

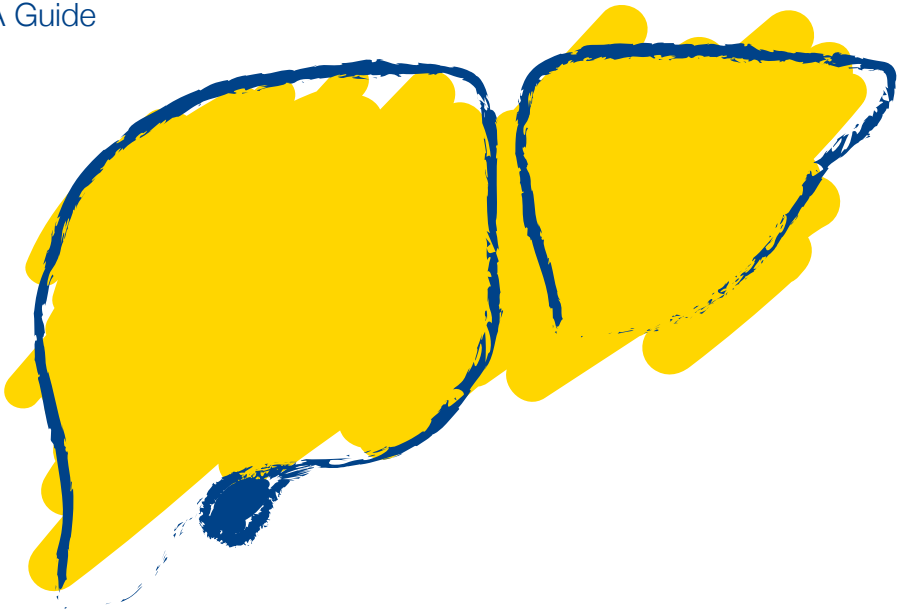


Children's Liver
Disease Foundation

fighting childhood
liver disease

Progressive Familial Intrahepatic Cholestasis (PFIC)

A Guide



An overview of PFIC including the different types,
causes, symptoms and treatment

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This information has primarily been written for:

- parents/carers of children and young people with PFIC

Others who may also find this information useful:

- young people with PFIC
- healthcare professionals who would like to find out more about the condition

It provides information on:

- types of PFIC
- symptoms
- diagnosis
- treatment
- possible complications

You may find it helpful to also read the following CLDF leaflets:

- Introduction to Liver Disease
- Nutrition
- Pruritus
- Portal Hypertension and Ascites

What is progressive familial intrahepatic cholestasis?

Progressive familial intrahepatic cholestasis (PFIC) is the name given to a group of conditions in which liver cells do not release a digestive fluid, called bile, properly. This leads to a build-up of bile inside the liver cell, known as cholestasis.

Cholestasis can damage the liver. The hepatocytes (liver cells) can start to die and become replaced with scar tissue. This leads to cirrhosis (severe scarring of the liver) which can cause a number of different problems. PFIC is a rare disorder which affects around 1 in 50,000 – 1 in 100,000 births and it affects males and females equally.

What is bile and why is it important?

PFIC is due to problems in the system which produces bile. The liver produces bile, which is a green/yellow liquid. The colour is due to bilirubin, a waste product produced when old red blood cells have been broken down in the spleen. Bile is made up of different substances, including:

- bile acids (help to digest fat)
- bilirubin
- cholesterol
- fats

- water ("95% of bile is water" *David Spraut et al 2009*)
- other waste products

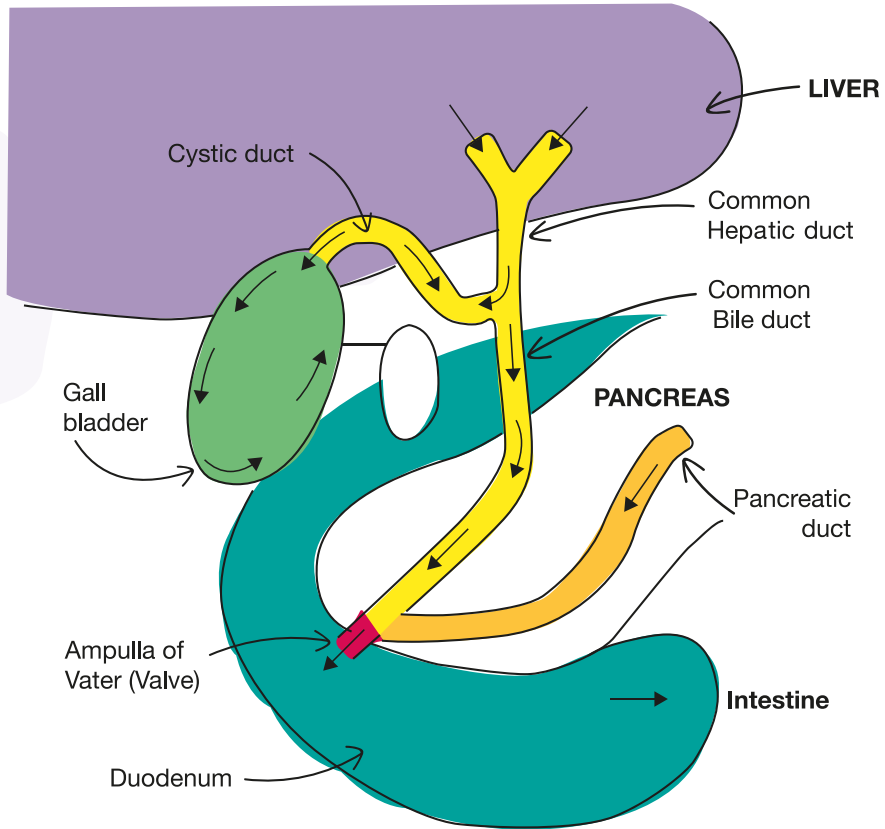


Figure 1: The Bile Duct System or 'Biliary Tree'

After bile has been produced by the liver it is transported to the gall bladder where it is stored. When food is eaten the gall bladder releases bile through bile ducts into the duodenum, part of the small intestine, to help with digestion and remove waste products.

Further down the intestine, in a part called the terminal ileum, most of the bile acids are reabsorbed back into the blood stream from the bile so they can return to the liver to be reused.

Bile has many functions:

- It helps the body to digest food by breaking fats down so they can be absorbed.
- It enables the body to absorb fat-soluble vitamins.
- It also helps the body get rid of waste products such as bilirubin and excess cholesterol which it passes out in the stool (poo).

What are the effects of PFIC?

As the liver becomes damaged there are a number of effects which can occur. These vary from child to child and can include:

Jaundice

Some of the bilirubin trapped in the liver passes back into the blood stream. It is carried around the body and is responsible for the yellow colouring of the whites of the eyes and the skin, known as jaundice.

Darker urine

Conjugated bilirubin is passed out in the urine making it more coloured than normal.

Discolouration of teeth

Due to jaundice being present while the teeth are forming/ growing. The higher calorie diet and/or medicines needed may also contribute to this.

Pale, smelly, greasy stools, frequently loose (diarrhoea)

These may float in the toilet and be more difficult to flush away, as they contain more undigested fat due to the reduced amount of bile flowing from the liver into the intestine.

Itching (pruritus)

One of the serious effects of PFIC is pruritus. It is an intense itch beneath the skin and can cause severe discomfort. It can be very difficult to control.

The cause of pruritus isn't completely understood but is thought to be due to the increased level of bile acids/salts in the blood caused by the bile not being made and excreted in the normal way. Itching may disturb sleep and contribute to fatigue, tiredness and irritability as well as reduced appetite, nausea and vomiting. There is a CLDF leaflet on pruritus which details the treatments available and includes advice from other parents on how to deal with severe itching.

Failure to thrive

This refers to poor weight gain and possibly slower growth due to the reduced absorption of fats.

Vitamin Deficiencies

(Especially the fat soluble vitamins A, D, E and K) — due to reduced absorption of:

Vitamin K — this is needed to make clotting factors that control bleeding. A deficiency may result in nose bleeds and bleeding from the gums.

Vitamin D — this is needed for strong healthy bones and teeth. A deficiency may result in weaker bones and/or rickets.

Vitamin E — this is needed for a healthy nervous system and the development of co-ordination.

Vitamin A — this is needed for good eyesight, particularly to see in the dark and for the eyes to adapt to changing light conditions.

Enlarged liver

This occurs due to inflammation and swelling in the liver.

Gall stones

This is the name given to the formation of solid particles within the gall bladder or bile duct system. If a stone blocks (obstructs) a bile duct this can cause severe pain and/or increased jaundice. In most cases gall stones are present but cause no problems. Gall stones increase the risk of cholangitis. This is an infection in the bile ducts which causes fever, general malaise/tiredness and can also cause discomfort/pain and increased jaundice.

Possible complications of PFIC

The bile trapped in the liver may cause progressive damage to the liver. This can cause it to become scarred (fibrosis) and hardened, eventually leading to severe scarring called cirrhosis. The effects of cirrhosis can include:

Portal hypertension

Due to the hardening of the liver there is increased resistance to the flow of blood from the intestines and spleen into the liver through the portal vein. This increased pressure is called portal hypertension. It can cause enlargement of the spleen and the development of oesophageal varices.

Swollen blood vessels in the lining of the oesophagus (food pipe) may result in bleeding from the gut. The child may vomit blood or pass black tarry stools.

Ascites (fluid retention in the abdomen)

Due to increased pressure in some of the blood vessels, and the reduced ability of the liver to make an important protein called albumin, excess fluid can collect in the abdomen.

There is a separate CLDF leaflet available on portal hypertension and ascites.

Liver failure

Eventually the severe scarring of the liver means it can no longer do its job of making proteins, like albumin and clotting proteins, and remove waste products. This is a late stage of advanced liver disease and the liver is said to be failing.

Increased risk of liver cancer

All forms of liver disease increase the risk of liver cancer, especially in patients with BSEP (bile salt export pump; a protein found in the liver) deficiency. Your child will be offered screening for hepatocellular carcinoma (a type of liver cancer) so any problems can be spotted at an early stage.

What causes PFIC?

PFIC is a genetic condition. Genes contain our DNA and provide instructions for the body to produce proteins. There are different forms of PFIC. The specific types of PFIC can only be identified by genetic testing. The three well recognised types are described here but as genetic testing improves more types will be identified. Currently some children appear to have all the features of PFIC but no disease-causing genes have been identified in their blood.

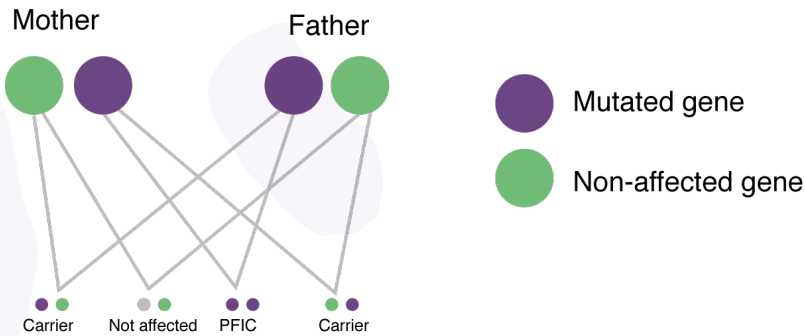
What are the chances of a child inheriting PFIC from their parents?

Each protein our cells make requires instructions from a matching pair of genes, one inherited from father, the other from mother. How the protein is made will be dictated by the stronger of these two genes. Genes with a mistake in them (mutation) are often weaker than healthy genes and it is only when a child receives two mutated genes that they develop the disease. Both parents must have at least one copy of the mutated gene in order for their child to inherit the disease. This is called an autosomal recessive inheritance pattern.

When both parents are carriers:

When an individual is a carrier it means they have one copy of the affected gene but they do not have the disease.

Both parents are carriers



Possible genes child will receive

If both parents are carriers then there is a chance that each parent will pass on the affected gene.

One out of four times, the child of two carriers will inherit two abnormal genes — one gene from each parent. These children will have PFIC.

One out of four times, their child will inherit two normal genes. These children will not have the mutated genes.

Two out of four times, their child will inherit one normal gene and one abnormal gene. This child will be a carrier like their parents.

FIC1 deficiency (PFIC1)

Mutations in the ATP8B1 gene cause deficiency of the FIC1 protein.

The exact mechanism by which the deficiency of FIC1 protein causes build up of bile in the liver cell leading to all the problems of cholestasis, and the other symptoms of PFIC1, is not clear.

PFIC1 often causes symptoms such as jaundice and itching in the first year of life. It can lead to a deficiency in fat-soluble vitamins as well as diarrhoea, slow growth, short stature, pancreatitis (inflammation of the pancreas), thicker skin and hearing problems. Without treatment the liver can become severely diseased and lead to liver failure before adulthood. Not everyone will have all of these issues as the severity differs between individuals.

FIC1 deficiency

This includes Benign Recurrent Intrahepatic Cholestasis (BRIC1) and PFIC1 which are now thought to be the same condition with different degrees of severity.

- Results from a defect in bile acid secretion which means bile is not formed properly
- Normal GGT (specific bile duct enzyme test) even if bilirubin level is high
- Presents with jaundice and pruritus
- High levels of serum bile acids
- Has a wide range of severity

Characteristics outside the liver:

- Diarrhoea or loose stools is common
- Slower growth and short stature is common
- Pancreatitis (inflammation of the pancreas) has been associated in some cases
- Thicker skin
- Hearing problems

It is common for many of the characteristics outside the liver to persist even after a successful liver transplant.

Specific features of BRIC 1:

- Recurrent episodes of symptoms which may be quite mild
- First sign is often itching (pruritus), jaundice may also occur
- First episode of symptoms can be at any age and may be precipitated by factors such as infection or medication
- Presentation at anything from two months to 47 years has been recorded
- Frequency and severity of episodes can vary greatly — once a year to once every ten years has been described, and generally reduces with age
- Duration of attacks can vary from several weeks to many months and in rare cases can even last for years
- Some patients with BRIC have no signs of liver damage

even in old age and after many attacks. However, others can have slowly progressive liver disease.

Specific features of PFIC1:

- May present in the first year of life with intense pruritus
- Signs of fat-soluble vitamin deficiencies are common
- Progresses to chronic liver disease at varying rates and to varying degrees of severity

BRIC1 and PFIC1 are the two ends of the same spectrum and the disease can be anywhere in between.

BSEP deficiency (PFIC2)

Mutations in the ABCB11 gene are responsible for deficiency of the BSEP protein.

This gene tells the body to make a protein called the bile salt export pump (BSEP). This protein is found in the liver and moves bile salts out of liver cells. Mutations in this gene cause bile acids to build up in liver cells causing damage. Fatty stools (poo) are common as well as severe pruritus. Growth may be slower than usual and gall stones can be common. There is an increased risk of liver cancer associated with BSEP deficiency.

BSEP deficiency

- The BSEP protein is either absent or significantly reduced. GGT levels in the blood are normal
- This protein is responsible for moving bile acids out of the liver cell into the bile

- Fatty stools are common
- Pruritus becomes severe
- Growth is usually significantly slowed
- Cirrhosis often occurs before the age of ten years
- Gall stones are common
- Generally have an excellent response to liver transplantation
- Milder forms (sometimes called BRIC2) have also been identified.
- There is a higher risk of liver cancer in this type of PFIC which makes regular monitoring particularly important.

MDR3 deficiency (PFIC3)

Mutations in the ABCB4 gene cause deficiency of the MDR3 protein.

This gene tells the body to make a protein which moves fats across the membranes of cells. These fats bind to bile acids outside of the liver cell in the small bile ducts. When there is a mutation in this gene there are fewer fats to bind to the bile acids. Bile acids can build up outside the liver cells and can cause damage to the bile ducts and liver.

Whilst PFIC1 and 2 tend to occur in infancy, PFIC3 can occur during infancy, childhood and even into young adulthood. Pruritus can be slightly less severe in PFIC3 in comparison to PFIC1 and 2 but the severity of the condition can differ between individuals. Damage to the bile ducts can occur, gall stones are common and there is a high risk of portal hypertension.

PFIC1 and PFIC2 represent around two out of three of all cases of PFIC. PFIC3 represents around one out of three cases.

MDR3 deficiency

- Caused by a protein called MDR3 either not being present or not working properly. MDR3 stands for multidrug resistance protein 3.
- High levels of GGT in the blood — this is an important difference from FIC1 and BSEP deficiencies
- Low level of phospholipids (specific type of fat) in the bile. Phospholipids appear to have some protective function in the bile ducts
- Pruritus tends to be milder
- Bile duct damage may occur
- Gallstones are common
- Higher risk of cholangitis
- High risk of portal hypertension
- Generally has an excellent response to liver transplantation
- There is a very wide range of severity

With advances in genetic testing other gene mutations will be found to explain the disease in children who have the features of PFIC but no genetic diagnosis. Recently mutations in the tight junction protein 2 (TJP2) gene have been described in children whose symptoms presented like PFIC1 or 2 with a normal GGT. This has also been called PFIC4. A mild form of liver disease associated with mutations in the TPJ2 gene was previously called familial hypercholanaemia.

How is PFIC diagnosed?

There are a number of tests which are used to diagnose PFIC:

Liver Function Tests

These are blood tests which may help to make the diagnosis. They can also be repeated at intervals to monitor the severity and progression of the disease. More on each specific test can be found in CLDF's leaflet: An Introduction to Liver Disease.

In particular gamma GT (GGT) is a type of liver enzyme which may help to distinguish between the types of PFIC.

The GGT levels in the blood are low or normal in FIC1 and BSEP deficiencies but raised in MDR3 deficiency.

Bile Acid Tests

These are more specialised blood and urine tests which can help to find out the type of PFIC disease someone has. It can take a little while for the test results to be available. Children with PFIC will have 10 to 20 times the normal bile salt concentration.

Genetic Tests

These are highly specialised blood tests. To carry out genetic testing, blood needs to be taken from the child and both parents, if possible. It may be several weeks before the results are available. In many cases antenatal diagnosis (diagnosis in the womb) can be offered for future pregnancies involving the same parents.

Scans and X-rays

Ultrasound scans may be used to assess and monitor:

- the size and consistency of the liver
- the spleen size
- the blood flow into and out of the liver

Bone X-rays — wrist x-rays in particular may be used to look for the early stages of rickets (bone weakness) developing.

Liver Biopsy — a small piece of liver tissue is taken out, using a special needle, and then examined under the microscope. An operation is not usually needed. Results from the liver biopsy are used to help make the diagnosis, to assess the severity of the disease and to advise about the future (prognosis). It is not usually necessary to repeat the biopsy. Further information can be found in CLDF's leaflet: An Introduction to Liver Disease.

Even with information from a liver biopsy it may be very difficult to distinguish PFIC from other types of liver disease which affect newborns. It can take months to diagnose PFIC and it takes even longer to determine the type of PFIC a child has.

MRI/MRCP — magnetic resonance imaging/magnetic resonance cholangiopancreatography — this is a form of scanning which uses special magnets to obtain a picture of the internal organs especially the bile ducts.

Isotope scan (DISIDA or HIDA scan) to show how well bile is being excreted from the liver.

MRI/MRCP and Isotope scans are often used to differentiate PFIC from other causes of liver disease.

How is PFIC treated?

There is no cure for PFIC but medicines, surgical treatments and changes to the diet can reduce the effects and complications of the condition. The treatments to be used will be recommended by the specialist depending on the features and severity of the condition and its effects.

Dietary Treatments

Dietary treatments used in children/young people with PFIC will depend on the specific symptoms and characteristics of the individual child.

Poor bile flow means that individuals with PFIC may not absorb fats and fat-soluble vitamins. This can lead to poor growth. Your child may be prescribed the following:

- **MCT (Medium Chain Triglyceride)**
MCT fat is absorbed more easily than other fats when bile

flow is poor, and is a good source of energy. MCT fat is not commonly found in foods but there are specialist milk formulas and supplements containing MCT available. Your dietitian will advise you if this is necessary.

- **Fat Soluble Vitamins (vitamins A, D, E and K)**

These are normally given orally although an injection may be needed.

- **Nasogastric Feeding**

If your child is not growing well because of their symptoms then overnight nasogastric feeding may be advised. This allows energy and protein to be given overnight. This involves a very fine, soft tube which is passed up the nostril, down the back of the throat and into the stomach. A specialist formula milk can then be given overnight using a pump. Parents/carers can be taught how to do this at home. For further information see CLDF's leaflet: Nutrition.

Medicines

Medicines given may include the following:

- **Cholestyramine (Questran®)**

This binds to bile acids in the gut and stops them being reabsorbed into the blood stream. This may reduce itching, although results vary. It shouldn't be given at the same time as vitamin supplements as it can stop them being absorbed properly.

- **Ursodeoxycholic Acid (urso, ursofalk or Destolit®)**

This helps to improve bile flow out of the liver which

can reduce jaundice and/or itching and can improve liver function. It has been found to be particularly useful in PFIC3 (also known as MDR3 deficiency).

- **Rifampicin**

This is a liver stimulant. It reduces itching in some patients. It can cause deterioration of liver function tests so it is used with caution in severe liver disease. Liver function tests are monitored to assess its effects. Rifampicin is a red colour and can cause urine to turn pink/red but this is harmless.

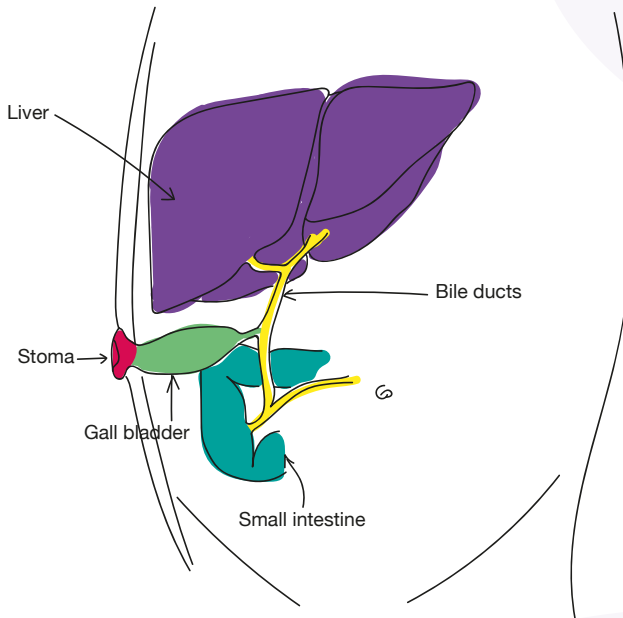
- Phenobarbitone, naltrexone, and ondansetron are other medicines which have been used to reduce itch in some children.

Potential Operations

A number of operations have been tried in liver centres around the world in an attempt to reduce the effects of PFIC with varying degrees of success. The specialist team (medical and surgical) will make a careful assessment of your child's condition before any of these procedures are recommended.

These procedures are not appropriate in all cases.

Figure 2: A diagram of a partial external biliary diversion



Partial external biliary drainage

This is an operation which is only suitable for patients who have not developed cirrhosis. It is usually only considered when all medical treatments have failed to control itching (pruritus).

The round end of the gall bladder is opened and brought out through the skin to form a stoma (surgically created opening) on the surface of the abdomen (figure 2). An adhesive bag is worn over the stoma to collect the bile produced. Sometimes a short section of the child's bowel is used to connect the gall bladder to the surface of the abdomen.

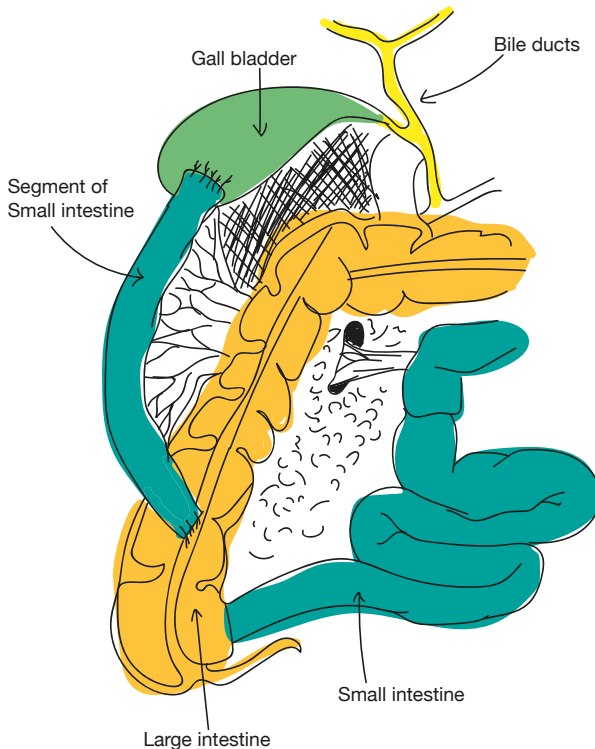
The aim of this is to remove some bile to reduce the amount of bile acids re-entering the circulation and reduce itching. This may, however, make malabsorption and vitamin deficiencies worse.

Important body 'salts' may also be lost and may need to be replaced by taking additional medication.

Partial internal biliary drainage

This is a new operation which is similar to the external diversion except a piece of bowel connects the gall bladder to the large intestine (figure 3). There is no need for an external bag. It can result in diarrhoea as more bile enters the large intestine, and it has not been evaluated in as many children as the external diversion.

Figure 3: A diagram showing the partial internal biliary drainage procedure



Internal ileal exclusion

This is a different operation in which a bypass is created around the distal ileum, this is the section of bowel where bile salts are usually reabsorbed. The aim of this operation is also to reduce the amount of bile salts reabsorbed into the blood stream. Diarrhoea is a possible complication, and other supplements may be needed as the terminal ileum is also important in the absorption of other food elements.

Liver transplant

This is a major operation with inherent risks, but a successful transplant can restore a good quality of life. Most children with PFIC will require a transplant at some point in their lives, whether as a child or in the future when they are adults. After a liver transplant children need to take anti-rejection medicines for the rest of their lives, have regular medical follow-ups and will be at risk of side effects from the medicines. However, transplant can prolong their lives with a significantly better quality of life. Liver transplantation is not suitable for all cases. To find out more about liver transplantation see CLDF's leaflet: Liver Transplantation.

Normally the non-liver features of PFIC1, such as diarrhoea and short stature, are not improved by surgical treatments, including transplantation. Occasionally after a transplant there can be recurrence of the original disease in the transplanted liver.

CLDF produces a wide variety of information resources for children and young people up to the age of 25 with liver disease, their families and the healthcare professionals who look after them. This information can be downloaded or ordered from CLDF's website www.childliverdisease.org. For further enquiries regarding CLDF's information please contact the Health and Research Information Manager by email at hrim@childliverdisease.org or call 0121 212 6029.

Thanks

The booklet has been written, edited and reviewed with the help of staff at each of the specialist paediatric liver centres: Birmingham Children's Hospital, King's College Hospital and Leeds Children's Hospital. Thank you to all of the staff involved who have made the production of this leaflet possible, and a special thanks to Mr Salahuddin Syed for providing medical illustrations.

Disclaimer

This leaflet provides general information but does not replace medical advice. It is important to contact your/your child's medical team if you have any worries or concerns.

Feedback and Information Sources

Information within this leaflet has been produced with input from the three specialist paediatric liver centres in the UK. To provide feedback on this leaflet, for more information on the content of this leaflet including references and how it was developed contact Children's Liver Disease Foundation: info@childliverdisease.org

This leaflet has been reviewed in April 2018. It is due to be reviewed by April 2021.

What is Children's Liver Disease Foundation (CLDF)?

CLDF is the UK's leading organisation dedicated to fighting all childhood liver diseases. CLDF provides information and support services to young people up to the age of 25 with liver conditions and their families, funds vital research into childhood liver disease and is a voice for everyone affected.

Are you a young person up to the age of 25 with a liver condition? CLDF's Families and Young People's teams are here for you, whether you want to talk about issues affecting you, meet and share with others, or just belong to a group which cares, knows what it's like and is fighting to make a difference. You are not alone.

If you are a parent/carer or family member then get in touch with CLDF's Families Team:

Phone: 0121 212 6023 **Email:** families@childliverdisease.org

If you are a young person and want to find out more about CLDF's services you can contact CLDF's Young People's Team:

Phone: 0121 212 6024 **Email:** youngpeople@childliverdisease.org

CLDF have a social media platform called **HIVE** for 13 – 24 year olds with a liver disease/transplant to make new friends, connect and share stories.

www.cldfhive.co.uk

Would you like to help us support the fight against childhood liver disease?

All of CLDF's work is funded entirely through voluntary donations and fundraising. Please help us to continue to support young people, families and adults diagnosed in childhood now and in the future. To find out more about fundraising and how you can join the fight against childhood liver disease you can visit: www.childliverdisease.org/get-involved. Alternatively, you can contact the fundraising team by email fundraising@childliverdisease.org or call **0121 212 6022**.

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