developed by a division of the National Institutes of Health, that examines the short-term and long-term safety of herbal preparations and dietary supplements.

SAFETY OF ACETAMINOPHEN (TYLENOL)

Therapeutic doses of acetaminophen (less than 2,000 mg per day) are safe for the general population, as well as for those who have chronic liver diseases, including cirrhosis. The only exception is for individuals who drink excessive amounts of alcohol. There is a general belief that people who have liver disease should completely avoid acetaminophen. The body eliminates therapeutic doses of acetaminophen, however, without any toxicity, even in the presence of advanced cirrhosis. Other pain medications, such as nonsteroidal anti-inflammatory drugs (ibuprofen, naproxen, indomethacin, etc.) may cause gastrointestinal bleeding and kidney toxicity. Thus

people who have esophageal or gastric varices and those with kidney dysfunction should avoid such drugs.

For individuals with cirrhosis, it is preferable to use acetaminophen carefully (never to exceed 2,000 mg per day) for pain management and avoid nonsteroidal anti-inflammatory drugs. Although narcotics could be used, they are likely to create addiction and may cause hepatic encephalopathy (confusion) in people who have cirrhosis.

MAINTAINING LIVER HEALTH

In pursuit of liver health, often people do more harm than good by taking supplements. Liver health can be maintained by avoiding harmful activities, minimizing alcohol intake, not using unproven herbal remedies, not over-supplementing with vitamins and minerals, and maintaining an ideal body weight through exercise and diet. Vaccination for hepatitis A and B and controlling diabetes or high cholesterol and triglyceride levels are also important. If liver disease is suspected, you should seek expert care to avoid progressive liver damage. Those with chronic liver diseases should follow up with a liver doctor.

TABLE 12.4. Maintaining liver health

Things to do	Things to watch out for
• vaccinate for hepatitis A and B • check for hepatitis B and C and treat if present • maintain ideal body weight with diet and exercise • control diabetes well (if present) • control cholesterol and triglycerides (if high) • seek expert help if a liver disease or fatty liver is suspected • learn about your liver disease, if it is diagnosed	• limit your alcohol intake (maximum of 2 drinks for men and 1 for women per day if there is no liver disease) • avoid high-risk behaviors • avoid herbal supplements • do not over-supplement with minerals and vitamins • do not ignore liver enzyme abnormalities • discuss any problems with your doctor before taking over-the-counter medications

MALNUTRITION IN LIVER DISEASE

Although the role of overnutrition in the context of fatty liver was discussed in detail in chapter 7, malnutrition is equally common in people with advanced liver disease. Many factors contribute to malnutrition, including malabsorption; increased or altered metabolism; loss of taste; inadequate intake of sodium due to salt restriction; hormonal changes; changes in the intestinal bacterial flora; or an ongoing inflammation. In addition, reduced physical activities or a lack of exercise may lead to further deterioration in muscle mass and strength. Malnutrition may make a person susceptible to infections and hepatic encephalopathy. Among transplant recipients, malnutrition may increase their recovery time and decrease their quality of life.

It may be useful to seek the help of a dietician with an interest in liver disease if you are suffering from cirrhosis. A detailed dietary recommendation is beyond the scope of this book, but general guidelines, based on published recommendations, are summarized in table 12.5.

Nutritional supplementation alone may not reduce a wasting away of muscles. For people with liver disease, a tolerable amount of exercise should be continued, after discussing an appropriate level of activity with their physician. There are websites that provide useful information with regard to graded exercise regimens, such as Wellness Toolbox (see "Further Reading"). Exercise should be started slowly (three to four days per week) and increased to daily exercise (walking up to 40 minutes daily). Those who are very debilitated may have to start with one to two minutes of walking, followed by resting for one to two minutes, and gradually build up the duration of their exercise. Walking could be indoors or outdoors.

TABLE 12.5. General dietary guidance for people with cirrhosis

Condition	Calories (kcal/kg body weight)	Protein (g/kg body weight)	Salt	Supplements	Special diet
Cirrhosis without complications	> 35	1.2–1.5	no added salt	one MVT	none

Advanced cirrhosis	> 35	1.2–1.5 (at least 1.5 if malnourished)	2 g (2000 mg)	one MVT and replace deficient minerals and vitamins*	late evening snack frequent small meals in those with HE BCAA in special circumstances

Note: MVT = over-the-counter multivitamin tablets; HE = hepatic encephalopathy; BCAA = branched chain amino acids.

*Vitamin D, iron, vitamin E, vitamin K, vitamin A, or zinc if deficient.

FURTHER READING

Taking care of your liver. American Liver Foundation. https://liverfoundation.org/for-patients/about-the-liver/health-wellness/#1507301343822-50491142-06d3/.

Diet and liver disease. British Liver Trust. https://britishlivertrust.org.uk/information-and-support/living-with-a-liver-condition/diet-and-liver-disease/.

Buchard B et al. Assessment of malnutrition, sarcopenia, and frailty in patients with cirrhosis: Which tools should we use in clinical practice? Nutrients 2020 Jan 9;12(1):186. https://doi.org/10.3390/nu12010186/.

Bunchorntavakul C, Reddy, KR. Review article: Malnutrition/sarcopenia and frailty in patients with cirrhosis. Aliment Pharmacol Ther. 2020 Jan;51(1):64–77. https://doi.org/10.1111/apt.15571/. Epub 2019 Nov 8.

Cirrhosis—Overview. Wellness Toolbox. https://wellnesstoolbox.ca/cirrhosis/.

European Association for the Study of the Liver. EASL clinical practice guidelines on nutrition in chronic liver disease. J. Hepatol. 2019 Jan;70: 172–193. https://doi.org/10.1016/j.jhep.2018.06.024/. Epub 2018 Aug 23.

LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. National Institute of Diabetes and Digestive and Kidney Diseases. www.ncbi.nlm.nih.gov/books/NBK547852/.

Tandon P et al. Exercise in cirrhosis: Translating evidence and experience to practice. J Hepatol. 2018 Nov;69:1164–1177. https://doi.org/10.1016/j.jhep.2018.06.017/. Epub 2018 Jun 30.

Traub J et al. Malnutrition in patients with liver cirrhosis. Nutrients 2021; 13:540. https://doi.org/10.3390/nu13020540/.

Patient Resources

ORGANIZATIONS

- American Association for the Study of Liver Diseases

  1001 North Fairfax Street, Suite 400

  Alexandria, VA 22314

  Tel: 703-299-9766

  Fax: 703-299-9622

  Email: aasld@aasld.org

  www.aasld.org

- American Liver Foundation

  39 Broadway, Suite 2700

  New York, NY 10006

  Tel: 212-668-1000

  Fax: 212-483-8179

  Hepatitis C helpline: 1-800-465-4837

  https://liverfoundation.org

- Centers for Disease Control and Prevention

  Division of Viral Hepatitis

  National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

  1600 Clifton Road, Mailstop G-37

  Atlanta, GA 30333

  Tel: 1-800-CDC-INFO (1-800-232-4636)

  TTY: 1-888-232-6348

www.cdc.gov/hepatitis/hcv/index.htm

- National Institute of Diabetes and Digestive and Kidney Diseases website

  LiverTox: Clinical and Research Information on Drug-Induced Liver Injury, www.ncbi.nlm.nih.gov/books/NBK547852/

Other Useful Organizations

- Hepatitis C Advocacy, https://hepcadvocacy.org
- Hepatitis B Foundation, www.hepb.org
- Hepatitis C Association, www.hepcassoc.org
- Hepatitis Foundation International, https://hepatitisfoundation.org

CLINICAL TRIALS

- ClinicalTrials.gov (a service of the National Institutes of Health), https://clinicaltrials.gov

MEDICATION ASSISTANCE PROGRAMS

- AbbVie, www.rxabbvie.com
- Genentech Patient Assistance for Pegasys and Copegus, 1-888-941-3331
- Gilead Patient Assistance for Sovaldi, 1-855-769-7284, www.mysupportpath.com
- Johnson & Johnson Patient Assistance Foundation, 1-800-652-6227, www.jjpaf.org
- Medicare, www.medicare.gov
- Patient Access Network (PAN) Foundation (for underinsured patients), 1-866-316-PANF (1-866-316-7263), www.panfoundation.org
- RxAssist, Patient Assistance Program Center, www.rxassist.org

FINDING A SPECIALIST

- American Association for Study of Liver Diseases, www.aasld.org

- American Gastroenterological Association, www.gastro.org
- American Liver Foundation, www.liverfoundation.org
- Infectious Disease Society of America, www.idsociety.org

LIVER TRANSPLANTATION

- United Network for Organ Sharing (UNOS)

  1100 Boulders Parkway, Suite 500

  P.O. Box 13770

  Richmond, VA 23225-8770

  Tel: 804-330-8602

  www.unos.org

MELD AND PELD CALCULATIONS

- Organ Procurement and Transplantation Network, Allocation Calculators, https://optn.transplant.hrsa.gov/resources/about-meld-and-peld/

DRUG INTERACTIONS

- University of Liverpool Interaction Checker, www.hep-druginteractions.org

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