

# Medical Information

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# Alagille Syndrome In Brief

**Alagille Syndrome** is a rare disorder characterized by a reduced number of small bile ducts (bile drainage tubules) within the liver (a condition known as bile duct paucity), combined with abnormalities in at least two other organs including the heart, eyes, spine, and kidneys. The syndrome is accompanied by distinctive facial appearance in many patients. Liver disease usually is the most severe part of Alagille Syndrome. The incidence of Alagille Syndrome is less than 1 in 100,000, but this number probably underestimates the frequency of the disorder, because many patients remain undiagnosed, including some with very mild disease who appear to be perfectly healthy. The diagnosis is difficult to make in some patients because the findings in other organs can be mild or variable, even in family members of a known patient. Family members may be affected very differently; one family member might have severe heart disease, another severe kidney disease, and a third severe liver disease.



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# Testing for Alagille Syndrome

Blood tests, called liver function tests, are used to assess the general state of the liver or biliary system. These tests indicate the presence of liver damage or inflammation by indirect measurement through the blood. Liver function tests alone cannot provide a diagnosis for Alagille Syndrome, but in combination with other tests and physical examination, they help in diagnosis and management.

**Please note:** The information on this page is compiled from several sources and is provided to help readers understand the type of tests that can be used to identify liver dysfunction. Liver function tests provide a useful tool for beginning the investigation of Alagille Syndrome and other liver and biliary system disorders. Interpretation of the tests is a sophisticated process that a physician places in the context of a patient's history, physical examination, and other tests that may be performed. Readers are advised to consult a physician for examination, diagnosis, and treatment.

- Alt and Ast
- Alkaline Phosphatase
- Bilirubin
- Albumin
- Prothrombin Time
- Beyond Liver Function



## Alt & Ast

Generally the most commonly used indicators of liver damage are the alanine aminotransferase (**ALT** or **SGPT**) and aspartate aminotransferase (**ALT** or **SGPT**). These enzymes normally are found in liver cells, but when liver cells are damaged, they leak out and make their way to the bloodstream. The **ALT** is considered a more specific indicator of liver inflammation than **AST**, because **AST** also is found in other organs such as the heart and skeletal muscle. In acute injury to the liver, the level of the **ALT** and **AST** may be used as a general measure of the degree of liver inflammation or damage. In chronic liver disease, however, this is not the case because these enzymes may be entirely within the normal range (usually less than 50 IU/l), even in the presence of cirrhosis (liver scarring).

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## Alkaline Phosphatase

This is the most frequently used test to detect obstruction in the biliary system. Elevation of alkaline phosphatase (an enzyme) may be found in a large number of common disorders, such as gallstone disease and alcohol abuse, as well as in rarer disorders, such as primary biliary cirrhosis or biliary tumors. This enzyme is found both in the liver and bile and leaks into the bloodstream in a similar manner as **ALT** and **AST**. It also is found in other organs, however, such as bone, placenta, and intestine. For this reason, it often is useful to measure another enzyme not found in these organs (either 5'-nucleotidase [5'-NT]) or gamma-glutamyl transpeptidase [**GGTP**] along with the alkaline phosphatase when the origin of the elevated enzyme (normal less than 115 IU/l) is not clear. Abnormalities of the 5'-NT or GGTP would then suggest liver or biliary tract disease.

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## Bilirubin

This is the main bile pigment in humans. When **bilirubin** is elevated, it causes yellow discoloration of the skin called **jaundice**. Bilirubin is formed primarily from the breakdown of a substance called **heme** (found in red blood cells). It is taken up from the blood, processed, and then secreted into the bile by the liver. There normally is a small amount of bilirubin in the blood in healthy individuals (less than 1.2 mg/dl). Conditions that cause increased formation of bilirubin (such as destruction of red blood cells), or decrease its removal from the bloodstream (as in liver dysfunction) may result in an increase in the level of bilirubin in the blood. Levels greater than 3 mg/dl usually are noticeable as jaundice. Because bilirubin may be elevated in many forms of liver or biliary disease, it is relatively non-specific. It is useful as a true liver function test, however, because it reflects the liver's ability to take up, process, and secrete bilirubin into the bile.

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## Albumin

**Albumin** is a major protein formed by the liver. Although there are many factors that can affect the level of albumin circulating in the bloodstream, chronic liver disease causes a decrease in the amount of albumin (normal greater than 3.5 mg/dl) produced, thus reducing the level of albumin in the blood.

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## Prothrombin

The **prothrombin time** (also called the "protime" or **PT**) is used to assess blood clotting. Blood clotting factors are proteins made by the liver. When the liver is significantly injured, these proteins are not produced normally. The **PT** also is a useful liver function test because there is a good correlation between abnormalities in coagulation measured by the **PT** and the degree of liver dysfunction. The values of the **PT** are usually expressed in seconds and compared to a control patient's blood (normal +/- 2 seconds of control).

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## Beyond Liver Function

Other highly specialized tests, such as a bile salt screen, may be used to indicate more specifically the presence of Alagille Syndrome. In addition, tests related to the heart (such as ultrasound [echo], electrocardiogram [**EKG**], and cardiac catheterization), vertebra (x-ray), eyes, and renal systems may be necessary. Liver functions tests and examination and test results related to other systems all will be used to determine if a patient has Alagille Syndrome or another liver or biliary system disorder.

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# Diagnosis of Alagille Syndrome

Diagnosing Alagille Syndrome can sometimes be very difficult. Here are is some information that should help.

- Genetic causes of Alagille Syndrome
- The Symptoms of Alagille Syndrome
- Other names for Alagille Syndrome

## Genetic Causes of Alagille Syndrome

Little is known about what actually causes Alagille Syndrome. It generally is inherited from one parent and there is a 50% chance that each child will develop the disorder. Each affected adult or child may have all or only a few of the features of the syndrome. Frequently a parent, brother, or sister of the affected child will share the facial appearance, heart murmur, or butterfly vertebrae, but have a completely normal liver and bile ducts.

A defect has been seen in chromosome #20 in a small number of patients with Alagille Syndrome. Only a small percentage of patients, however, have a visible defect in this area of chromosome #20, but it is expected that many or all patients will have a defect in the actual structural gene itself. Genetic research is targeted at identifying the actual gene, which will eventually enable doctors to provide prenatal testing for families, better therapy, and better understanding of the abnormalities in this syndrome.



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# Symptoms of Alagille Syndrome

Jaundice, pale, loose, stools, and poor growth within the first three months of life are early symptoms of Alagille Syndrome. Later there is persistent jaundice, itching, fatty deposits in the skin (xanthomas), and stunted growth and development early in childhood. Other features of Alagille Syndrome include abnormalities in the cardiovascular system (heart and lungs), spinal column, eye, and kidney. Each of these is discussed briefly below.

## Liver Disease

The liver disease in Alagille Syndrome can be highly variable. A typical infant with the syndrome might have jaundice in the first days or months of life. This commonly worsens throughout the first few years, and is accompanied by "cholestasis" (a significant reduction in bile flow and each of its components). Bile is secreted by the liver through many small bile ducts into one large bile duct (the common bile duct) and eventually into the intestines. Bile is composed of bilirubin, bile salts, cholesterol, and certain metals such as copper. When bile flow is decreased, each of its components builds up in the body.

In patients with severe Alagille Syndrome, this cholestasis can be more severe than in any other liver disorder. Bilirubin builds up in the body, causing jaundice, yellow eyes, and an abnormal skin color. The bile salt accumulation in the body leads to severe itching. Bile salts are important molecules necessary for fat absorption, and when they cannot be secreted into bile, the absorption of fat and certain vitamins is severely decreased. Cholesterol excretion also is decreased; toddlers may have cholesterol levels of over 1,000 where approximately 150 is normal. Cholesterol and fat deposits (xanthomas) occur in the skin, as hard, whitish nodules in areas of trauma or pressure.

A typical course of liver disease with Alagille Syndrome is worsening cholestasis for several years, with some improvement after that time. Research at the Children's Hospital of Philadelphia has recently shown that the liver may develop the ability to secrete bile through the larger bile ducts, which are close to the exit point of the liver. In addition to explaining the clinical improvement of cholestasis, this finding may give some clues for therapy.

### Heart Disease

The cardiovascular system is affected in many patients with Alagille Syndrome. Symptoms range from congenital heart disease, the most common of which is tetralogy of Fallot, to less dangerous, but much more common peripheral pulmonic stenosis. This is condition in which the pulmonary arteries (connecting the heart to the lungs) and their branches are diminished in size. This causes a heart murmur (extra heart sounds). Peripheral pulmonic stenosis can, on rare occasions, be quite severe, but in most patients all that is required is long-term follow-up.

### Kidney Disease

The kidneys may be affected either early in life or in adulthood. In infancy, there may be renal failure, which usually improves, or there may be problems with the kidney tubules. There are also other less common kidney problems. Some patients may have kidney failure at an older age. Infants with kidney disease need separate medications to support the kidneys.

### Abnormalities

There are several eye findings in patients with Alagille Syndrome. The most common is posterior embryotoxon, which is a thickened area of tissue in the front of the eye, which appears is about 90% of patients. It does not interfere with vision. Some patients also may have Axenfeld's anomaly, which is seen as strands in the front part (the iris) of the eye. Occasionally, patients will have a predisposition to glaucoma, or an abnormality in the shape of the cornea that can usually be corrected with contact lenses. If vitamin deficiencies persist, the retina can be damaged and there can be problems with night blindness, tunnel vision, or a syndrome similar to retinitis pigmentosa (a disease of the retina).

### Eye Abnormalities

#### Skeletal Abnormalities

Patients also may have bone abnormalities. "Butterfly vertebrae," in which the shape of the bones in the spinal column may look like the wings of a butterfly on x-ray, are seen in about 30% to 50% of patients. This is useful diagnostically to identify the syndrome, but does not usually cause any problem for the patient. There also can be significant bone thinning due to the malabsorption of fat soluble vitamins, especially vitamin D. This can result in fractures of the major bones in the leg (the femurs) from minimal injuries.

## Neurological Abnormalities

### Facial Features

Many physicians think there is a specific facial appearance shared by people with Alagille Syndrome that make them easily recognizable. The features include a prominent, broad forehead, deep-set eyes, a straight nose, and a small pointed chin.

### Complications



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## Other Names for Alagille Syndrome

Other names for Alagille Syndrome most frequently encountered in medical literature and in talking with health care professionals include:

- Arteriohepatic Dysplasia (AHD)
- Watson-Alagille Syndrome
- Syndromic Bile Duct Paucity (SBDP)
- Syndromic Hepatic Ductular Hypoplasia
- Syndromic Intrahepatic Biliary Hypoplasia
- Cholestasis with Peripheral Pulmonary Stenosis
- Intrahepatic Biliary Atresia or Dysgenesis



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# Genetic Causes of Alagille Syndrome

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Syndromic Intrahepatic Biliary Hypoplasia  
Cholestasis with Peripheral Pulmonary Stenosis  
Intrahepatic Biliary Atresia or Dysgenesis

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# Treatment

Trying to increase the flow of bile from the liver, maintaining normal growth and development, and preventing or correcting any specific nutritional deficiencies that often develop are key factors in treating Alagille Syndrome. This usually is accomplished by monitoring a patient's growth, development, and nutritional status, and by prescribing medications or vitamins when necessary. The liver functions most frequently watched by doctors and nutritionists are discussed briefly below.

It is important to note that the severity of the effects described in this section vary from patient to patient and the advice of a doctor or nutritionist should be sought to determine the treatment, if any, that is needed in each specific case.

- Absorption of fat soluble vitamins
- Bile Flow
- Blood Cholesterol
- Digestion

# Absorption

Feeding adequate numbers of calories to children with Alagille Syndrome is usually not difficult. Getting adequate numbers of calories absorbed, however, is sometimes a great challenge. Some patients may malabsorb 40% of the calories they eat. For these patients, it may not be possible to eat the extra needed calories, and the insertion of a feeding tube may help tremendously. This tube allows the delivery of large quantities of nutrients overnight, including formulas that may not seem very tasty to infants and young children. Nasogastric tubes are temporary and can be removed at any time. A direct gastric tube (G-tube) is placed for children with long-term needs. This type of tube can be placed without open surgery, by endoscopically guiding insertion of the tube ("PEG placement"--percutaneous endoscopic gastrostomy). Blood tests are used to diagnose vitamin deficiencies and large oral vitamin doses usually can correct any problems that arise.



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# Bile Flow

Because bile flow from the liver to the intestine is slow in Alagille Syndrome, medications designed to increase bile flow are prescribed. These medications also may relieve itching caused by buildup of bile in the blood and skin. Commonly prescribed medications include Cholestyramine (brand name Questran) to remove excess bile acids by binding with them to prevent their absorption, to reduce persistent itching caused by bile acids, and to lower cholesterol levels; and Ursodiol (brand name Actigall) to decrease secretion of cholesterol into bile by suppressing production and secretion of cholesterol by the liver. Other medications, such as antihistamines, also may be used to relieve itching.



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# Life Expectancy

The overall life expectancy for children with Alagille Syndrome is unknown, but depends on several factors: the severity of cholestasis and scarring in the liver, whether heart or lung problems develop because of narrowing in the pulmonary arteries, and the presence of infections or other problems related to poor nutrition. Patients with Alagille Syndrome generally have a much better outcome than children with some other liver disorders that may present at the same age. Many adults with Alagille Syndrome are leading normal lives.



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# The History of Alagille Syndrome

Daniel Alagille, M.D., at the Unite d'Hepatologie, Departement de Pediatrie, Hopital de Bicetre, Paris, France, first wrote about Alagille Syndrome in 1969. The article was co-authored with Dr. E.C. Habib and Dr. N. Thamassin, and focused on the features of Alagille Syndrome that distinguish it from other liver disorders. This first article was in French, of course, and it wasn't until 1975 that articles were printed in English.

More recent research on Alagille Syndrome has focused on identifying the location of the gene that causes this disorder, and studying the symptoms and treatment by following patients over several years. Research is occurring in both the United States and Europe, including in Dr. Alagille's laboratory in France under the guidance of Dr. Michele Hadchouel and Dr. Jean-Francois Deleuze. In the United States, clinical and genetic research supported by several grants is occurring most notably at the Children's Hospital of Philadelphia under the guidance of David A. Piccoli, M.D., Nancy Spinner, M.D., Elizabeth Rand, M.D., and Sidney Heyman, MD., among others; other institutions, such as The Children's Hospital, Denver CO, also are involved in important research. Thanks to Dr. Alagille and others dedicated to researching and understanding this rare condition, Alagille Syndrome is now becoming recognized more frequently among patients with chronic liver disorder.



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# Liver Transplantation

A small number of patients with Alagille Syndrome go on to have end-stage liver disease and require transplantation. The term liver failure means that the liver is no longer able to produce important body proteins and regulate metabolism correctly. Alagille Syndrome is a much less common reason for liver transplantation than biliary atresia. Approximately 10 to 15 patients per year are transplanted in North America for Alagille Syndrome for various reasons, including:

- Severe liver scarring (cirrhosis) and liver failure (about 15% of patients with Alagille Syndrome experience this).
- Severe itching, which is not responsive to any medical therapies
- Portal hypertension (a build up of pressure in the liver that results in bleeding from swollen blood vessels [varices] in the esophagus).
- Severe growth failure.



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