



# You, Your Liver and Alpha-1

Skinny Little Reference Guide



### THE LIVER IN ALPHA-1 ANTITRYPSIN DEFICIENCY

Alpha-1 Antitrypsin Deficiency, or Alpha-1, is a genetic condition that can cause disease of the lungs, liver, skin, and blood vessels. Although the first descriptions of Alpha-1 pointed to its role in the promotion of lung disease in adults, in fact, Alpha-1 is primarily a condition caused by problems in the liver. Liver disease in Alpha-1 can occur in newborns, children, and adults. This guide is intended to be used by the parent of a child with Apha-1, or an individual who has Alpha-1, and by their healthcare providers.

It is always important to confirm the diagnosis of Alpha-1 if this has not been done. The diagnosis of Alpha-1 rests on identifying the presence of abnormal AAT protein (usually the Z protein) in a sample of the patient's blood (phenotype or "PI-type" testing). Diagnosis can also be made by looking for abnormalities in the AAT gene, again by testing a sample of blood. Usually these tests are accompanied by a measurement of AAT level in the blood.

### **INTRODUCTION TO ALPHA-1 LIVER DISEASE**

Normally, the alpha-1 antitrypsin protein or AAT is made in large quantities within the liver and then released into the blood. However, individuals who carry two abnormal genes for Alpha-1 (usually two "Z" genes, with the "M" gene considered normal) produce an abnormal AAT protein which is unable to be released from the liver cells. Therefore, the AAT accumulates within the liver, resulting in a deficiency, or low levels, of AAT in the blood. While the lung damage in Alpha 1 appears to be directly related to the low blood level of AAT, the liver is thought to be damaged by the unusual internal buildup of the abnormal Z protein.

Additional information about Alpha-1 is available in AlphaNet's Big Fat Reference Guide to Alpha-1 (the BFRG), which is available on the AlphaNet website (www.alphanet.org). Copyright© AlphaNet, Inc. 2009 Since most of the research into Alpha-1 liver disease has been performed on the Z protein, we will use Z as the basis for this guide. There are many other types of AAT gene variants that can cause Alpha-1 and some may have slightly different mechanisms.



**KEY LEARNING:** While the lung damage in Alpha 1 appears to be directly related to the low blood level of AAT, the liver is thought to be damaged by the unusual internal buildup of the abnormal AAT protein.

In order to begin to understand the liver disease associated with Alpha-1 it is useful to review the basic functions of the liver under normal conditions and to discuss the medical techniques used to assess liver health.

## FUNCTIONS OF THE NORMAL LIVER

The functions of the liver remain pretty much the same throughout someone's life, from birth through old age, although a newborn's liver may require time to fully mature.

**SYNTHETIC FUNCTION.** The liver manufactures a large number of proteins and other substances crucial to the normal function of many parts of the body. Many components of the liquid, non-cellular portion of the blood are made in the liver. Some of these substances are critical to normal blood clotting, important in allowing normal distribution of salts, fluid and nutrients to the body via the blood stream, and vital to supplying energy to the body during exercise and fasting.



**IT'S A FACT:** The liver is the body's filter and distribution center. Part of its function removes waste while it also generates life-sustaining proteins and substances to keep the body working smoothly.

**DIGESTIVE FUNCTION.** All of the blood leaving the intestines passes through the liver so that nutrients from food can be properly processed, stored, or distributed to other parts of the body. The liver also produces a substance called bile. As bile is produced by liver cells it is stored in the gallbladder until a meal is eaten. Then the bile drains into the intestine, via a tube called the bile

duct, to mix with food and to assist in fat digestion and removal of nutrients present within certain fats. The bile is then removed from the intestine, transferred to the blood stream for transport back to the liver, and then recycled by liver cells to be used again. A portion of bile remains within the intestinal contents and this is what gives stool its characteristic brown color.

The liver has its very own unique blood supply called the "portal circulation." The portal circulation carries blood from the intestines and stomach to the liver and spleen. The portal circulation becomes more important later, when we discuss liver diseases.

**EXCRETORY FUNCTION.** The liver participates in waste removal from the body in several ways. First, toxins ingested with food are cleared by the liver as the blood from the intestines passes through. Some of those wastes are then processed within liver cells into substances useful to the body and some wastes are inactivated within liver cells, transferred into the bile, drained into the intestine and then eliminated in the stool. Some wastes from other parts of the body are transferred to the liver by the blood stream for processing and/or removal via the bile and stool.

A similar mechanism is used by the body to clear certain drugs and medications from the circulation. These medications are broken down and inactivated in the liver, then sent out of the body in the bile or urine.

### **VISITS WITH YOUR HEALTHCARE PROVIDER**

You may seek medical attention because you're just not feeling well or because you've noticed a change in your usual health or are experiencing a particular problem or symptom and are especially concerned because you have Alpha-1. You may seek medical attention because you have Alpha-1 and are expecting a child. It is natural to wonder what the risks are of that child being born with Alpha-1 and whether liver disease might occur during their childhood.



**CROSS-REFERENCE:** Alpha-1 genetic considerations are discussed in the Big Fat Reference Guide to Alpha-1 available at www.AlphaNet.org.

Whatever the reason for seeking medical care, the initial visit with your healthcare provider will involve a thorough medical history and physical examination as well as a variety of medical assessments in order to determine if there is a problem and what to do about it.

#### **GENERAL LIVER HEALTH ASSESSMENT**

Physicians use many features of the patient's history and physical examination, combined with other tests to form an overall opinion about whether the liver is functioning properly.

**MEDICAL HISTORY.** First, the doctor may explore the patient's health history for any features that could point to previous, unrecognized liver problems. This might include reviewing any history of jaundice (yellow skin and eyes) either as an infant, child, or adult, as well as any history of previous surgery, gallstones, kidney stones, serious injuries, hospitalizations, blood transfusions, or other significant health events. The doctor will often review similar information about the patient's close family members. Doctors will also commonly review risk factors and known exposures to certain infections that can involve the liver. These may include hepatitis A, B, or C, tuberculosis, HIV, and/or sexually transmitted diseases. Other risk factors include cancer and immune diseases. A complete list of medications, herbs, and dietary supplements the patient has used as well as alcohol and drug use and toxic exposures at work is usually obtained. All of these can have a significant influence on liver health and should be thoroughly discussed with the doctor. The questions may be different for adults and children with Alpha-1.

Individuals may be asked about specific symptoms which, if present, might be suspicious for liver problems but might not by themselves be conclusive.

#### For example:

- Diarrhea can have many causes, but is often reported in both adults and children with abnormalities of bile flow and inadequate fat digestion.
- Itching is a common complaint of patients with significant liver disease. This itching is caused by buildup within the skin of waste products that are not being adequately removed from the blood by the liver.
- Symptoms of abdominal pain, indigestion, or vomiting are also rather non-specific, but are commonly seen in patients with liver disease.

Excessive scar tissue can build up within the liver, from Alpha-1 or from a variety of other liver problems. This liver scaring is called cirrhosis. **Cirrhosis** can disrupt blood flow from the intestine through the liver leading to excessively high pressure and abnormal blood flow in vessels in other parts of the body. The medical term for this problem is **portal hypertension** ("portal" meaning the blood vessel from the intestine to the liver and "hypertension" meaning unusually high pressure and abnormal flow within this vessel). Portal hypertension can cause the patient to vomit blood and/or pass blood in bowel movements, as well as suffer other problems such as abdominal swelling and bloating. Physicians will want to know about any occurrence of unusual bleeding. Bleeding problems may be related to poor vitamin K absorption or poor liver synthetic function. Similarly, the doctor will want to know about any unusual sleepiness or change in mental alertness because these can also be related to an otherwise silent deterioration of the liver.



#### IT'S A FACT: The liver and nutrition are intimately linked.

Analysis of a number of health factors may figure into a doctor's assessment of the contribution of the liver to a patient's nutritional status. Simple measures like height, weight, calculation of percent body fat, calculation of lean body mass (amount of non-fat body tissue) or a similar assessment called body mass index (BMI) are often very useful, especially in growing children.

Evaluation of the speed and quality of wound healing, the quality of a patient's skin and hair, and measurement of various blood protein levels also can be informative regarding a person's nutritional status and the possible contribution of liver disease.

Any history of potential liver problems will include questions about alcohol consumption. While excessive use of alcoholic beverages are the leading cause of liver problems in the world, sometimes even casual consumption of alcohol can increase the risk of liver injury in those with other risk factors, including Alpha-1.

**PHYSICAL EXAMINATION.** When a physician proceeds to the physical examination, he or she will pay special attention to body features that may relate to liver disease. First, a doctor is likely to look carefully at the patient's skin for various rashes that can be related to liver disease and for signs of scratching from liver-related itching. Itching is often related to jaundice. **Jaundice** is a yellow discoloration of the skin caused by accumulation of a waste product called bilirubin. Bilirubin is removed from the body by the liver but this removal may be hampered by liver disease. Yellow discoloration of the shine solution of the whites of the eyes can occur by the same process.



**DIG IN:** It's important to realize that newborns often have jaundice unrelated to Alpha-1 liver disease.

It's important to realize that newborns often have jaundice unrelated to Alpha-1 liver disease. This very common type of jaundice is related to the breakdown of red blood cells and the inability of the immature liver to handle the bilirubin created by this breakdown. There are blood tests that can be done to distinguish this common type of newborn jaundice from the jaundice caused by liver damage.

Sometimes, unusual clusters of veins are visible on the skin of patients with liver disease who otherwise have very few symptoms. Occasionally, around a patient's navel, very large veins will appear filled with blood that has accumulated because of portal hypertension.

Careful examination of the hands and feet may reveal swelling that could be a sign of abnormal fluid and salt retention, a condition that could be caused by liver problems. Physicians look for a mild change in shape of the fingers and toes called "clubbing" which can occur in patients with lung disease or liver disease of various causes. The doctor will examine the heart and lungs carefully as liver-related problems can cause significant alterations in heart and lung function.

Examination of the abdomen may reveal important information about liver health. The liver is located in the right upper portion of the abdomen. In an infant, the liver can take up a large portion of the entire abdomen. An enlarged liver may be felt. The liver may be painful to the touch or it may feel rough to the doctor through the skin. It may be harder in consistency than normal or be an unusual shape. Any of these findings raise suspicion for liver disease.

## **KEY LEARNING:** Ascites is a sign of relatively severe liver disease.

The spleen is a large organ on the left side of the abdomen. It can become swollen in the presence of liver disease, especially as a result of the abnormal blood flow of portal hypertension. Fluid can accumulate within the abdomen itself. This excess fluid is called ascites and can usually be detected during the physical examination. **Ascites** is a sign of relatively severe liver disease. Finally, examination of the anus and rectum may reveal hemorrhoids, unusually enlarged and painful blood vessels, which can also be a sign of the abnormal blood flow of portal hypertension.

**LABORATORY EVALUATIONS.** Laboratory testing is an important part of an overall general liver assessment. These tests will each look at specific functions of the liver.

**GENERAL LIVER TESTING.** Many diagnostic tests of liver health are available which can give either general information about the condition of the liver or can point specifically to certain diseases. Some of the most common blood tests are the **AST** and **ALT** (previously called SGOT and SGPT). These tests

are part of a panel of blood tests commonly called liver function tests or LFTs. The AST and ALT are chemicals or enzymes found normally within liver cells and which leak out into the blood at a very slow rate. However, if liver cells are irritated or damaged, then these chemicals leak out at a faster rate and the blood levels increase. In general, the higher the blood level the greater the injury to the liver cells.



#### **GOOD NEWS:** AST and ALT are commonly elevated in infants with Alpha-1; but in most of these infants, these elevations return to normal during the first two years of life.

Adults with Alpha-1 rarely have elevations of these liver tests unless there is significant liver injury. Unfortunately, these liver enzymes may not be elevated in people whose liver injury is occurring at a low level over many months or years, as is the case in many adults with chronic liver injury due to Alpha-1.

Alkaline phosphatase (alk phos) and gamma glutamyl transferase (GGT or yGT) are chemicals normally found within the cells of the bile ducts, the tubes that drain the bile from the liver to the intestine, and if elevated in the blood suggest injury to the bile cells. General tests of blood count, blood iron level, and blood salts (electrolytes such as sodium, potassium, chloride, and bicarbonate) are often abnormal in liver disease, although they can't point to one specific condition. However, for a person at risk of liver disease, low blood counts could be a sign of unrecognized bleeding.

Liver disease can affect many organs of the body so blood tests looking at other body systems may be done. **Serum creatinine** and **blood urea nitrogen (BUN)** may be measured to look at kidney function. Amylase and lipase levels look for damage to the pancreas. The pancreas is an abdominal organ important in digestion and, since the bile duct that drains bile from the liver to the intestine passes through the pancreas, liver and bile duct disease can sometimes cause damage to the pancreas. Blood levels of a chemical called **alpha fetoprotein** are often elevated in patients with various cancers, including liver cancer. Since Alpha-1 is a risk factor for the development of liver cancer, periodic measurements of alpha fetoprotein may be reassuring.

In addition to the above testing used to understand the general health of the liver, other laboratory tests can be used to examine some of the specific functions of the liver.

**SYNTHETIC FUNCTION TESTING.** Evaluation of the synthetic or manufacturing functions of the liver most often involves measurement of blood levels of substances produced within the liver. Albumin is a commonly measured protein whose function is to assist in the transport of salts and nutrients throughout the body. Often, tests of blood clotting are performed such as the **Prothrombin Time (PT)** and **Activated Partial Thromboplastin**  **Time (aPTT or PTT).** These tests can be abnormal if blood levels of proteins normally made in the liver and required for blood clotting are too low. However, other problems can also lead to abnormal PT/PTT test results including the action of certain drugs.

**DIGESTIVE FUNCTION TESTING.** One effective way to evaluate the digestive function of the liver involves measurement of fat soluble vitamin levels within the blood. Bile from the liver drained into the intestines is critical for the normal digestion and adsorption of fat soluble vitamins. Blood levels of the fat soluble vitamins A, D, and E can be used by doctors for this type of nutritional assessment, especially in children.



**IT'S A FACT:** Patients with significant liver disease will often be low in vitamin K.

Vitamin K is another fat soluble vitamin that plays a crucial role in blood clotting and on the results of the PT/PTT tests discussed above. While vitamin K deficiency can lead to serious bleeding, in milder vitamin K deficiency the only sign may be abnormal PT/PTT test results. Since doctors often cannot tell whether vitamin K is low because of poor absorption of this vitamin or poor manufacturing of clotting factors, it is usual to simply treat an abnormal PT/PTT with supplemental vitamin K.

**EXCRETORY/DETOXIFICATION FUNCTION TESTING.** The most commonly used method to asses this function of the liver is the measurement of blood **bilirubin levels**. Bilirubin is a waste product of the body eliminated by the liver through the bile. There are several types of bilirubin in blood and levels of certain types will be abnormally high if liver excretory function is abnormal. However, other types of blood bilirubin can be unrelated to liver function and so it is important that the physician distinguish between the types of bilirubin.

As liver function deteriorates, the liver becomes unable to handle the products of protein digestion. When proteins are digested, the chemical ammonia is released into the blood and the cells of a normal liver break this ammonia down into less toxic components. A failing liver will allow ammonia to escape from the portal circulation and move into the general circulation without being broken down. This leads to increased levels of ammonia throughout the body. When ammonia levels become significantly elevated, symptoms such as unusual sleepiness, changes in thinking and personality, and tremors can occur. Measurements of ammonia are generally collected by sampling the blood from an artery. Elevated ammonia levels can be a sign of severe liver disease. **OTHER DIAGNOSTIC TESTS.** CT scans ("CAT" scans) or ultrasound examinations make excellent pictures of the liver and can reveal birth defects, traumatic injuries, gallstones in the gallbladder, tumors in the liver, or changes in the fat, water, or scar tissue content of the liver. These changes can signal the presence of liver disease. Sometimes endoscopy is performed. Endoscopy is a technique where a flexible lighted tube with a miniature TV camera at its end is passed through the mouth or into the rectum to examine the stomach and/or intestines directly. These examinations can identify abnormal blood vessels associated with portal hypertension or look for other intestinal problems commonly associated with liver disease. A special endoscopic procedure, called ERCP, can be used to evaluate the bile ducts and even treat gallstones.

Your healthcare provider may recommend a liver biopsy. Liver biopsy is performed to obtain a sample of liver cells that can be examined directly under a microscope. Sedatives and pain medicines are usually given to relax the patient and, after washing the area with an antiseptic solution, local anaesthetic is injected under the skin in the right side of the upper abdomen where the lower ribs are. A needle is then inserted between the ribs directly into the liver to remove a sample about the size of a toothpick. While potentially very valuable in developing an understanding of a patient's liver problems, the procedure is invasive and carries a small but real risk of complications.



**KEY LEARNING:** Liver biopsies are not required for the diagnosis of Alpha-1 or Alpha-1 liver disease.

Liver biopsies are not required for the diagnosis of Alpha-1 or Alpha-1 liver disease, but may be useful in separating Alpha-1 liver disease from other causes of liver damage such as infections, toxic exposures, or injuries.

#### **INITIAL OUTPATIENT VISIT**

While a newborn with severe liver problems is often treated in the hospital setting, many children and adults with milder liver disease are followed as outpatients. The initial outpatient visit after the diagnosis of Alpha-1-related liver disease should focus on evaluating and treating existing problems and preventing new complications.

As described previously, a thorough history and physical examination focusing on general liver health will be completed. Findings such as low weight, poor childhood growth, or abnormalities found during the physical examination which may indicate portal hypertension or abnormalities of the liver itself are usually taken very seriously and may require further testing. In most situations, an initial basic laboratory evaluation of the liver would be sent off at the time of this first visit. Typically, these laboratory tests include:

- blood measurements of AST/ALT BUN
- bilirubinalbumin,

- creatinine
  - amylase lipase
- PT/PTT and the fat soluble vitamins (A, D, and/or E)
- electrolytes

• testing for Viral Hepatitis

These tests were described in detail on pages 6-9. Depending on the age and history of the patient, additional testing may be needed.

An ultrasound study or CT scan is often useful if more detailed information is required. These studies show the current state of the organs in the abdomen and can also help evaluate for liver cancer or portal hypertension. Liver biopsy may be recommended to evaluate for other causes of liver damage. Vaccination against hepatitis A and B viruses is commonly begun at this time in individuals who have not already been immunized. In cases of low weight, poor growth, or low blood vitamins levels, nutritional supplementation can be started with either specific vitamins or general strategies to increase caloric intake. If liver disease is very advanced, then various treatments of ascites, bleeding, portal hypertension, swelling, pain, and itching are available.



**BURNING ISSUE:** Because all adults with Alpha-1 are at risk for lung disease, your healthcare provider will monitor you for signs of lung disease.

#### FOLLOW-UP OUTPATIENT VISITS

Once an initial assessment of the degree of liver injury, if any, is complete then a plan for ongoing monitoring can be made. If there is no evidence of liver disease then children may continue routine health maintenance visits with their primary physician with yearly or even less frequent checkups with a pediatric gastrointestinal specialist. Adults with no evidence of liver disease are often followed by a primary physician comfortable with specifically monitoring the liver and a referral to a liver specialist is only made if problems are detected. Yearly monitoring of basic liver blood tests (AST/ALT, bilirubin, alk phos, GGT, LDH, PT/PTT, albumin) for both adults and children, and specialized testing every few years for the small possibility of liver cancer in adults may be all the health maintenance that is required. Many adults and children will have mildly elevated AST/ALT without any further development of liver disease and can also be followed by a primary physician knowledgeable in liver disease. If there are indications of more significant disease, then more intensive monitoring by a liver specialist knowledgeable in Alpha-1 is recommended. This monitoring usually includes regular growth and nutritional evaluation, routine liver and blood tests, repeated imaging studies such as CT scan or ultrasound, and careful supervision for the presence of complications of liver disease such as ascites, portal hypertension or bleeding, or significant decreases in liver function.

## CAUSE AND THERAPY OF AAT ASSOCIATED LIVER DISEASE

The mechanisms leading to the accumulation of abnormal AAT protein within liver cells have been uncovered over the past two decades. The abnormal AAT protein, especially the Z-type AAT, folds abnormally and allows other nearby abnormal AAT molecules to "stick to one another" and join into large collections of molecules. This process is called polymerization. These AAT aggregates can actually be seen under the microscope as "granules" within the cells of the liver.



The exact mechanisms by which this accumulation of the abnormal AAT protein within liver cells leads to liver injury and disease in Alpha-1 are still unknown. We do know that individuals with an unusual form of Alpha-1, those with the Null deficiency, don't get Alpha-1 liver disease. Since individuals with the Null deficiency make no AAT in the liver and therefore have no accumulation of abnormal AAT protein, it is reasonable to assume that the presence of this accumulated protein leads to liver disease in individuals with the other types of Alpha-1, such as the Z-type. People with the Null deficiency are at high risk of lung disease, just as other Alpha-1 patients are.

At present, there is no specific therapy for the liver disease associated with Alpha-1 other than general treatments used for many different liver problems. Since liver damage does not appear to be related to a lack of AAT in the blood, augmentation therapy (Prolastin<sup>®</sup>, Zemaira<sup>®</sup>, or Aralast<sup>™</sup> in the U.S.) is not used in the treatment of liver disease. Instead, management focuses on preventing the general complications of chronic liver disease and on the rapid and effective treatment of problems that cannot be avoided.



## **BURNING ISSUE:** Smoking cessation in adults with Alpha-1 and in parents of children with Alpha-1 is imperative.

All patients are urgently cautioned against cigarette smoking because of the greatly increased risk of life-threatening lung damage in Alpha-1, although there is no known link between smoking and AAT liver disease. Smoking prevention in children should be paramount. Second hand tobacco smoke is thought to pose as great a risk to persons with Alpha-1 as smoking itself and children should be guarded against exposure to second hand tobacco smoke.

Alcohol in excess can cause liver damage even in healthy people, and it is likely that people with pre-existing liver disease may be more susceptible to the liver-toxic effects of alcohol. There has been very little study of the effects of alcohol on the liver in Alpha-1.



**KEY LEARNING:** Most liver specialists would recommend no alcohol or at least very minimal intake for any individual with Alpha-1 whether or not there is any evidence of liver damage.

12

#### THERAPY FOR SPECIFIC LIVER PROBLEMS

**POOR DIGESTIVE FUNCTION.** In infants and children, maintenance of normal growth and nutritional status is one of the most important goals. Some infants and children are treated with supplemental feedings through feeding tubes if oral feedings and growth are inadequate. Poor growth and problems with oral feedings in infants with Alpha-1 have been noted for unknown reasons even in those infants without serious liver problems.

Jaundice, blood tests with poor bile flow (cholestasis), low blood levels of fat soluble vitamins, or chronic diarrhea without an infection may mean that fats are not being well digested. If poor fat digestion is present, monitoring and the addition of fat soluble vitamins can prevent serious complications. These complications might include life-threatening bleeding from vitamin K deficiency, rickets (bone damage in children) from vitamin D deficiency, neurological problems (blindness, confusion) from vitamin A deficiency, or peripheral neuropathy (nerve damage in the extremities) from vitamin E deficiency.

**POOR EXCRETORY/DETOXIFICATION FUNCTION.** Children or

adults with significant cholestasis (abnormally low bile flow) can develop severe itching from high blood levels of bile waste products. This can have a significant impact on sleep, school and work performance, and overall quality of life. Treatment with antihistamines to block itching, oral medicines that try to remove excess bile waste from the intestines (binding resins such as cholestyramine), treatment with special ultraviolet lights (phototherapy), and drugs that help increase bile flow (ursodeoxycholic acid) may provide some relief, although these may not cure the problem.

In cases of severe liver damage, the buildup of ammonia and other waste products that the liver is unable to remove from the body can cause excessive sleepiness and confusion. Since ammonia is made when the body breaks down proteins, adults with liver disease severe enough to cause elevations of blood ammonia levels are often placed on protein restricted diets. Sometimes oral medicines (such as lactulose) are used to help flush the intestines of waste products which then improves mental function.

**POOR SYNTHETIC FUNCTION.** Many problems in the body can develop if the liver is making inadequate quantities of proteins for the blood such as albumin and blood clotting factors. If blood albumin levels are low, the distribution of salt and water throughout the body can be disrupted, swelling can occur and fluid can accumulate within the abdomen (ascites). In adults, one of the first treatments for this problem is to limit dietary salt intake.



## **GOOD ADVICE:** Limiting salt intake can help control swelling in the body.

Limiting the salt in children's diets is sometimes done, however this is difficult to supervise and may have a negative impact on the child's quality of life. Next, a variety of diuretics (drugs that remove excess fluid from the body) can be used to get the kidneys to increase the elimination of urine and therefore decrease the amount of salt accumulated within the body. Finally, fluid can be drained from the abdomen with a needle in a simple and generally safe procedure called paracentesis, although repeated treatments are commonly needed. Sometimes intravenous treatments with albumin are given which will temporarily increase the albumin level of the blood.

If blood clotting tests in a person with liver disease are abnormal, often a dose of vitamin K is given as the cause may be poor vitamin K digestion. However, often the vitamin K level is normal but blood clotting is still abnormal due to the poor manufacture of Vitamin K within the liver. This situation is much more difficult to treat. If the person is actively bleeding, or if surgery or some other invasive procedure is planned then intravenous fresh frozen plasma (FFP, the liquid part of blood) can be given in an attempt to stop or prevent bleeding, However, the restoration of blood clotting from FFP treatments only lasts a few hours and generally does not prevent future bleeding. Therefore, FFP is generally not given in patients who are stable and doing well, even if blood clotting tests are abnormal.

**CIRRHOSIS AND PORTAL HYPERTENSION.** The development of cirrhosis and portal hypertension is common if Alpha-1 associated liver disease becomes severe. Cirrhosis and portal circulation are discussed on page 4. Some children and adults with these conditions have no symptoms and live normally for decades without other health problems. Therefore, invasive and risky treatments for these conditions are generally recommended only for persons who are having significant health problems such as poor growth in children, excessive swelling or pain, or serious bleeding.

Cirrhosis and portal hypertension can contribute to swelling and ascites. When this happens, the initial treatment plans typically will involve diet, diuretics, and paracentesis.

Most patients with portal hypertension are instructed to avoid aspirin, acetaminophen, ibuprofen, or other so called, non-steroidal anti-inflammatory drugs (NSAIDS), because they can make serious bleeding in liver disease patients more likely. However, most individuals with mild to moderate chronic liver disease can safely take occasional, normal-size doses of acetaminophen

14

as directed by their doctor. If excessive bleeding from the esophagus (the tube connecting the throat to the stomach), stomach, intestines, or rectum does occur as a result of portal hypertension then a variety of treatment options are available.



# **DIG IN:** Acetaminophen (such as Tylenol) overdose can cause liver damage.

Treatments with an endoscope, a flexible tube with a camera, inserted into the esophagus from the mouth, can often reduce or prevent esophageal bleeding, as can a variety of oral and intravenous medications. If the liver disease is advanced, then the bleeding can be serious enough to require blood transfusions. In some cases, surgery in the abdomen (shunt surgery) can be performed to re-route some of the blood flow away from the bleeding vessels. However, this type of surgery carries the risk of reducing the removal of wastes from the blood by the liver and can actually worsen symptoms of sleepiness and confusion.

In other cases, especially if the patient is waiting for a liver transplant, a less invasive shunt procedure can be performed called TIPS (trans-jugular intrahepatic porto-systemic shunt). A TIPS is performed with special instruments inserted into the patient's blood vessels, similar to a cardiac catheterization, and can reduce the risk of esophageal bleeding without as much risk of post-operative confusion. However, the altered blood flow from TIPS often only lasts a few weeks or months and therefore may need to be repeated if the person does not receive a liver transplant during that time.

**TREATMENT OF INFECTIONS.** Chronic liver disease can reduce the effectiveness of the immune system, and therefore patients and their doctors should be aware of signs of serious infection that would lead the patient to seek medical evaluation. First, any fever in a person with significant liver disease should lead to at least a telephone contact with a physician.

This is especially important if there is also abdominal pain, vomiting, diarrhea, bleeding, or jaundice, in combination or alone if they are a significant change or are long lasting. Typical, non-liver related infections, like the flu, can be more severe and require more aggressive treatments if a person has severe liver disease.



**GOOD ADVICE:** Any person with significant liver disease should call their physician if they have a fever.

In addition, liver disease patients can develop severe bacterial blood infections, infections of the bile ducts in the liver itself and bacterial infections of fluid within the abdomen. Sometimes blood tests, paracentesis or liver biopsies are needed as a part of the evaluation and sometimes treatments can be started without significant amounts of testing. Antibiotics, often administered intravenously, are the most common treatment but sometimes endoscopy and/or x-ray tests are used as part of the evaluation or treatment.

### LIVER TRANSPLANTATION

If liver disease becomes life-threatening, either because of portal hypertension with major bleeding or because of decreased ability of the liver to perform its synthetic and/or detoxifying function, the final treatment available at this time is liver transplantation. In liver transplantation, the diseased liver is surgically removed from the body of the patient and a new, normal liver is surgically inserted in its place by re-connecting all the blood vessels and bile ducts. In some liver conditions, a relative can offer to provide part of their liver for transplantation. This is called a 'living related donor' transplant. This has the advantage that the liver is available when needed and there is a better chance for a "good match" between the donor liver and the recipient's immune system. The only perfect match is one from an identical twin. In general, Alpha-1 patients in need of a liver transplant are not good candidates for a living related donor transplant because, since Alpha-1 is a genetic disease, the likelihood that any close relative will have at least one and perhaps two abnormal genes is fairly high (and is 100% for an identical twin). Most centers will not transplant a liver from an Alpha-1-related donor for fear that the new liver will be at increased risk of injury in the future.

Therefore, the source for livers for individuals with Alpha-1 (and many others with end-stage liver disease) is generally an unrelated donor who has been declared brain-dead and who has made it known that they would like their organs harvested for transplantation. Since the body's immune system will see this transplanted organ as a foreign "invader" and try to attack it, there are a number of things that must be done to allow the new liver to survive and thrive within the recipient's abdomen.

First, tests must be performed to assess the donor and recipients cells and blood type so that a "good match" can be found. Second, the recipient of a liver transplant is given powerful medications to suppress the immune system and prevent the body from rejecting the new organ.

This immunosuppression is a double-edged sword, however. While these medications can be very effective at reducing the rejection of the new liver,

they can also leave the body undefended should real "foreign invaders" such as viruses, bacteria, and funguses appear on the scene. Serious infections are common during the early days and months following a major organ transplant such as a liver.

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# **GOOD NEWS:** Liver transplantation has become a highly successful and long-term solution to life threatening end-stage liver disease.

Successful liver transplantation can provide decades of healthy life. For an individual with Alpha-1 who receives a liver transplant, there is the added benefit that the new, normal liver now manufactures normal quantities of normal AAT. Essentially, liver transplantation cures Alpha-1! It is important to realize that even though the transplanted liver has two normal human AAT genes and makes normal amounts of AAT protein; all the other cells of the body still have their abnormal AAT genes. Thus, a child who receives a liver transplant due to Alpha-1 liver disease and grows to be a healthy adult, still needs to realize that they can pass the abnormal AAT genes to any future offspring through their sperm or eggs which have the same bad genes that they always did.

So if liver transplantation is so good, why not transplant all individuals with Alpha-1? There are several reasons. First and foremost, there are not even enough donor livers available to treat individuals currently awaiting liver transplants to save their lives. Second, while liver transplantation has become quite successful, it is still a major surgical procedure with associated complications and even a significant mortality rate.

**WAITING FOR A LIVER TRANSPLANT.** As mentioned above, needing a liver transplant and getting one are two different things. If an individual with Alpha-1 has liver disease severe enough to require a liver transplant, then the first step is to be evaluated at a liver transplant center.



**KEY LEARNING:** Based on bilirubin, PT and creatinine tests, an adult will be assigned a number representing the severity of your liver disease. This score is called the MELD score for adults or the PELD score for children under 12 years of age. MELD = Model for End-Stage Liver Disease; PELD = Pediatric End-stage Liver Disease.

The tests that make up the MELD score are the bilirubin, the PT, and the creatinine (see details on page 7 & 8). Based on these tests, a potential transplant recipient will be assigned a score between 6 and 40, with 6 being less ill and 40 being gravely ill. The PELD calculation is a bit more complex but takes into account a number of issues related to childhood liver disease. When a donor liver becomes available to a given transplant center or area, the patient with the highest MELD or PELD score that has a good tissue match will receive the liver. There are priority exceptions called Status 1 that allow someone to move to the top of the list. Basically, Status 1 is given to a patient who has had the sudden and rapid onset of liver failure and is not expected to live more than a few hours.

Even if your score is high, there are several things that can prevent you from receiving a liver transplant, even if your liver disease is severe. You cannot have a transplant if you have:

- cancer in another part of your body
- serious heart, lung, or nerve disease
- active alcohol or illegal drug abuse
- an active, severe infection
- inability to follow your doctor's instructions

Since individuals with Alpha-1 liver disease may also have significant lung disease from their Alpha-1, this is sometimes a roadblock to getting a liver transplant.

#### LIVER CANCER

A brief word about liver cancer needs to be included. There is a definite increased risk of primary cancer of the liver (hepatocellular carcinoma). This is a rare form of liver cancer that is rare even in individuals with Alpha-1 – it's just not as rare in Alpha-1 as it is in the general population. The reason to test for this cancer with alpha fetoprotein and with abdominal ultrasound is that if caught in an early stage, the surgical treatment of this tumor (cutting out the part of the liver with the cancer in it) can be curative.

### UNANSWERED QUESTIONS AND THE FUTURE OF ALPHA-1 LIVER DISEASE

**UNANSWERED QUESTIONS.** While we know that the liver is the primary organ involved in the production of AAT protein and that it is problems with this production that lead to the AAT deficiency in the blood and liver disease in some individuals, we really have no answer to the questions regarding why some children and some adults get liver disease from Alpha-1 while others do not.

About 2% of children born with Z-type Alpha-1 develop liver failure requiring transplantation during the first two years of life. Most infants born with two Z genes have abnormal liver function tests during this same time period but for those who don't develop significant liver disease, these tests usually return to normal during childhood. Some investigators have suggested that there is a problem with the mechanism in the liver that handles accumulated proteins in the 2% who get severe liver injury and perhaps this work will lead to therapies to prevent this.

In adults, most individuals with Alpha-1 will not develop clinically significant liver disease. If liver disease does occur, it is often very mild and chronic, remaining stable for years. However, there are a number of adults who develop liver disease suddenly and have a rapid downhill course that results in liver transplantation. As far as we know at present, there is nothing that distinguishes those with mild, chronic liver injury from those with rapidly progressive, sudden onset disease.

Studies have shown that most older individuals with Alpha-1 (over 65 years old) have liver scaring that can be seen under the microscope, even though their liver function tests are entirely normal. This suggests that all or most individuals with Alpha-1 have ongoing, low levels of liver injury throughout their lives. Fortunately, the liver can tolerate this type of injury and still perform its normal functions as discussed at the start of this guide. Why the injury becomes too severe for the liver to tolerate in some individuals and not others is a major unanswered question at this time. It is believed that environmental factors and perhaps additional genetic factors may play roles in promoting such injury.

**THE FUTURE.** While it is clear that there is still a lot to learn, work is proceeding to use what we do know to develop new therapies for Alpha-1. Since we know that both the deficiency in the blood that leads to lung disease, and the liver problems themselves are caused by the accumulation of abnormal protein within liver cells, scientists are trying to develop drugs that will cause the trapped AAT protein in liver cells to move out of these cells and into the blood. This would have the dual advantages of relieving the injury to liver cells and pushing this protein into the blood where it can bathe the tissues of the body and especially the lungs. Such a drug could represent a potential cure for this genetic condition.

In addition to therapies to treat or prevent Alpha-1-related disease, work is moving forward on diagnostic tests that have the potential to detect mild or early liver injury more accurately than current methods.

**RESOURCES.** For additional information about Alpha-1 and Alpha-1-related liver and lung problems please visit the following resources:

Alpha-1 Foundation www.alphaone.org 877-228-7321

Alpha-1 Association www.alpha1.org 800-521-3025

AlphaNet www.alphanet.org 800-577-2638

#### American Liver Foundation

www.liverfoundation.org 866-455-4837

UNOS – United Network for Organ Sharing unos.org 800-292-9548

NIDDK – National Institute of Diabetes and Digestive and Kidney Diseases www2.niddk.nih.gov

301-496-3583 800-891-5389 (digestive)

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AlphaNet is a not-for-profit organization providing disease management services and support to individuals affected by Alpha-1 through a staff of medical professionals and specially trained AlphaNet Patient Services Coordinators, available 24 hours a day, 7 days a week. To learn more about ADMAP or to find the AlphaNet Coordinator nearest you, visit our website (www.alphanet.org).