

University Hospital for
Children and Adolescents



Information For Parents and Patients

**Progressive Familial
Intrahepatic Cholestasis**

PFIC



**Universitätsklinikum
Tübingen**



European Reference Network

for rare or low prevalence
complex diseases



Hepatological Diseases
(ERN RARE-LIVER)

Authors: Anna Baumgarten-Heepe, PD. Dr. Dr. Ekkehard Sturm

Pediatric Gastroenterology/ Hepatology
Childrens Hospital Tübingen

Hoppe-Seyler-Str. 1 | 72076 Tübingen

Illustrations by Johanna Heepe (7 years old)

July 29th 2020



**Universitätsklinikum
Tübingen**

Dear family of a PFIC sick child, dear PFIC patient,

You probably learned recently about the presumed or confirmed diagnosis of your child or yourself called progressive familial intrahepatic cholestasis (PFIC). With this information leaflet we would like to give you information about the cause of PFIC, about necessary diagnostic procedures and available therapies. Further information and support can be obtained from the team of your hospital with expertise in pediatric or adult hepatology.

Content

1.	WHAT IS PFIC?	1
2.	THE HEALTHY LIVER	2
3.	THE FIRST SYMPTOMS	4
4.	BACKGROUND AND DEVELOPMENT OF PFIC	5
5.	WHAT CAN THE DOCTOR DO? – DIAGNOSIS AND THERAPY	9
6.	WHAT CAN WE (AS PARENTS) DO?	13
7.	WHO CAN HELP?	15
8.	GLOSSARY	16
9.	REFERENCES	19

1. What is PFIC?

PFIC is caused by rare genetic defects, and only one child in 50,000 to 100,000 suffers from it. In patients with PFIC, the transport of bile components from the liver to the intestine is disturbed. This means that bile components build up in the liver and in the blood. In many cases, the consequences of the disorder are limited to severe itching, in others, it can also lead to jaundice, failure to thrive, cirrhosis, liver failure and liver cancer.

PFIC = progressive familial intrahepatic cholestasis

**= PFIC Type 1-3, different forms of the disease
with different genetic defects**

PFIC is most often diagnosed in infancy and in toddlers, in milder cases first in school-age children, adolescence and in adulthood (though rarely). The severity of the symptoms, the course of the disease and the treatment options vary from person to person. There are medicines that can help manage the symptoms and slow the progression of the disease. Liver transplant is currently the only curative treatment. In the future, gene therapy is likely to be an option

2. The healthy liver

The liver is the most important metabolic organ in our body. Nutrients are transported from the intestine to the liver via the portal vein and broken down. Some are also stored in the liver (for example, fat-soluble vitamins).

The liver also produces the proteins of the blood plasma that are important for transport, the immune system and blood clotting. End products of metabolism and foreign substances are converted into a form that can be removed from the body (excretion). Thus the liver plays a major role in detoxification.

In addition, the liver is the largest gland in the body and produces bile, which is either released directly into the small intestine or, when not needed, stored in the gallbladder for later excretion.

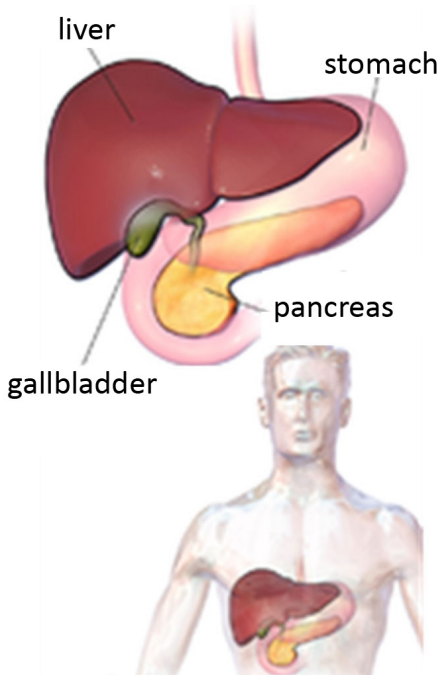


Figure 1: Liver and gallbladder with anatomic details

Bile is a liquid that contains large amounts of bile acids, which are synthesized in the liver from cholesterol, a major body fat. Furthermore it includes bilirubin, giving it a yellow-greenish colour. Bilirubin is a breakdown product of the red blood cells and is normally excreted via the stool. Bile helps with the absorption of fat and fat-soluble vitamins (A, D, E, K) in the small intestine.

In order to avoid the need to constantly produce new bile acids, a large proportion of bile is reabsorbed into blood in the lower part of the small intestine (ileum) and transported back to the liver (the enterohepatic circulation) so it can be used again. A small part of bile is excreted via the stool and with it waste products like Bilirubin or toxic substances.

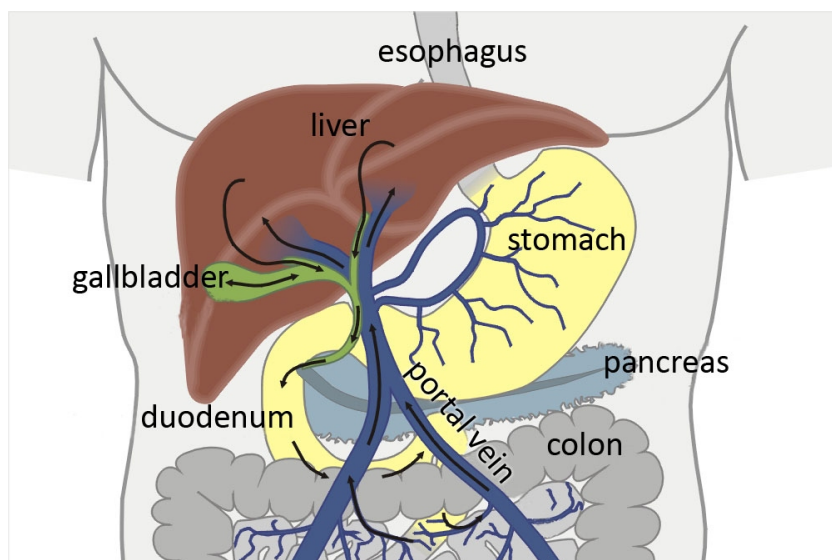


Figure 2: enterohepatic circle

3. The First Symptoms

Usually parents take their child to the doctor for the first time because he or she is constantly scratching.



Because PFIC is rare and not known to all doctors in general practice, this may be mistaken at first for a skin disease such as atopic dermatitis (eczema). Children with severe PFIC and also grown-ups may suffer from extreme itching and will scratch themselves until they are sore. This can lead to sleeping difficulties, irritability and exhaustion.

Severely affected children may also be seen by doctors in early infancy after prolonged jaundice.

Perhaps you have already noticed that your child is not growing and gaining weight as expected for his or her age? This might be another reason to visit the doctor and ask for advice. One reason for this may be that the liver is not working properly and there is poor absorption of fat and fat-soluble vitamins.



4. Background and development of PFIC

PFIC is caused by rare genetic defects. It only develops when a child inherits the PFIC gene variants (mutations; indicated in red in) from BOTH parents.

If both parents are healthy but carry a PFIC gene variant, the risk of the child developing PFIC is 25% (see Figure 3).

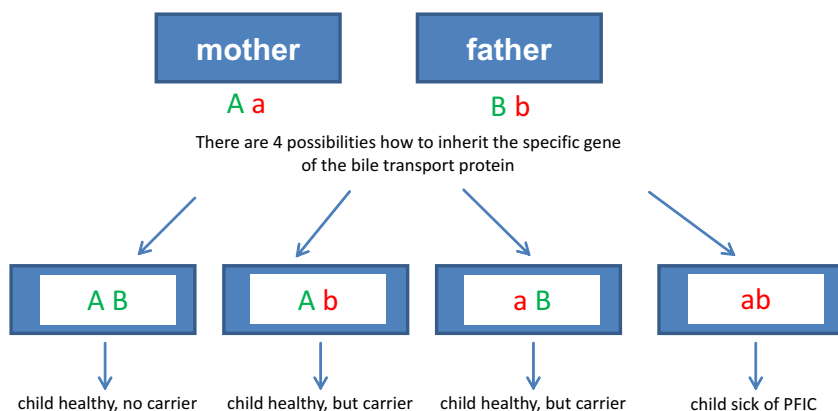


Figure 3: Scheme of inheriting the PFIC gene defect from parents to children

Status of “carrier” (see) means that people are healthy in many cases but may develop symptoms in some situations (e.g., pregnancy, severe infection, intolerance of drugs).

So far, 3 main types of PFIC and their causative genetic defect have been described, but there are more subtypes and more are expected to be identified in the future. They differ depending on which transport protein is defective (see Figure 4). This in turn affects the symptoms and their severity.

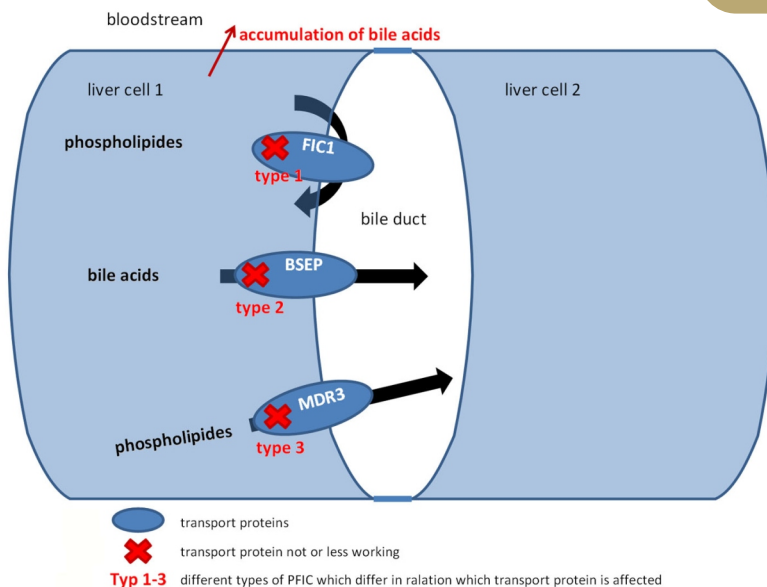


Figure 4: Affected transport proteins and related type of PFIC (rarely in PFIC affected proteins are not included in the figure)

In all 3 types, the formation of bile and its transport into the bile ducts is impaired, which causes the bile acids to remain in the liver cells and a backflow of them into the bloodstream.

They then circulate around the body, contributing to the stressful itching. The bile acids are also toxic for the liver cells and areas nearby. As a result, scar tissue is formed in the liver called fibrosis. Jaundice (a yellowish tinge to the skin and whites of the eyes) is a sign of a build-up of bilirubin in the blood and tissues.

Because fat and fat-soluble vitamins A, D, E and K are less easily absorbed due to reduced bile flow in PFIC, growth and developmental delays may occur. In addition unabsorbed fat is transported further along the large intestine leading to pale, fatty stool (steatorrhea) and in some cases to diarrhoea. Vitamin deficiencies can lead to further complications (see Table 1).

Table 1: Fat soluble vitamins and results of vitamin deficiency provoked by PFIC

Vitamin A	Impairments of vision (night blindness), susceptibility to infections
Vitamin E	Disorders of coordination, functional impairment and developmental disorders of the nervous system
Vitamin D	Rachitis (weakening and softening of bones))
Vitamin K	Bleeding disorders (gum and nose bleeding)), in severe cases cerebral bleeding

Background and development of PFIC



In very severe cases, the fibrosis (which can be reversible at first) described above progresses to cirrhosis. This state of disease is characterized by scarring that affects the function of the liver and is rarely reversible. High blood pressure may develop in the portal vein. This causes what doctors call hypertension and results in spleen enlargement and swelling of the blood vessels (varices) in the lower oesophagus (food pipe) or stomach, which may lead to vomiting of blood. A build-up of fluid in the abdominal cavity can occur which is called ascites. In some children, the final stage of liver failure is reached before the age of 10, which makes a liver transplant necessary. In rare cases liver cancer can develop.

5. What Can the Doctor Do? – Diagnosis and Therapy

It may take a long time before a PFIC disease is clearly identified. The ERN RARE-Liver network with its centres across Europe is working to shorten this period significantly making the diagnosis more rapidly. This is important for appropriate therapy to be started as soon as possible.

As a first diagnostic step, blood is taken from the child and the lab uses it to analyze liver function tests (bilirubin, enzyme GGT and serum bile acid, coagulation values, albumin). These blood tests are also checked in routine follow-ups. With the help of imaging techniques such as ultrasound, the size of the liver and the spleen can be determined, and the blood flow to the liver can be measured. X-rays can be used to determine whether bone density has decreased due to vitamin D deficiency.

Often, the treating doctors will propose to perform a liver biopsy to better assess the liver damage. A very small cylinder of tissue is taken from the liver then. Anaesthesia or sedation is given when taking liver biopsies. Specialists then examine this sample using a microscope. The risks of the procedure are low for the vast majority of patients. If your doctor recommends this procedure for you or your child, you will receive detailed information about it in advance.

To determine the type of PFIC, a genetic test (analysis of the affected parts of the genetic information) is often carried out. The blood of the parents may be also required to confirm the diagnosis. The results can take two weeks or more to arrive (depends on local conditions).

Once the diagnosis has been made, the therapy is determined. The choice of medication for PFIC ultimately depends on the extent of the symptoms. The main purpose of these drugs is to relieve the symptoms and help slow down the progression of the disease.

What Can the Doctor Do? - Diagnosis and Therapy

Medications frequently used in PFIC:

- Ursodeoxycholic acid
- Fat soluble vitamins
- Rifampicin (off- label use)
- iBAT inhibitors

A common treatment goal is to reduce the extremely stressful itching by lowering the concentration of bile acid in the blood. Ursodeoxycholic acid or rifampicin are often used in early stages to improve bile transport and metabolism. Importantly, at this stage none of the typical drugs described have been specifically tested and formally approved for their use in PFIC by the regulatory agencies. Thus, their use is considered “off-label”. Two new medicines are being tested in clinical studies for their potential use in PFIC. They inhibit the reuptake of bile acids in the intestine allowing them to be excreted with the stool and thereby decreasing bile acid overload in the liver. These drugs belong to the group of so-called iBAT inhibitors. Lastly, depending on the mutations identified in you or in your child, some specific drugs aiming to correct the consequence of the mutations may be proposed (targeted pharmacotherapy).

If the growth and development of the child is impaired by PFIC, doctors prescribe a formula diet whose energy and fat content is often adapted to the special needs of children with liver disease. To improve the vitamin levels, fat-soluble vitamins are prescribed as tablets, drops or injections. Although children with PFIC need more energy from food because of the difficulty with absorbing the fats from it, they often have a poor appetite. This means that in rare cases they need to be fed by a tube that goes to the stomach via the nose (a nasogastric tube) to provide nutritional support.

What Can the Doctor Do? – Diagnosis and Therapy

If the medications do not work, symptoms can be alleviated by surgery in selected cases. In bile duct drainage, the bile acids can be drained or diverted so fewer bile acids return from the small intestine back into the blood and then to the liver.

The drainage is either "external" through an exit (stoma) to the abdominal wall (see figure 5) or "internal" with a bypass. Here the gallbladder is connected to the large intestine, thus bypassing the end of the small intestine (ileum). A small part of the small intestine is converted to function as a connection from the gallbladder to the abdominal wall or colon.

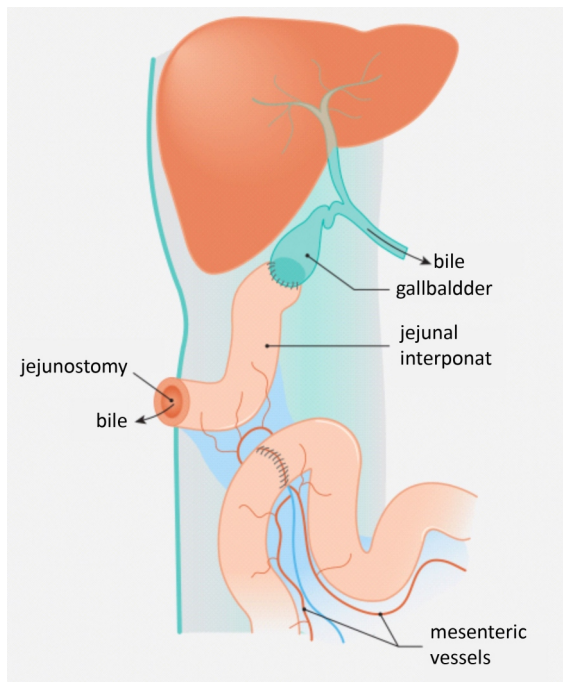


Figure 5: External bile duct drainage with stoma

Your doctor will provide you with comprehensive information about the benefits and risks before such a procedure is planned.

If these therapies do not bring about the hoped-for relief, your child may need a liver transplant.



In some cases, living donor liver transplant is an option whereby a healthy person donates part of his or her own liver to the PFIC patient. However, this operation should only be performed after careful consideration of the advantages and disadvantages. Children do very well after liver transplantation and regain a high level of quality of life. However, lifelong immunosuppressive medication will be necessary in most cases to prevent the body rejecting the new liver. Some complications of liver transplantation may be specific of the type of PFIC your child is suffering from. You will receive detailed information about this procedure by the multidisciplinary team taking care of your child and you as a family, if it is thought that your child will benefit from a liver transplant.

6. What can we (as Parents) Do?

Itching is probably the most bothersome symptom of PFIC, which affects the whole family. Moisturising ointments could give you or your child some relief. It can sometimes be helpful to cool the skin with a cooling (but not cold) bath or cooler room temperature at home.

Dress you or your child mainly in cotton clothing; do not buy wool or polyester clothes. Keep your or your child's nails short. To prevent scratching at night, put the hands in cotton gloves or choose overalls. During the day, distraction (walks, listening to music playground, meeting playmates) can help to temporarily get along with the itching.



At home, ensure a healthy and balanced diet and stay relaxed during meals. There are no foods that you or your child with PFIC should not eat. Does your child have a special formula diet? Anyway, let him or her join the family at the table and eat as balanced and regularly as the rest of the family. This is important for the development of healthy eating habits.

If your baby is fed via a nasogastric tube, you are the expert at home for the tube and the connection to the pump. You will be trained for this by the paediatric or nutrition team of your hospital.

Feeding via a tube may be daunting at first, but it can also be a relief for you, as your child will then reliably receive the energy and vitamins he or she needs for growth.

You should also take care of yourself. Do not forget to eat, sleep and relax regularly. Maybe you can take turns with your partner in caring for your child. It can help to talk about your situation with other affected families or with friends. In this way you can recharge your batteries and be a good support for your child.



7. Who Can Help?

Further information on caring for your child and caring for your child at home can be obtained from the pediatric gastroenterology/ hepatology team at your hospital.

If you are looking for further information online, look for trusted sources of reliable and up-to-date information such as:

- European Reference Network RARE LIVER: www.rare-liver.eu/
- Children's Liver Disease Foundation: <https://childliverdisease.org/>
- British Liver Trust: www.britishlivertrust.org.uk
- Information about rare diseases:
<https://www.orpha.net/consor/cgi-bin/index.php?lng=EN>

8. Glossary

Bile

Ingredients of bile are bile acids, phospholipids (e.g. lecithine), bilirubin, electrolytes and water. These are produced in the hepatocytes (liver cells) and excreted either directly in the gut or stored in the gallbladder (see below). Bile is necessary for the digestion of fat.

Bilirubin

... is an end product of red blood cells and is excreted via the bile. Its colour is yellow. When liver and/or bile metabolism is disturbed, bilirubin builds up in the body and higher levels than normal are circulating in the blood stream. It is the bilirubin that turns the skin and eyes yellow.

Cholestasis

... is a disorder where bile flow from the liver to the small intestine is decreased. There can be mechanically (e.g. gallstones) or metabolic (disruption of bile production) reasons for this issue. It leads to more bile in liver and blood stream which in turn causes pruritus (itch). Less bile in the gut causes lower absorption of fat from the diet and leads to stool discolouration.

Enterohepatic circulation

... is a kind of bile recycling. Bile acids are excreted in the duodenum (first part of the small intestine) and then 95% are reabsorbed in the ileum (last part of the small intestine), allowing the body to keep up with the high demand for bile acids to digest fats.

Excreted/ excretion

... to excrete means to remove from the body.

Fatsoluble vitamins

... are the vitamins A, D, E and K. "Fat-soluble" means that they have similar chemical characteristics to fats. Thus, with the help of bile, they are absorbed in the same way as fats. These are stored in the liver, unlike water soluble vitamins.

Gall bladder

... The gallbladder stores bile. If the liver excretes more bile than is needed for the absorption of fat, the bile is sent back from the gut and into the gallbladder.

Gene defect / Genetic disease

... is an abnormality in one or more locations in the genetic material (DNA). These defects are also called mutations. And may originate from external factors (such as radiation or nicotine) or internal ones. Gene defects can be inherited. If the gene contains the information to build up a protein with a specific function (like transportation through a cell membrane), the defect might lead to the loss of that function or to a protein with less function.

Ileum

... Last part of the small intestine where bile is reabsorbed.

Itching

... Itching (also called pruritus) is an extremely sore indication of PFIC involving the skin. Skin irritations can also occur because of scratching the affected skin.

The cause of the itching is not yet completely understood but it is thought to be caused by the large amount of bile in the blood stream. The itching can affect the whole body or specific areas.

The burden of itching is very wearing and is often underestimated. Many patients report that it is worse in the evening and at night.

Jaundice

... is caused by increased bilirubin concentrations in the blood. It then gets into the body tissues and builds up. First the whites of the eyes turn yellow, then the skin develops a yellowish tinge. There might be several reasons for jaundice but they're all related to disorders of liver or bile.

Pruritus

...See itching

Stoma

... describes a connection of an inner organ with the skin. It serves as a way for intaking (nutrients, vitamins) or excretion (stool, bile, urine) if the normal way is disturbed.

9. References

- (1) Antiga, Lorenzo D' (Hrsg.): Pediatric Hepatology and Liver Transplantation. Springer: 2019.
- (2) Rodeck, B.; Zimmer, K.-P.(Hrsg.): Pädiatrische Gastroenterologie, Hepatologie und Ernährung. 2. Auflage. Springer:2013
- (3) Slavetinsky, C.J.; Sturm, E.: Störungen der Gallemetabolisation bei Kindern und Jugendlichen, Kinder – und Jugendmedizin: 2020
- (4) Sturm, E.: Causes and Consequences of Cholestasis, Universität Groningen, Niederlande: 2003
- (5) Rodeck, B.; Zimmer, K.-P.(Hrsg.): Pädiatrische Gastroenterologie, Hepatologie und Ernährung. 2. Auflage. Springer:2013

Table of Figures

FIGURE 1: LIVER AND GALLBLADDER WITH ANATOMIC DETAILS
[Blausen.com staff. "Blausen gallery 2014". Wikiversity Journal of Medicine. DOI:10.15347/wjm/2014. 010. ISSN 20018762.]

FIGURE 2: ENTEROHEPATIC CIRCULATION
[<https://commons.wikimedia.org/w/index.php?curid=324246>,
<https://creativecommons.org/licenses/by-sa/2.5/deed.de>]

FIGURE 3: SCHEME OF INHERITING THE PFIC GENE DEFECT FROM PARENTS TO CHILDREN

FIGURE 4: AFFECTED TRANSPORT PROTEINS AND RELATED TYPE OF PFIC

FIGURE 5: EXTERNAL BILE DUCT DRAINAGE WITH STOMA
[from: Slavetinsky, C.J.; Sturm, E.: Störungen der Gallemetabolisation bei Kindern und Jugendlichen]



**Klinik für Kinder-
und Jugendmedizin**
Universitätsklinikum
Tübingen