PFIC VOICES

Progressive Familial Intrahepatic Cholestasis

A Guide for Patients and Families

What information is contained in this PFIC pamphlet, and who is it for?

PFIC stands for progressive familial intrahepatic cholestasis. It's a rare liver condition that requires medical attention and support. This pamphlet provides an overview of PFIC, how it is diagnosed and places you and your family can turn to for support. This overview is for the PFIC community and others who wish to learn basic information about this serious condition.

What is PFIC?

Progressive familial intrahepatic cholestasis (PFIC) is a rare genetic liver disease that affects infants and children. In many cases, patients diagnosed with PFIC experience end-stage liver disease by 10 years old.[1] A serious consequence of PFIC is severe itching that can lead to sleepless nights for the whole family. If left unprotected, babies may even scratch through their skin causing bleeding, scabs, and wounds.

PFIC is estimated to impact one in every 50,000 to 100,000 children born worldwide.[2] As a result of a genetic defect, bile acids accumulate in the liver and bloodstream, causing progressive symptoms both within and, sometimes, outside the liver. Families are desperate for relief.

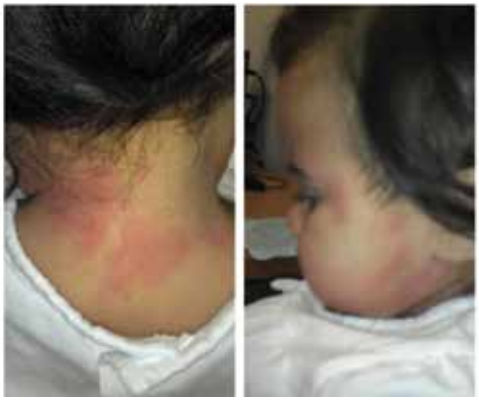
Normal Liver Function

The liver has many functions, including breaking down fats and absorbing vitamins. It does this with the help of bile, a liquid that is released from the liver into the bile ducts. Typically, approximately 95 percent of bile acids are recirculated to the liver.[3] The liver also has other important functions, including removing toxins and making proteins that are for blood clotting.

What Happens in PFIC

In PFIC, the liver is unable to excrete bile acids as the result of a genetic defect, so they accumulate to high levels in the liver and in the bloodstream. This causes symptoms, such as jaundice (yellowing) and pruritus (severe itching), as well as other symptoms of progressive liver disease. Patients with progressive liver disease may have difficulty removing toxins from the blood and clotting. An inability to excrete bile acids can also lead to fat malabsorption, failure to thrive, and deficiencies in vitamins A, D, E, and K.

Signs and Symptoms



PFIC can cause signs and symptoms that may vary by person. Here are some that parents and physicians have described:

Severe itching (pruritus). Severe itching is the most disruptive symptom in the day-to-day lives of children with PFIC. It can cause sleepless nights and daytime fatigue. Children may not even be able to focus at school. And when children can't sleep, parents do not sleep, either. Continuous scratching and scabs that are left behind can lead to poor self-esteem and social challenges.[4] A common cold and feeling hot (from exercise or weather) may worsen the itching.

Nutritional problems. People with PFIC have difficulty absorbing fats and fat-soluble vitamins, such as vitamins A, D, E and K. As a result, they may have poor growth and development, as well as reduced immune system function.[4]

Liver problems. The accumulation of bile acids damages the liver over time. In the early stages, children appear jaundiced, or yellow in color. Many people with PFIC will suffer from end-stage liver disease by the age of 10.[1] Only one third of people with PFIC reach adulthood with their native liver.

Other signs and symptoms. Some patients experience enlarged liver and spleen, diarrhea, hemorrhage (bleeding), high blood pressure, gastrointestinal bleeding, pale stools, pancreatitis, gallstones, and rickets.

"The itching associated with PFIC is life-changing for the child and the family. Children with PFIC are unable to sleep, and their development and ability to learn and grow suffer. Parents have to restrain their child to try to prevent them from scratching until they bleed. It's heartbreaking. It can become so debilitating that the itching brings us to recommend liver transplantation for the child. The itching can be that bad."

Dr. Jaime Chu
Pediatric Hepatologist
Mount Sinai Medical Center
New York
Consultant to Albireo

A Parent's Perspective

"When Sylvie was three weeks old, I noticed that when she was drinking her bottle, she would itch extensively on her face and her eyes. And I thought that was odd. The more she would get into her feeding, the itchier she'd get. I told my pediatrician and the doctors at the hospital. All of them said it was eczema or dry skin, so I used lotion for a long time. Nothing worked. It almost made it worse, because she would wipe the lotion into her eyes, and then she'd start screaming.

After we got the diagnosis of PFIC, the itching was the most debilitating thing for us. To get that managed was so important for everyday life and quality of life. And we just don't have that yet. We have these amazing days and horrible days. And I think, if we can manage that itching and getting her stable, that would be a miracle."

Season, mother of a daughter with PFIC

How is PFIC Diagnosed?

PFIC is often diagnosed in infancy. Parents may take their baby to the hospital because of jaundice that does not subside or itching that will not go away. Doctors will try to rule out other, more common causes of jaundice first. A pediatrician may recommend sending a patient to a liver specialist for special tests, including blood tests, imaging, or liver biopsy. Physicians who specialize in the digestive system or gastrointestinal system are called gastroenterologists. Physicians who specialize in liver diseases are called hepatologists.

A PFIC diagnosis can be confirmed with a genetic test, which is performed on a blood sample. A genetic test may help identify affected genes and support a PFIC diagnosis. PFIC may be caused by a mutation in different genes, including: ATP8B1, ABCB11 and ABCB4.[4]

PFIC is an autosomal recessive disorder. This means that a child must inherit the same affected gene from both parents for the disease to be present. If the child only inherits the affected gene from one parent, he or she will be a "carrier" but will not have the disease. This is why some children in a family may be affected by PFIC, while others are not.

Living with PFIC

There are no approved therapies to treat PFIC. Patients and their families should consult their healthcare providers for guidance on PFIC management. The following topics may be considered:

- **Skincare:** Patients with PFIC may have sensitive skin. It may be beneficial to cover skin as much as possible and to keep nails short.
- **Nutrition:** Talk with your doctor about possible ways to help manage nutritional deficiencies.
- **Risk of Infections:** Even minor illnesses may worsen PFIC symptoms. Talk with your doctor about precautions that could help.

No two patients with PFIC are alike. Patients and parents should consult their healthcare providers for guidance on what may work best for them.

Surgical Interventions

When disease management alone is not enough to provide relief from itching, or when liver disease progresses, families may consider surgical options, including biliary diversion and liver transplantation.

Biliary Diversion. In surgical biliary diversion (or partial exterior biliary diversion, PEBD), bile is diverted out through the abdominal wall and, typically, collected in an ostomy bag outside the body. PEBD may provide relief for months or even years, but may not be a permanent solution.[5] A less common approach called ileal exclusion (or internal biliary diversion), involves bypassing part of the small intestine and connecting it to the colon.

Liver Transplantation. Liver transplantation may be an option for some patients who experience progressing liver disease or severe itching.[6,7] Like all major surgeries, it has significant risks. Even when it is successful, it requires the patient to receive life-long immunosuppressive therapy to prevent the body from rejecting the new liver.

For some PFIC patients, itching becomes so severe and disruptive to daily life that their families choose liver transplantation to get relief.

A Note from PFIC Advocacy Leaders

PFIC can be a devastating diagnosis—not just for the patients and their parents, but for siblings, families, and the communities in which they live. And though the number of children diagnosed with PFIC are few, there is a community here to support you.

I'd like to introduce you to the **Progressive Familial Intrahepatic Cholestasis Advocacy and Resource Network (PFIC Network)**. Our mission is to improve the lives of patients and families worldwide affected by PFIC. We support research programs, provide educational materials, match families for peer support, and participate in advocacy opportunities. Learn more about our work at PFIC.org.

We are proud to work with Albireo Pharma, a company committed to supporting people with PFIC, their families, and healthcare providers with resources to better understand the disease. Because of companies like Albireo, working to find treatments for rare liver diseases like PFIC, we have hope for a brighter tomorrow.

Yours truly,

Emily Ventura, Melanie Karakaidos and Tara Kearns
Leaders of the PFIC Network

A Message from a PFIC Expert

In my clinical practice at King's College Hospital, I've worked with many families who are coping with PFIC. One of the most difficult aspects of this disease is the impact it has, not just on diagnosed children, but on parents, siblings and others who provide care. Sleepless nights, a tireless search for answers, and concern about the future are consistent themes.

As healthcare providers, we have a range of tools that we use to try to alleviate symptoms and slow the progression of disease. Our current surgical options may work for some patients, but there are limitations and risks. Better therapies are urgently needed.

The good news is that much research is being done by academics and within industry. We are learning more about intrahepatic cholestasis every day—from genetics and disease progression to better ways to manage different manifestations. As the medical community continues to find a better path forward, parents should continue to advocate and reach out for support when needed. There is reason to be hopeful, and we will not stop persevering until we have better tools to offer to the PFIC community.

Richard Thompson, M.D., Ph.D.
Institute of Liver Studies
King's College Hospital
London
Consultant to Albireo

Hope for Patients and Families

Research is underway, seeking better treatment options for people with PFIC, and resources are available to help patients and families.

PFIC Advocacy and Resource Network aims to improve the lives of patients and families worldwide affected by PFIC.
PFIC.org

Childhood Liver Disease Research Network (ChiLDReN) offers medical and patient advocacy support with clinical sites and research labs in the U.S.
Childrennetwork.org

Children's Liver Disease Foundation (CLDF) is a UK-based charity dedicated to pediatric liver diseases. Download the CLDF PFIC brochure here: https://www.childliverdisease.org/wp-content/uploads/2018/01/PFIC.pdf.
Childliverdisease.org

ClinicalTrials.gov provides the public with information on clinical studies on a wide range of diseases and conditions, including PFIC.
Clinicaltrials.gov

Global Genes is an advocacy organization committed to supporting the rare disease community.
GlobalGenes.org

American Liver Foundation (ALF) is a national, voluntary nonprofit organization dedicated to the prevention, treatment, and cure of hepatitis and other liver diseases through research, education, and advocacy.
LiverFoundation.org

The National Organization for Rare Disorders (NORD), an independent non-profit founded over 35 years ago, is leading the fight to improve the lives of patients with rare diseases. It does this by supporting patients and organizations, accelerating research, providing education, driving public policy and spreading awareness.
Rarediseases.org

"I would describe my daughter as a fighter. She has been through hell and back. It's amazing to see her perseverance. Despite it all, she is so happy, just a joy."

About Albireo

Albireo is committed to supporting people with PFIC, their families, and healthcare providers with resources to better understand and manage this devastating disease. The company is focused on the development of novel bile acid modulators to treat rare pediatric liver diseases, such as PFIC.

albireopharma.com

Special thanks to organizations and the families living with PFIC for their support and contributions.

Global Genes® Allies in Rare Disease

pfic

Children's Liver Disease Foundation
fighting childhood liver disease

NORD® National Organization for Rare Disorders

Albireo

References

1. Mehl A, Bohorquez H, Serrano MS, et al. Liver transplantation and the management of progressive familial intrahepatic cholestasis in children. World J Transplant. 2016;6(2):278-90.
2. Davit-Spraul, Gonzales E, Baussan C, Jacquemin E. Progressive familial intrahepatic cholestasis. Orphanet J Rare Dis. 2009;4:1.
3. Chiang JYL. Bile Acid Metabolism and Signaling. Compr Physiol. 2013;3(3):1191–1212.
4. Srivastava A. Progressive Familial Intrahepatic Cholestasis. J Clin Exp Hepatol 2014;4:25-36.
5. Bull LN, Pawlikowska L, Strautnieks S, et al. Outcomes of surgical management of familial intrahepatic cholestasis 1 and bile salt export protein deficiencies. Hepatol Commun 2018;2(5):515-528.
6. Alissa FT, Jaffe R, Shneider BL. Update on progressive familial intrahepatic cholestasis. J Pediatr Gastroenterol Nutr. 2008;46(3):241-52.
7. Pawlikowska L, Strautnieks S, Jankowska I, et al. Differences in presentation and progression between severe FIC1 and BSEP deficiencies. J Hepatol. 2010;53(1):170-8.