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Optimizing Pediatric outcomes in Progressive Familial Intrahepatic Cholestasis (PFIC): Current treatments and Future safer strategies

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Abstract

PFIC is a very rare genetic liver disease that mainly affects infants and children. This is a disease that occurs when defective genes encoding proteins in bile formation and transport cause cholestasis, a condition in which bile cannot flow through the liver favorably because of the buildup of toxic bile acids. Cholestasis that continues over a long period of time causes related signs such as continuing injury to the liver, serious itching (pruritus), dietary deficiencies and delays in growth; this can lead, more often than not, to the development of cirrhosis or liver failure. Gene mutations, including ATP8B1, ABCB11 and ABCB4, that are somehow most commonly associated with PFIC actually lead to different clinical subtypes of the overall disease. Management is currently aimed at symptomatic control and the slowing of disease progression with nutritional support, ursodeoxycholic acid, antipruritic agents, biliary diversion techniques and liver transplantation in advanced cases. Novel therapeutic options have becoming available over the last years, particularly ileal bile acid transporter (IBAT) inhibitors that effectively decrease bile acid reabsorption at the terminal ileum leading to novel remedies for cholestatic symptoms. Also, recent developments in gene-directed therapies have opened exciting avenues for targeted treatment of the underlying

genetic lesions in PFIC. Here, we review PFIC with a focus on the genetic basis, pathophysiology, clinical features and potential therapeutic options, elucidating new approaches that could enhance long-term outcomes while decreasing the requirement for liver transplantation in affected children.

Keywords: Progressive Familial Intrahepatic Cholestasis, PFIC, cholestasis, pediatric liver disease, IBAT inhibitors, gene therapy, liver transplantation.

1. Introduction

Progressive Familial Intrahepatic Cholestasis (PFIC) is a collection of rare inherited cholestatic disorders that are caused by defective bile secretion from hepatocytes. PFIC is a key, though uncommon, cause of chronic liver disease in paediatric populations and typically occurs early during life. The disorder is due to mutations of genes encoding proteins that support bile acid transport and maintain function of the canalicular membrane. Bile outflow obstruction leads to retention of bile acids in the liver, causing progressive hepatocellular injury and fibrosis, ultimately resulting in cirrhosis.

PFIC usually accounts for children who had nonstop jaundice, severe itching, hepatomegaly and failure to thrive [19-21] along with deficiencies of fat-soluble vitamins. The disease is chronic and can impact both physical development and quality of life. Without timely recognition and proper management, many patients develop end-stage liver disease needing a liver transplant.

Improvements in molecular genetic techniques have enhanced the knowledge of PFIC and allowed the identification of additional gene mutations causing disease, including ATP8B1,ABCBC11,ABCBC4,TJP2 and MYO5B. Such findings have not only improved diagnosing precision but also aided in the formulation of targeted therapy options. For the past 4 decades, traditional management mainly comprised nutritional support, symptom relief, and surgical interventions; novel innovations in this area have shifted the focus toward disease-specific treatments.

New-generation ileal bile acid transporter (IBAT) inhibitors represent a very promising nonsurgical option to mitigate bile acid accumulation and relieve pruritus. Even more recently, new gene therapy approaches have the potential to fix the underlying genetic defects in causing disease. The ongoing development of these new therapies to improve long-term outcomes in this rare pediatric disease may be life-altering, even life-saving, for many affected.

This review gives an overview of the current concepts regarding PFIC, the genetic background, pathophysiology, clinical features and areas of treatment with a focus on recent therapeutic developments and perspectives intended to optimally care for all children suffering from this disorder.

2. Epidemiology

Progressive Familial Intrahepatic Cholestasis (PFIC) is a rare genetic liver disorder that represents a small but significant fraction of global pediatriccholestatic diseases. The incidence is estimated to be between 1 in ~50,000 and 1 in 100,000 live births but the true prevalence may be even higher due to underdiagnosis and lack of access to genetic testing in many regions. The typical pattern of inheritance is autosomal recessive, and since it can be found in several regions across the world, including where consanguinity is prevalent.

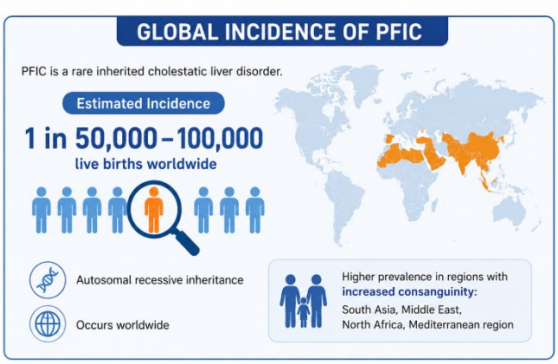

Figure 1: Global Incidence of PFIC

The condition commonly becomes apparent in infancy or early childhood, although the age of presentation is dependent upon the underlying genetic subtype. PFIC types 1 and 2 typically manifest by the first year of life, frequently associated with a more rapid clinical progression, whereas PFIC type 3 can be diagnosed later in childhood or adolescence. There is equal inheritance for males and females (the disorder is not sex-linked).

In recent years, acknowledgment of PFIC and its molecular basis has improved considerably with advances in molecular diagnostics. Most common monogenetic causes emerge from higher-centered, specialized pediatrichepatology studies which have identified the following mutations ATP8B1, ABCB11 and ABCB4.. PFIC is now well-established as an important etiological factor of chronic cholestatic liver disease and paediatric liver transplantation in some countries, including India. Data from Tertiary Care Centres show that PFIC2 and PFIC3 are the most commonly diagnosed affected subtypes in children.

PFIC is more than just a burden of liver complications. Chronic cholestasis, severe itching (pruritus), malnutrition and stunted growth lead to a decreased quality of life in patients as well as caregivers due to repeated hospitalizations. PFIC continues to represent one of the most important causes of morbidity and liver transplantation in children, although advances have occurred in diagnosis and management. That said, ongoing progress in the field of genomics may ultimately lead to more effective targeted therapies and a renewed interest in early genetic screening of at-risk children in the years ahead that can help limit progression of disease and complications later into life.

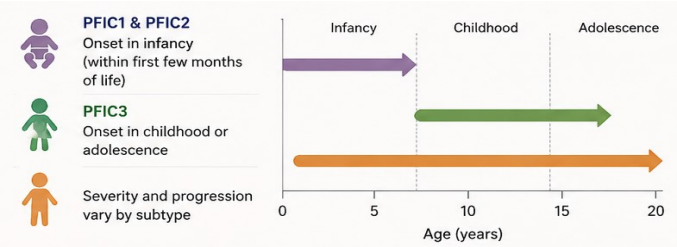

Figure 2: Age of Onset

3. Causes

The causes of progressive familial intrahepatic cholestasis (PFIC) are inherited mutations that particularly affect the transport and/or secretion of various constituents of bile from hepatocytes into the bile canaliculi. These genetic defects in bile flow cause the bile acids to accumulate within the liver. Continuous bile acid retention induces hepatocellular injury, inflammatory processes, fibrosis and progressive liver dysfunction. Mutations in ATP8B1, ABCB11, and ABCB4 are linked to the most classical forms of PFIC that each exhibit a unique molecular defect and clinical phenotypes.

3.1. FIC1-deficiency-related Phospholipid Translocation and Defective Membrane Stability (PFIC1)

PFIC type 1 is caused by mutations in the ATP8B1, which expresses Familial Intrahepatic Cholestasis Protein 1 (FIC1). This protein acts as a phospholipid flippase and is necessary for maintaining he structural organization and lipid composition of the canalicular membrane. Membrane integrity is important for efficient bile generation and transport function.

The loss of FIC1 function perturbs membrane organization and increases the susceptibility of hepatocytes to cytotoxic effects induced by accumulating bile acids. With cholestasis, as bile secretion is compromised, the liver continues to become increasingly injured. As ATP8B1 is expressed in many extrahepatic tissues, patients can also get chronic diarrhea and pancreatitis, growth retardation and hearing abnormalities. The onset of clinical manifestations typically occurs in infancy and is generally characterized by prolonged jaundice, debilitating pruritus, malabsorption, and a failure to thrive.

3.2. Bile acid transportation dysfunction – BSEP deficiency (PFIC2)

PFIC type 2 is due to mutations in the ABCB11 gene that encodes the bile salt export pump (BSEP). Bile salt export pump (BSEP) is the major bile acid extrusion transporter from hepatocyte to the canaliculus. This transport process is essential to the normal flow of bile and prevention of intracellular bile acid accumulation. BSEP deficiency or dysfunction leads to defective bile acid excretion and toxic bile acids build up in hepatocytes. These accumulated bile acids can cause oxidative stress, mitochondrial dysfunction, inflammation and apoptosis of hepatocyte which promotes progressive hepatic injury. Among these four types, PFIC2 is considered the most severe form of the disease and what typically presents in infancy with a triad of varying degree pruritus, jaundice, hepatomegaly and growth failure. Affected children are at increased risk of developing cirrhosis, hepatic failure and occasionally hepatocellular carcinoma at a young age.

3.3. MDR3 Deficiency Phosphatidylcholine Phospholipid Secretion Defect (PFIC3)

PFIC type 3 is caused by mutations to the ABCB4 gene that encodes Multidrug Resistance Protein 3 (MDR3). The bile component phosphatidylcholine is taken up into bile by MDR3. Phosphatidylcholine [PC] joins bile acids to form mixed micelles which shield the biliary epithelium from bile acidss emulsification damage.

Impairment of MDR3 function reduces phosphatidylcholine secretion, leading to bile with increased detergent activity. This harmful bile damages the biliary epithelium, resulting in a cascade of severe chronic injury leading to inflammation, cholangiocyte proliferation and ductular reaction plus scarring (fibrosis), culminating in an irrevocable cholestatic liver disease. PFIC, like PFIC1 and PFIC2, presents as cholestasis; however PFIC3 is typically associated with high gamma-glutamyltransferase (GGT) levels, and presents in later childhood or adolescence. Clinical features includes pruritus, jaundice, hepatosplenomegaly, portal hypertension and gallstones formation. Ursodeoxycholic acid therapy results in partial clinical response in some patients, but liver transplantation is often necessary with longer follow-up in advanced cases.

3.4. Additional Genetic Causes

While ATP8B1, ABCB11 and ABCB4 mutations represent classical genetic causes of Progressive Familial Intrahepatic Cholestasis (PFIC), the development of these fields has led to major advances regarding previously unrecognised genetic factors for PFIC. Many more additional genes have been identified that cause PFIC-like cholestatic disorders by influencing bile secretion, hepatocyte polarity and canalicular membrane integrity. These findings underline the genetic variability of PFIC and have increased diagnostic and phenotype classification accuracy.

TJP2 Deficiency (PFIC4)

Well, a couple of things first is that mutations in TJP2 gene which encodes Tight Junction Protein 2 reversibly destabilizes tight junctions between hepatocytes. Disruption of tight junctions promotes the leakage of bile components into the liver parenchyma, leading to hepatocyte injury, inflammation and progressive fibrosis. Patients frequently present with cholestasis in infancy or childhood and may develop early liver cirrhosis.

FXR Deficiency (PFIC5)

Hepatocyte-specific loss-of-function mutations of NR1H4 result in the deficiency of Farnesoid X Receptor (FXR) which is a member of the nuclear receptor family and regulates bile acid synthesis, transport and homeostasis [2]. Reduction of FXR action leads to bile acid overloading in the hepatocyte and additive severity of cholestatic liver disease. Patients can often develop cholestasis at a young age and progressive liver dysfunction.

MYO5B-Associated Cholestasis (PFIC6)

MYO5B (myosin Vb) functions in intracellular trafficking and plays a role in the appropriate localization of bile transport proteins. Mutations in this gene disrupt the trafficking of transporters to the canalicular membrane, leading to abnormal bile secretion. Clinically, the manifestations are quite heterogeneous, from cholestasis representation to more complex syndromes related to intestinal dysfunction.

USP53 Deficiency

Recently, variants of the USP53 gene have been implicated to cholestatic liver disease5. While the mechanism is poorly understood, USP53 is thought to function in some maintenance of tight junction stability. Loss of function might result in bile leakage or cholestasis, as well as chronic hepatic injury.

Other Emerging Genetic Defects

Other genes such as KIF12, SLC51A and ZFYVE19 have also been associated with uncommon dominant hereditary cholestasis. Additional studies are still being conducted to identify new genetic mutations affecting bile acid transport and liver function. These discoveries are enhancing knowledge of the mechanisms underlying diseases, while potentially paving the way for tailored therapeutic methods.

The description of these new genetic aetiologies has expanded our classification of PFIC, and highlights the value of extensive genetic investigation in children presenting with unexplained cholestatic liver disease. Timely and accurate molecular diagnosis is fundamental for prognostication, selection of treatment and genetic counseling of the affected families.

3.5.Genetic Basis and Types of PFIC

PFIC can be classified into several types depending on the mutated gene and the function of the affected protein:

PFIC Type	Gene Defect	Protein Affected	Function Normally
PFIC1	ATP8B1	FIC1 (familial intrahepatic cholestasis 1 protein)	Maintains bile canalicular membrane stability & phospholipid flipping
PFIC2	ABCB11	BSEP (Bile Salt Export Pump)	Exports bile acids from liver cells into bile canaliculi
PFIC3	ABCB4	MDR3 (Multidrug Resistance Protein 3)	Transports phosphatidylcholine into bile to protect bile ducts

Table 1: Genetic basis and types of PFIC

Genetic mutations in these genes lead to aberrant bile flow which present in different disease severities. PFIC1 and PFIC2 often appears in the first months of life associated with severe pruritus an early cirrhosis, however PFIC3 can appear later in childhood or adolescent years with elevated gamma-glutamyltransferase (GGT) levels.

4. Pathophysiology

4.1. Normal Bile Formation and Enterohepatic Circulation

Bile acids are synthesised from cholesterol in hepatocytes and are crucial for the digestion and absorption of dietary lipids. After their synthesis, bile acids are exported into bile canaliculi across the canalicular membrane through the action of a limited number of specific transport proteins. Bile then travels down the biliary tract into the intestine, where it helps to emulsify and absorb fat.

Most bile acids are reabsorbed by the terminal ileum after their digestive function is performed, and delivered back to the liver via portal circulation. This efficient recycling process is called enterohepatic circulation that recycles bile acids and maintains bile acid homeostasis. Under physiological conditions, balance of bile acid synthesis, secretion and re-absorption prevent toxic accumulation within hepatocytes while maintaining normal liver function.

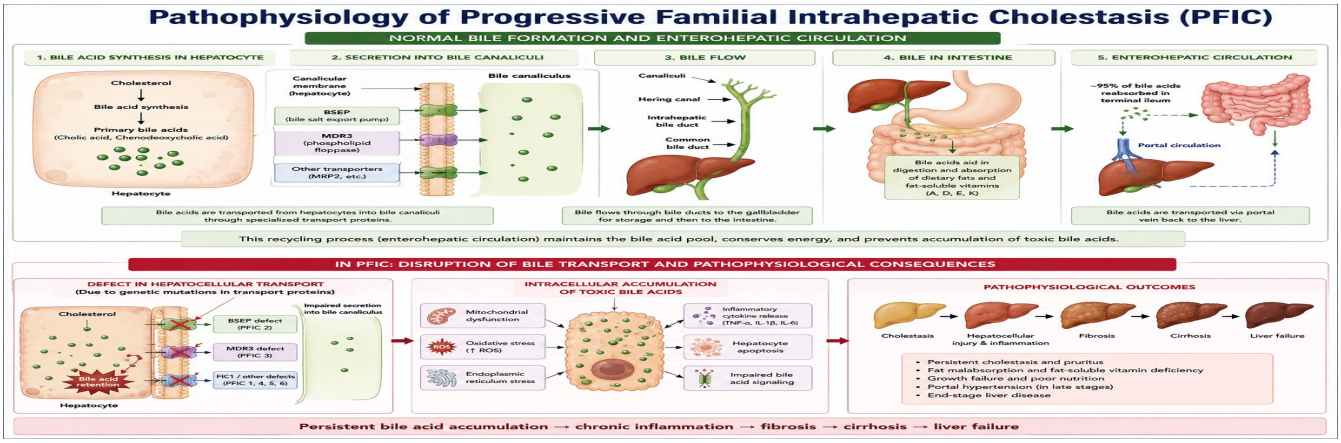

Figure 3: Normal Bile Formation and Enterohepatic Circulation

4.2. Impaired Canalicular Membrane Function in PFIC1

Loss-of-function mutations in ATP8B1, which encodes FIC1 protein, leads to PFIC type 1. FIC1 plays a role in keeping structural integrity and phospholipid asymmetry of the canalicular membrane. These roles ensure the functionality of membrane stability and underlying bile transport proteins.

Defective FIC1 compromises membrane integrity, leading to decreased bile secretion and increased vulnerability of hepatocytes to bile acid-induced injury. Chronic cholestasis associated with accumulation of bile acids in the liver occurs first, leading to inflammation and progressive hepatic injury. Because ATP8B1 is expressed in multiple extrahepatic tissues, some patients may present with features of liver disease in addition to chronic diarrhea, pancreatic dysfunction and growth impairment.

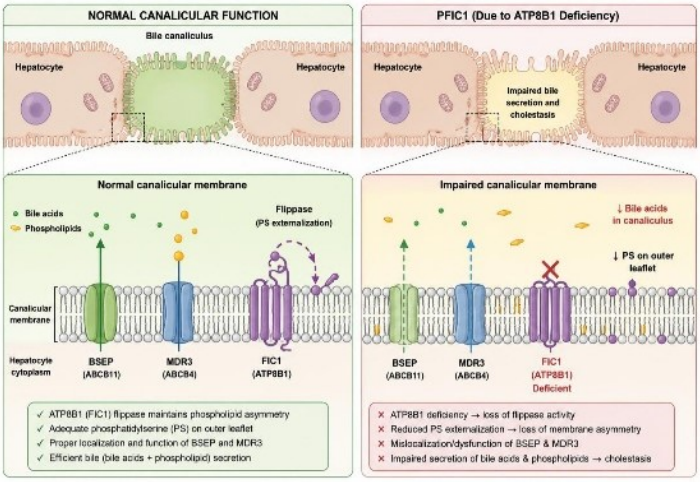

Figure 4: Impaired Canalicular Membrane Function in PFIC1

4.3. Defective Bile Acid Excretion in PFIC2

PFIC type 2 is due to mutations in the ABCB11 gene surrounding Bile Salt Export Pump (BSEP). Bile salts export pump (BSEP) is the main bile acids export channel, transporting them from hepatocytes to the bile canaliculi. Bile salt export pump (BSEP) loss of function, as occurs in cholestatic liver diseases, markedly impairs bile acid excretion and causes toxic biliary accumulation and intracellular retention of hydrophobic bile acids.

Bile acid overload at the cellular level triggers many cell injury pathways, including oxidative stress and mitochondrial dysfunction, and inflammatory mediators. Continued hepatocellular injury drives fibrosis and leads to progression towards cirrhosis. PFIC2 may have a more aggressive clinical trajectory in comparison to other PFIC subtypes, while patient-related liver failure can occur during early childhood. In addition, chronic cell damage generally predisposes patients to hepatocellular carcinoma.

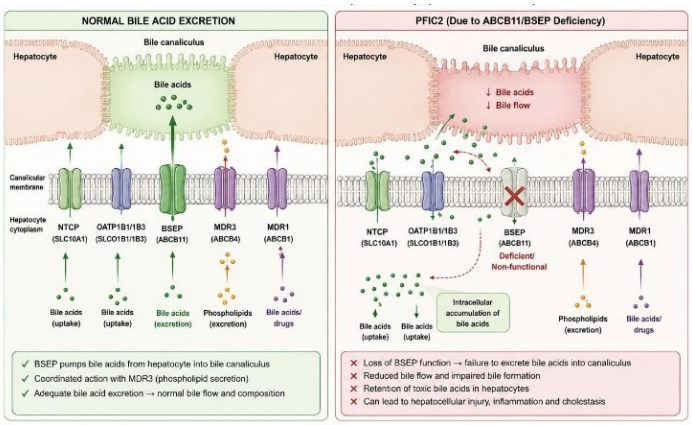

Figure 5: Defective Bile Acid Excretion in PFIC2

4.4. Toxic Bile Composition in PFIC3

Example of acquiring PFIC type 3PFIC type 3 is the result of mutations in which the ABCB4 gene, encodes Multidrug Resistance Protein 3 (MDR3) Phosphatidylcholine (PC) secretion into bile is mediated by MDR3, which coalesces with bile acids and facilitates the formation of protective mixed micelles. They also reduce the detergent effect of bile acids on biliary epithelium by forming these micelles.

Impaired MDR3 function results in decreased phosphatidylcholine secretion, leading to a more toxic bile environment for the bile ducts. Chronic exposure of the biliary epithelium to injurious bile acids induces epithelial damage, inflammation and ductular expansion. These alterations eventually lead to progressive fibrosis and chronic liver disease [6]. In contrast to PFIC1 and PFIC2, which are typically associated with normal or only mildly elevated GGT levels due to lack of a bile duct injury signal in the absence of adequate canalicular bile flow, PFIC3 is specifically characterized by substantially increased GGT levels consistent with trafficking defects also resulting in ongoing bile duct injury.

The molecular defects that underlie PFIC disrupt normal bile formation and transport in a manner that cumulatively leads to chronic cholestasis and progressive liver injury. Although the underlyingmechanisms are subtype specific, there is a central role for sustained bile acid-mediated toxicity in progression of all these diseases and their complications.

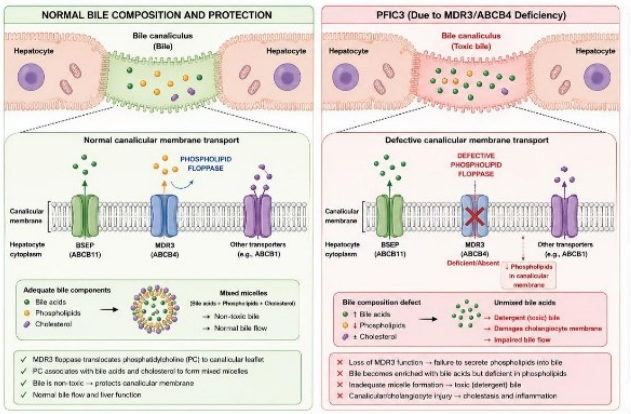

Figure 6: Toxic Bile Composition in PFIC3

4.5. Cellular Mechanisms of Hepatocellular Injury

In PFIC, the intracellular accumulation of bile acids due to defective bile transport is the main process that leads to the progression of liver damage. In the absence of any pathologies, bile acids are involved throughout digestion and readily excreted into the biliary system. Yet, inhibition of bile formation results in persistent accumulation of bile acids in hepatocytes triggering cellular signaling pathways implicated in liver injury.

Top among them is the production of reactive oxygen species, ROS, which causes oxidative stress that harms proteins, lipids and nucleic acids within cells. However, excessive oxidative stress exceeds the antioxidant capacity of cells and therefore disrupts normal cellular functions and predisposes hepatocytes to injury.

So mitochondrial dysfunction is also a key component in the disease evolution. Toxic bile acids cause mitochondrial membrane dysfunction, decrease ATP production and lower cellular energy availability. This metabolic abnormality leads to hepatocyte dysfunction and cell death.

Moreover, increased bile acids may induce endoplasmic reticulum (ER) stress due to its impact on normal protein folding and processing. Chronic stress responses trigger inflammatory signaling cascades and induce apoptosis. Damaged hepatocytes secrete cytokines and chemokines which attract inflammatory cells to the liver, causing more tissue damage.

The synergistic effects of oxidative stress, mitochondrial impairment along with inflammation and apoptosis lead to a progressive loss of functioning hepatocytes. An ultimately progressive series of pathological processes underlies cholestasis, chronic liver injury, and advanced liver disease over time.

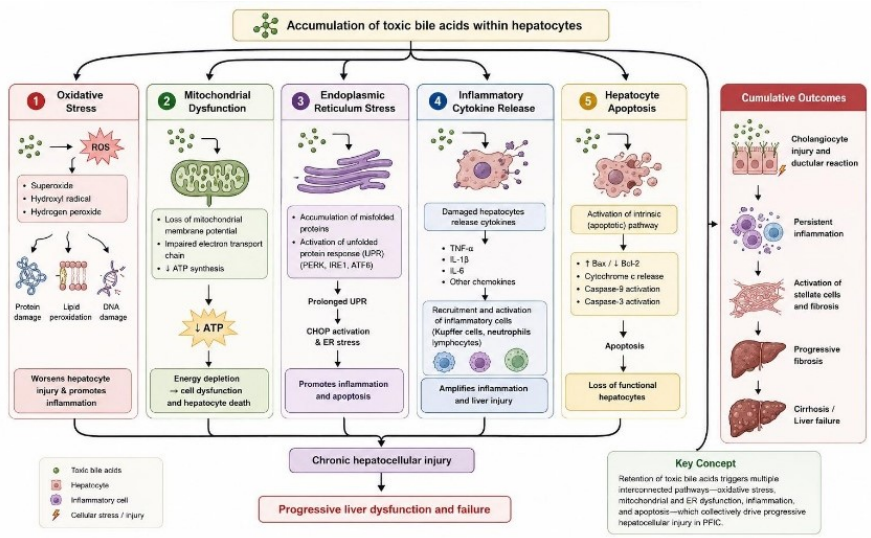

Figure 7: Cellular Mechanisms of Hepatocellular Injury

4.6. Development of Fibrosis and Cirrhosis

After time the injurious stimuli lead to continued hepatocellular injury, followed by chronic inflammation which triggers a wound-healing response in the liver. Kupffer cells, which are the resident macrophages of the liver, release pro-inflammatory and profibrogenic mediators in response to repeating stimulation by toxic bile acids. These mediators activate hepatic stellate cells and change them into collagen-producing myofibroblasts.

Activated stellate cells secrete large quantities of matrix proteins including collagen into the liver. With advancing fibrosis, the normal liver architecture is progressively distorted, which in turn disrupts hepatic blood flow and impairs liver function.

Fibrosis manifests to varying degrees and occurs at different rates for PFIC subtypes but persistent cholestatic injury ultimately results in the development of regenerative nodules encircled by fibrotic tissue, a pathognomonic feature of cirrhosis. Cirrhotic change is associated with many, debilitating clinical sequelae including portal hypertension, splenomegaly, ascites, variceal bleeding in addition to coagulopathy and hepatic encephalopathy [1].

In its most severe form it is called acute liver failure and the liver stops performing essential metabolic and synthetic functions. Liver transplantation continues to be the standard treatment for many patients with end-stage disease. Thus, elucidating the underlying pathophysiologic mechanisms of fibrosis and cirrhosis is crucial for formulating therapies to prevent disease progression and optimize long-term outcomes in PFIC-affected children.

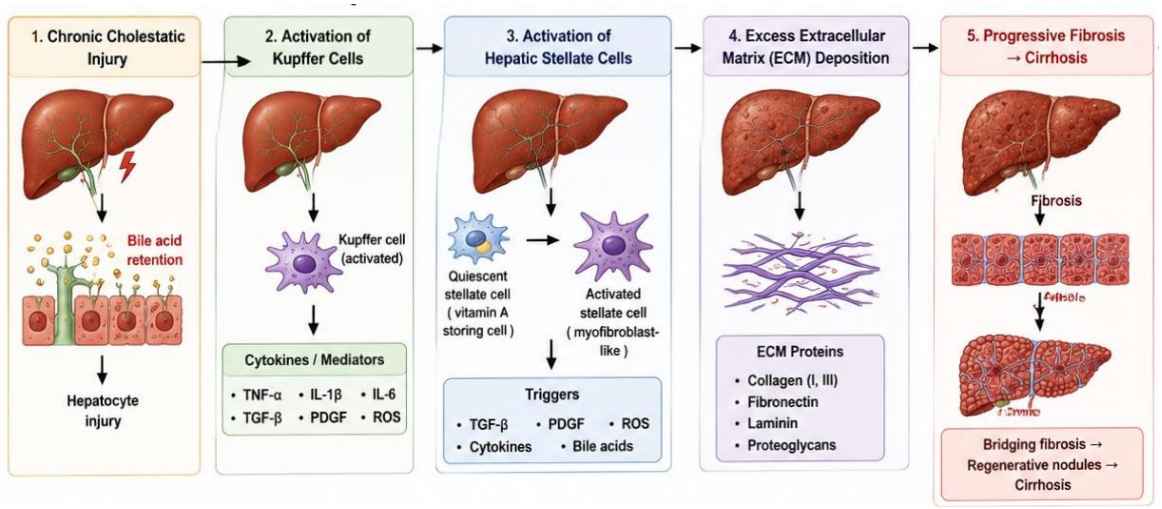

Figure 8: Development of Fibrosis and Cirrhosis

5. Clinical Manifestations

Clinical presentation of PFIC is largely dependent on both the severity of cholestasis and the genetic defect themselves. Patients often begin showing symptoms in infancy or early childhood, but the age at which symptoms develop varies by subtype of PFIC. The disease involves a gradual impairment of bile flow, leading to bile acid retention in the liver and blood.

Prolonged jaundice is often one of the first clinical signs, followed by dark urine and pale stools due to decreased biliary excretion of bilirubin. Severe pruritus is a characteristic sign of PFIC and often poses the most difficult symptom to alleviate in children with this disorder. Associated problems: — chronic itch may cause excoriations, sleep disturbances, irritability, and behavioral changes and there is a serious decrease in quality of life.

Hepatomegaly is frequently seen as a result of continued liver injury, and the later-development splenomegaly may be due to portal hypertension. Children with chronic liver disease and disturbed fat absorption often suffer from poor weight gain, growth retardation, and failure to thrive.

The most significant consequence of long-standing cholestasis is the deficiency of fat soluble vitamins, particularly A, D, E and K. These deficiencies can present with visual changes, rickets/osteopenia, neuromuscular disturbances and bleeding. Nutritional deficiency also results in delayed physical growth and higher risk of infections.

Absnormalities on laboratory testing usually consist of high serum bile acid concentrations, conjugated hyperbilirubinemia and hepatic enzyme elevation to develop. Gamma-glutamyltransferase (GGT) values are valuable diagnostic clues, with a normal or low value in PFIC1 and PFIC2, and an elevated value is characteristic of PFIC3.

In advanced diseases, hepatic fibrosis can progress to cirrhosis and portal hypertension. Consequently, patients with advanced disease may develop complications including ascites, varicealhemorrhage, coagulopathy, recurrent infections and so-called hepatic encephalopathy. In severe cases this can result in progressive liver failure and the need for a liver transplant due to end stage liver disease.

PFIC clinical spectrum varies from pure cholestasis with mild symptoms to aggressively progressive liver disease. Thus, The early recognition of the distinctive clinical hallmarks are crucial to offer a quick diagnosis and genetic assessment, and treatment.

Clinical Feature	Manifestation
Cholestasis	Persistent jaundice, dark urine, pale stools
Pruritus	Severe itching, sleep disturbance, irritability
Growth & Nutrition	Failure to thrive, malnutrition, growth retardation
Hepatic Findings	Hepatomegaly, splenomegaly
Vitamin Deficiencies	Vitamins A, D, E, K deficiency
Advanced Disease	Fibrosis, cirrhosis, portal hypertension
End-stage Complications	Ascites, variceal bleeding, hepatic encephalopathy, liver failure

Table 2: Major Clinical Manifestations of PFIC

6. Current Management Approaches

Treatment of PFIC focuses on alleviating cholestasis, controlling symptoms, preventing nutritional deficiencies and/or arresting disease progression in order to improve quality of life. Treatment strategies depend on disease severity, genetic subtype and responses to therapy. Management is mainly supportive, with pharmacological treatment, and at later stages the use of surgical procedures or liver transplantation.

6.1. Supportive and Medical Therapy

Supportive and medical therapy are extremely effective in alleviating the symptoms of PFIC, improving nutritional status, and enhancing the health related quality o life (HRQOL) and overall well-being of a child. Because chronic cholestasis hampers fat digestion and absorption, patients typically develop malnutrition and deficiencies of vitamin A, D, E, and K (especially in children).

Nutritional Optimization

Because PFIC reduces the flow of bile, these children are prone to malnutrition owing to disturbed fat digestion and absorption. Nutritional support thus represents an integral aspect of management. High-calorie diets supplemented with medium-chain triglycerides (MCTs) are typically advised, as they can be absorbed without the need for bile acids. Fat soluble vitamins (A, D, E and K) supplementation is crucial for avoid complications from vitamin deficiency as well is important to achieve normal growth and development.

Management of Pruritis

PFIC is often associated with pruritus, which may be the most troubling of its symptoms (eg, sleep disturbance and teasing/social difficulties) significantly impairing quality of life. A variety of pharmacological agents are utilized to relieve pruritus and enhance patient comfort. Cholestyramine inhibits intestinal bile acid reabsorption; rifampicin induces hepatic metabolism and removal of pruritogenic compounds. Antihistamines may be given as adjunctive therapy especially in order to improve sleep, however the effect on cholestatic pruritus alone is usually rather limited.

Ursodeoxycholic Acid Therapy

Ursodeoxycholic acid (UDCA) is still one of the most popularly used drugs in PFIC management. With regulation of the bile flow, it acts in reducing hydrophobic bile acids and also has an important cytoprotective effect for hepatocytes and cholangiocytes. Improvement in biochemical parameters with UDCA is most apparent in PFIC3 and may ameliorate disease progression. As a result response to treatment is variant in different PFIC subtypes.

6.2. Surgical Interventions

Surgical treatments are reserved for those who either have more advanced disease that medical therapy cannot adequately control or in whom supportive treatment has proven ineffective.

Partial Biliary Diversion Procedures

In patients with refractory cholestasis and debilitating pruritus despite maximal medical therapy, surgical disruption of the enterohepatic circulation may be an option. Partial external biliary diversion (PEBD) and partial internal biliary diversion (PIBD) decrease intestinal absorption of bile acids so as to reduce hepatic accumulation of bile acid.

All of these approaches have been linked with symptomatic relief (including pruritus, serum bile acid concentrations, liver function parameters and health-related quality of life). The maximum advantage is typically seen when surgical treatment precedes the initial advancement of moderate fibrosis or cirrhosis.

Liver Transplantation

Liver transplantation is still the only curative option for early stage patients with end-stage liver disease, decompensated cirrhosis, severe growth failure or intractable pruritus unresponsive to medical and surgical therapies. By addressing the intrinsically faulty liver, transplantation restores normal secretion and excretion of bile and represents a substantial improvement in both survival and quality of life.

Although liver transplantation is the only curative treatment for patients with end-stage liver disease, it carries a substantial burden of perioperative risk, the need for lifelong immunosuppressive therapy to prevent graft rejection and increased risk of opportunistic infections. As a result, much research is still directed towards developing less invasive and more targeted therapeutic.

6.3. Multidisciplinary Care

PFIC management relies on a multidisciplinary team of pediatrichepatologists, gastroenterologists, dietitians, surgeons and genetic counselors as well as clinical pharmacists. Monitoring of growth parameters, nutritional status, liver function & treatment response is essential for providing the best outcomes. Prompt patient evaluation and customized therapy can postpone the advancement of liver illness and lower the need for whole organ transplant.

While the management strategies in current practice have undoubtedly improved outcomes for patients, they largely mitigate the effects of impaired bile flow rather than directly targeting the underlying genetic defect. This limitation has prompted the development of new targeted therapies, such as ileal bile acid transporter (IBAT) inhibitors and gene-based therapies, which may change the future management of PFIC.

Treatment Approach	Purpose	Clinical Benefit
Nutritional support and vitamin supplementation	Correct malnutrition and vitamin deficiencies	Improved growth and development
Ursodeoxycholic acid (UDCA)	Enhance bile flow and reduce bile toxicity	Delays disease progression, especially in PFIC3
Cholestyramine	Reduces intestinal bile acid reabsorption	Relief of pruritus
Rifampicin	Enhances bile acid metabolism	Reduction of itching
PEBD / PIBD	Interrupt enterohepatic circulation	Improved pruritus and liver function
Liver transplantation	Replacement of diseased liver	Curative option for advanced disease

Table 3 : Current Management Approaches in PFIC

7. Emerging medical advances – IBAT inhibitors

New treatments for Progressive Familial Intrahepatic Cholestasis (PFIC) have concentrated on targeting bile acids as they are the key pathogenic mediators of hepatic injury in PFIC. Among these new treatments, Ileal Bile Acid Transporter (IBAT) inhibitors are small molecules that inhibit the absorption of bile acids in the gut and have raised interest as a potential non-surgical approach to reducing cholestasis in patients with PFIC.

The ileal bile acid transporter (IBAT), which is also called the apical sodium-dependent bile acid transporter (ASBT), is present at the terminal ileum and mediates several steps of reuptake from the intestinal lumen of bile acids. Approximately 95% of bile acids are absorbed and returned to the liver through an enterohepatic circulation under normal physiological conditions. In PFIC the impaired secretion of bile causes accumulation of toxic bile acids in hepatocytes resulting in progressive liver damage and severe pruritus. Further recycling of bile acids further increases hepatic burden and can promote disease progression.

IBAT inhibitors work by selectively inhibiting ileal bile acid re-absorption. Such interruption of the enterohepatic circulation leads to enhanced fecal elimination of bile salts and reduces return back to liver. This specialized enterohepatic recirculation in turn reduces the amplitude of hepatic bile acid accumulation, which helps to resolve cholestasis and mitigate continued hepatocellular injury.

Of the agents which are now in development, odevixibat and maralixibat have shown significant promise to date in children with PFIC. Clinical studies have demonstrated marked decreases in serum bile acid levels along with improvements in pruritus severity. Especially important is the relief of itching, as chronic pruritus is one of the most disabling PFIC symptoms and severely affects sleep quality, emotional status, and general quality of life.

Besides alleviating symptoms, treatment with IBAT inhibitors have demonstrated to improve growth parameters, nutritional status and functioning in everyday life. Such benefits may diminish indications for surgical interventions such as biliary diversion and postpone progression to liver transplantation in some patients.

IBAT inhibitors are generally well tolerated. Diarrhea, abdominal pain and mild gastrointestinal (GI) discomfort have been the most frequently reported adverse effects. These generally can be managed and rarely result in treatment discontinuation. However, longer-term follow-up is still needed to assess continued benefits and any impact on fat-soluble vitamin absorption.

In summary, the emergence of IBAT inhibitors as a class of medicines in PFIC therapy represents an important milestone whereby these agents have not only symptomatic benefit but target a key pathophysiological mechanism. These agents are the subject of ongoing and recently conducted clinical trials and post-marketing studies that will provide an improved understanding of their long-term impact on disease progression, transplant-free survival, and overall prognosis. With the growing body of evidence, it is anticipated that IBAT inhibitors will become a cornerstone treatment for incipient and overt PFIC and may significantly improve health outcomes for affected children.

8. Future safer strategies – gene therapy

Although current treatment options can alleviate symptoms and slow disease progression in Progressive Familial Intrahepatic Cholestasis (PFIC), they do not correct the underlying genetic abnormalities responsible for the disorder. Advances in molecular medicine have therefore shifted attention toward gene therapy as a potential disease-modifying and curative approach. By targeting the root cause of PFIC, gene therapy offers the possibility of restoring

normal bile secretion and preventing the progression of chronic liver disease.

In gene therapy, a normal copy of an abnormal or nonfunctional gene is introduced into hepatocytes to restore the synthesis of important bile transport proteins. Of the different delivery systems currently being explored, adeno-associated virus (AAV) vectors have recently emerged as one of the most successful platforms due to their relative safety over other gene therapy modalities, low immunogenicity and ability to achieve high levels of transcription in liver cells.

8.1. AAV- Mediated Gene Delivery

Adeno associated viruses: Small, non-pathogenic viral vectors that are well studied and frequently used for gene therapy due to their good safety profile and ability to efficiently deliver genetic material specifically to liver tissue. Here, these vectors are engineered to deliver a normal copy of the mutant gene associated with PFIC disease (ATP8B1, ABCB11, ABCB4).

After administration, the AAV vector carries the therapeutic gene to liver where it enters hepatocytes and provides the necessary genetic material needed for protein production. Thanks to their low immunogenicity and low risk of genomic disruption compared with other delivery systems, AAV vectors are especially attractive for pediatric applications. This gene expression lasting support, sequentially improves, on

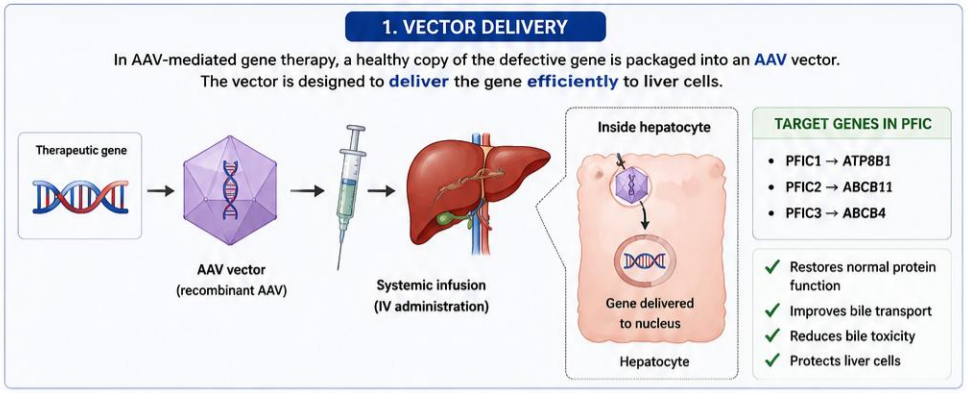

Figure 9: Vector Delivery

8.2. Targeting Hepatocytes

Successful delivery of the therapeutic gene to hepatocytes (the main biliary-producing and secreting cells) is critical for effective gene therapy. Adeno-associated virus (AAV) vectors have a natural propensity to spread towards liver, allowing in vivo targeted delivery to hepatocytes following intravenous administration.

Inside the cell, however, the therapeutic gene is delivered to the nucleus, but it assumes an episomal form and stays mainly as an unrecombined transgene rather than integrating into the host genome. This minimizes the potential for insertional mutations but enables continued expression of the protein secreted by the transduced cells. Because correction of the transport defects leading to PFIC can restore critical bile acid handling and BSEP primary biliary secretion pathways, direct modeling in hepatocytes is particularly beneficial.

Novel constructs are being engineered to leverage liver-targeted delivery, transduction efficiency and durability of expression which may all further enhance the chance of obtaining a clinically meaningfultherapeutic effect.

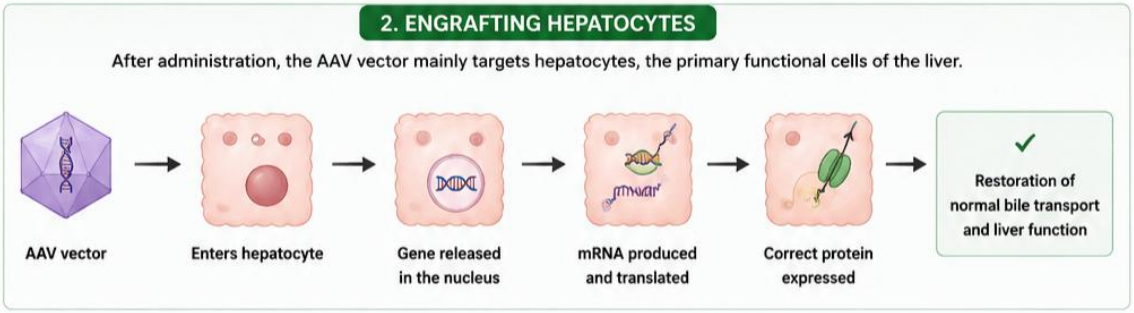

Figure 10: Targeting Hepatocytes

8.3. Restoration of Protein Function

Gene Therapy: One of the main goals is to correct or restore expression and function of proteins that are not produced properly because of genetic mutation. With restoration of the transport protein through a functional gene delivery to hepatocytes, they are able to synthesize the bile secretion transporter and hence reduce cholestasis.

Restoration of MDR3–mediated phosphatidylcholine transport as a result of ABCB4 gene replacement, for example, may restore back to normal bile composition less toxic in nature mitigating injury on the biliary epithelium. In a similar manner, correction of ABCB11 mutations can restore BSEP function in order to facilitate the effective exportation of bile acids from hepatocytes. The restoration of ATP8B1 function might stabilize the canalicular membrane and promote normal bile flow.

Correcting the primary molecular defect has the potential to decrease bile acid overload, prevent on-going liver injury and retard the development of fibrosis while preserving hepatic function. If confirmed safe and effective in proper clinical trials, this strategy may be able to decrease the reliance on liver transplantation dramatically and provide children with PFIC with a potentially curative treatment option.

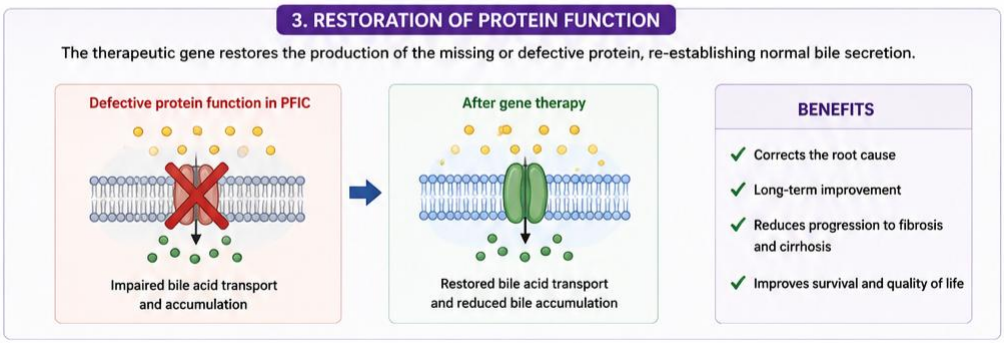

Figure 11: Restoration of Protein Function

8.4. Potential Clinical Benefits

The data from these preclinical and phase I–II clinical studies have been very promising, showing improvements in bile secretion (with many of the drugs studied) as well as improved liver histology and biochemical markers of cholestasis. And if verified in larger clinical studies, gene therapy presents certain clearly significant points:

- Fixing The Underlying Genetic Defect
- Decreased hepatic bile acid retention
- Delay or prevention of cirrhosis and fibrosis
- Reduced requirement of liver transplantation
- Increased quality of life and long-term survival
- Tailor therapies based on genetic subtype

Gene therapy, whereby the underlying cause of disease is targeted rather than its sequelae, is one of the cornerstones underlying precision medicine in paediatric hepatology.

9. Discussion

Background: Progressive Familial Intrahepatic Cholestasis (PFIC) is a rare disorder with few prospective studies, and as such they represent a difficult but important group of inherited cholestatic diseases, commonly associated with considerable morbidity and early progression to end-stage liver disease. Since then, advancements in molecular genetics have significantly advanced the understanding of disease mechanisms that has improved PFIC subtype classification and assisted in development of mechanism-based treatments.

Management of PFIC has traditionally focused on supportive care to control symptoms, improve nutritional status and slow disease progression. Nutritional supplementation, ursodeoxycholic acid therapy and antipruritic agents are still important therapeutic approaches, especially in the early stages of disease. Nevertheless, these treatments mostly ameliorate the clinical manifestations of cholestasis rather than correct the underlying genetic defect.

Ileal bile acid transporter (IBAT) inhibitors were the first major breakthrough in PFIC treatment. These agents directly inhibit a major pathogenic mechanism of cholestatic liver injury through reducing enterohepatic recycling of bile acids. Excelent tests have been developed able to securely reduce serum bile acid concentrations and improve pruritus, sleep quality, and the overall quality of life in patients with cholestatic liver diseases. Thus, the conclusion of these results is that selective pharmacological therapies may play a role in alleviating disease burden and postponing surgical method options.

Another area of great promise is the use of gene therapy in pediatrichepatology. In contrast to conventional therapies, gene-based events aim at correcting the molecular deficiencies mediating defective bile secretion. Gene delivery approaches via the AAV have improved over the past two decades and, while these advances are still at a relatively early stage of development for ABCB4-associated disease, preclinical results are promising. The remaining challenges include long-term safety, durability of expression, immune responses to transgenes and ease of access to treatment, all obstacles before gene therapy could change PFIC care from symptom relief to disease modification.

However, despite these advances in the therapy approaches, numerous limitations still contribute to unsatisfying clinical outcomes for patients. Owing to the delay of diagnosis, mild availability of genetic testing &high cost therapy,limited access to specialized healthcare are still big hurdles due insufficient resources. In addition, information on the long-term efficacy of newer therapies are evolving still. Ongoing clinical trials, multidisciplinary international networks and the incorporation of tailored therapeutic approaches based on genomic alteration specificities will be critical to improve the prognosis for affected children.

In summary, the new landscape in PFIC combines a transition from supportive care towards targeted molecular therapies. More research is being conducted, and as science advances over time, these treatment avenues may prove to be safer, more effective methods of care or even a cure for patients with this rare but potentially deadly liver disorder.

10. Conclusion

Progressive Familial Intrahepatic Cholestasis (PFIC) is a group of rare but severe inherited liver diseases that are characterized by impaired bile secretion due to genetics, chronic cholestasis leading to progressive hepatic injury. Without treatment, the disease can progress to fibrosis, cirrhosis, liver failure, and a significant decrease in quality of life. The most important step is the subclassification of PFIC types to allow therapeutic choices and genomic diagnosis should be done as early as possible, preferably in neonates.

Although survival and symptom control have improved in these patients with the advent of different management strategies, such as nutritional support, ursodeoxycholic acid therapy, antipruritic medications, biliary diversion procedures, and to date even liver transplantation can be offered. However, these methods are typically restricted by limited disease control and the inability to correct the fundamental genetic defect.

Recently, improvements in targeted therapies (e.g., IBAT inhibitors) have opened personalized access to reduce bile acid accumulation less invasively and improve clinical outcomes. At the same time, new advances in gene therapy raise hopes that normal bile transport could eventually be restored at a molecular level with potential for prolonged correction of the disease.

Ultimately, precision medicine—the integration of early genetic diagnosis with targeted therapeutic approaches—is likely to shape the management of PFIC in the years to come. Further exploration of molecular mechanisms, new pharmacological agents and gene-based interventions may subsequently improve prognosis, further decrease the need for liver transplantation and increase long-term health related quality of life in these children. With ongoing scientific progress, more effective and safer treatments for PFIC will soon become reality.

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