For illustrative purposes only. Does not reflect a liver with ChLD.

In cholestatic liver diseases (ChLD) such as PFIC and ALGS...

The symptoms you see are warning signs of the progression you don't

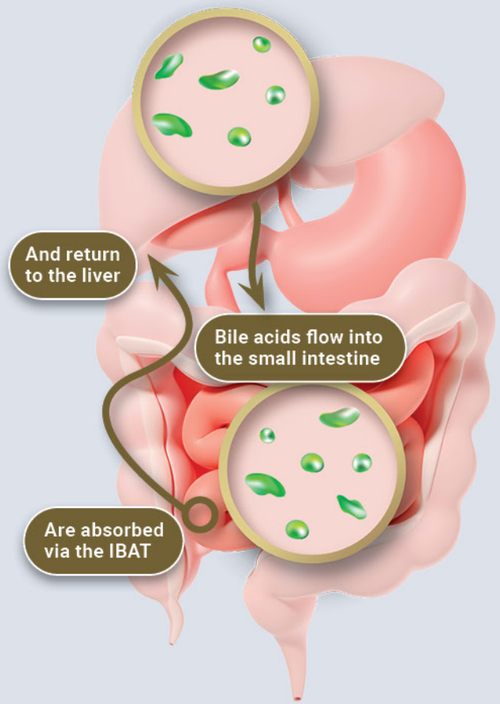
While presentation may vary, pruritus, elevated serum bile acid, and failure to thrive are the classic warning signs of ChLD. Because of its progressive nature, ChLD may advance toward liver damage, end-stage liver disease, and life-altering liver transplantation.[1-8] When you see the signs of danger, don't wait to act.

It's time to see the deeper danger of ChLD.

All images are actor portrayals.

ALGS=Alagille syndrome; PFIC=progressive familial intrahepatic cholestasis; sBA=serum bile acid.

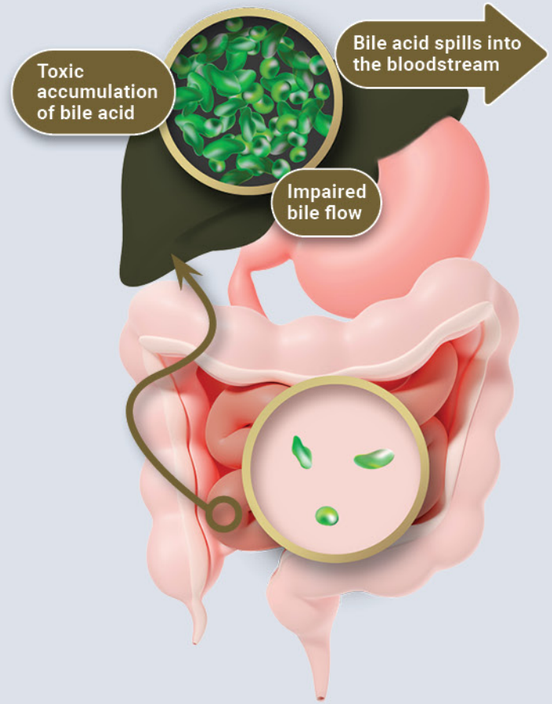
Cholestatic liver diseases (ChLD) are chronic, progressive conditions that require urgent attention



Normal

In physiologic enterohepatic circulation

- Bile acids are synthesized in liver cells and secreted into bile via the bile salt export pump (BSEP)[2]
- Most bile acids are reabsorbed from the terminal ileum via the ileal bile acid transporter (IBAT) and return to the liver via portal circulation[2]



ChLD

In PFIC and ALGS

- Healthy enterohepatic circulation is disrupted by an impairment in bile flow from the liver to the intestines[2,6,10]
- This leads to a toxic accumulation of bile acid as it builds up in the liver, damaging tissues[2]
- Excess bile acid also “spills over” into the bloodstream, elevating sBA[2]

Healthy hepatic and gastrointestinal functions are dependent on proper bile formation and flow.[1,2] Bile acids serve 2 critical functions

1. Helping to dispose of metabolic waste products excreted by the liver[1,9]
2. Emulsifying nutritional lipids to facilitate digestion and absorption[2]

When left untreated, ChLD can progress to liver fibrosis, cirrhosis, liver failure, and even death[2,5,6,8]

Chronic ChLD affects bile flow and can lead to a toxic accumulation in the liver

PFIC

Progressive familial intrahepatic cholestasis

PFIC results in disrupted hepatocyte and/or intrahepatic bile duct function and commonly presents in early infancy but can manifest later in life.[2,3]

10%-15%

of all ChLD cases in children are PFIC, a heterogeneous group of rare, life-threatening, autosomal recessive cholestatic liver diseases.[2,10]

The estimated incidence of PFIC is **1 in every 50,000 to 100,000 births**[3]

In a retrospective analysis of 130 PFIC 1 patients from the NAPPED consortium[11]

of patients with PFIC 1 survived to age 18 with their native liver—without surgery, the likelihood of liver failure is high.[11]

In a retrospective analysis of 264 PFIC 2 patients from the NAPPED consortium[12]

of patients with PFIC 2 survived to age 18 with their native liver—without surgery, the likelihood of liver failure is high.[12]

ALGS

Alagille syndrome

ALGS is a rare, multisystem, autosomal-dominant, life-threatening disease caused by genetic mutations. It is one of the most common forms of an inherited cholestatic liver disease in children.[8,13]

1 in every 30,000 to 45,000 individuals are estimated to have an ALGS diagnosis.[14]

In a retrospective analysis of 1,433 children with clinically and/or genetically confirmed ALGS[15]

of patients with ALGS survived to age 18 with their native liver.[15]

Treating cholestasis is vital to addressing the drastic impact PFIC and ALGS have on patients' overall health and quality of life[2]

ChLD=cholestatic liver diseases; NAPPED=NAtural course and Prognosis of PFIC and Effect of biliary Diversion.

Untreated ChLD results in a variety of severe consequences for patients

Failure to thrive due to insufficient weight gain, delayed growth, and deficient bone health

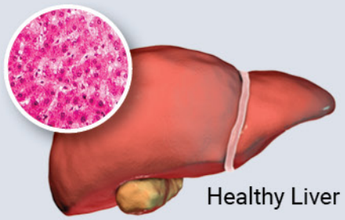
- Cholestasis affects the ability to absorb fat-soluble vitamins (FSV), leading to malnutrition, poor growth, FSV deficiency, risk for weakened bone strength, and fracture[16,17]

Need for surgical intervention

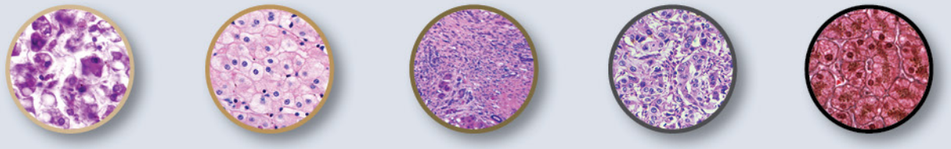
- Diversion procedures can help improve symptoms and delay disease progression, but there are risks involved and it may not completely resolve ChLD symptoms[10,18]
- Eventually liver transplantation may be needed[10,14]

Irreversible progression of liver disease leading to liver transplantation and possible fatal complications

- Fibrosis, cirrhosis, liver failure, and even death may occur if ChLD is not managed[2,5,6,8]



Healthy Liver



Inflammation | Fibrosis | Cirrhosis | Liver Cancer | End-Stage Liver Disease

ALT=alanine aminotransferase; APRI=aspartate aminotransferase to platelet ratio index; AST=aspartate aminotransferase; CB=conjugated bilirubin; ChLD=cholestatic liver diseases.

Recognizing the signals of ChLD early is key to addressing its impact on patients

ChLD can be identified by several common signals associated with disease progression

Elevated sBA

High sBA may be a prognostic biomarker for native liver survival in PFIC 1 and PFIC 2.[11,12]* In ALGS, sBA levels are not always evaluated routinely; however, total bilirubin, ALT, AST, APRI, and CB have been identified as additional prognostic markers for native liver survival.[15]

Cholestatic pruritus, or itch

Cholestatic pruritus may lead to life-altering symptoms, such as cutaneous mutilation, difficulty sleeping, and impaired school performance.[19,20]

Failure to thrive

When a child with ChLD has a height and weight that are significantly below other children of similar age and sex, they may be diagnosed with failure to thrive.[5,6,8,19,21]

Malabsorption, malnutrition, and FSV deficiency are likely the main causes of these growth impairments in PFIC and ALGS.[5,6,8,19,21]

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Does not reflect a liver with ChLD.

Other indicators of ChLD include jaundice and discolored stools

Jaundice occurs when bilirubin, a biliary pigment, accumulates in tissues like the skin, eyes, and mucus membranes. In ChLD, this happens due to improper elimination of biliary substances in the liver.[6,10]

Excretory symptoms are also common, including dark urine and pale, discolored, or acholic stools.[17]

These manifestations lead to an array of physical symptoms and emotional distress, severely impacting quality of life of both patients and caregivers[2,8,10,19,22-24]

*Based on retrospective analyses of 130 PFIC 1 and 264 PFIC 2 patients from the NAPPED consortium.

sBA is one possible indicator of ChLD and may play a role in pruritus

Patients with PFIC and ALGS both present with elevated levels of sBA[3,5,6,19]

Elevated sBA may be linked to pruritus, a signature symptom in PFIC and ALGS[3,5-7,25]

Hypothesized pathogenesis of pruritus

There are numerous possible pruritogens involved in pruritus, including sBA, endogenous opioids, and steroid metabolites. While the exact causes of cholestatic pruritus are unclear, one hypothesis is a causative relationship between elevated sBA and pruritus through multiple pathways.[26]

Cholestatic liver
Bile acids in the liver build up, then spill over into the bloodstream[2]

Skin
Nerve ends under the skin are stimulated[26]

Brain
Nerves send itch signals to the spinal cord and brain[26]

Itch
Increased pruritic response[26]

It is important to know that severity of pruritus differs from patient to patient and may not always directly correlate with their sBA levels[10,25,27]

Pruritus is a classic warning sign of ChLD that may warrant serious and prompt attention[2,28]

ChLD=cholestatic liver diseases.

Pruritus is a debilitating and challenging symptom in ChLD

The impact of pruritus extends beyond scratching and can lead to issues including, but not limited to

- Cutaneous mutilation, scarring[19,20]
- Sleep deprivation[19,20]
- Disrupted school activity[19,20]
- Emotional distress[2,20]
- Impact on caregiver's personal and family activities[22,23]
- Impact on caregiver's employment and finances[22,24,29]

Despite the considerable burden of disease, pruritus is often underreported[30,31]

- Patients experiencing chronic illnesses are motivated to accommodate symptoms
- They often adapt to symptoms like pruritus, minimizing the true impact and accepting symptomatic disease as their new normal

Intractable pruritus is considered the most bothersome symptom of ChLD, interfering with the quality of life of both patients and caregivers[2,19,20,22-24,29]

Pruritus has a substantial impact on activities of daily living

Strong correlations between sleep disturbances and self-reported QoL have been observed in patients with ChLD

60%

of PFIC caregivers report that their child needed soothing or help falling asleep due to itching.[32*]

53%

of ALGS patients and caregivers report difficulty falling asleep due to itching and 59% report difficulties staying asleep.[20†]

When pruritus remains uncontrolled, patients with ChLD also report issues with[7,20,33]

- School performance
- Overall mood
- Daily activities

Failure to thrive due to ChLD causes detrimental delays in growth and development

In PFIC and ALGS, failure to thrive is associated with

- Impaired growth[8,21]
- Poor weight gain[8,21]
- Use of a feeding tube (ALGS patients)[23]

Failure to thrive in PFIC

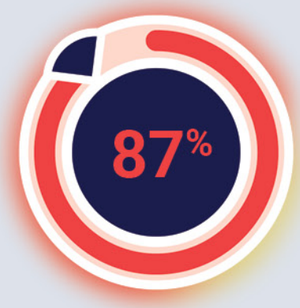
Failure to thrive has been reported in 90% of PFIC 1 patients.[21]

PFIC 1 and PFIC 2 patients may also present with sequelae of vitamin deficiency, including[21]
Coagulopathy • Rickets • Seizures

Failure to thrive in ALGS

Reports of significant growth deficiencies and failure to thrive are as high as 87% in patients with ALGS.[8]

Malabsorption of vital nutrients in patients with ALGS can also lead to[14]
Rickets • Vision problems • Poor coordination
Developmental delays • Blood clotting problems



*Based on responses from 62 caregivers in a study to validate the PRUCISION™ ObsRO tool for patients with PFIC.

†Based on responses from 24 caregivers and 12 patients in a study to validate the PRUCISION™ ObsRO tool for patients with ALGS.

ChLD=cholestatic liver diseases; ObsRO=observer-reported outcomes; QoL=quality of life.

Caregivers and their families share the burden of ChLD

Caring for a child with any rare disease can have a considerable impact on a caregiver's physical and mental health[34]

1 in 3 rate their physical health as fair or poor[34]

In a study of caregivers for children with PFIC[22]

Of the 22 caregivers who participated in the study

86% had difficulty sleeping

82% reported impacts on personal relationships

HOME

Of the 16 caregivers who were currently working a paying job

73% were prevented from progressing in their career or working more hours

36% missed years of employment*

WORK & CAREER

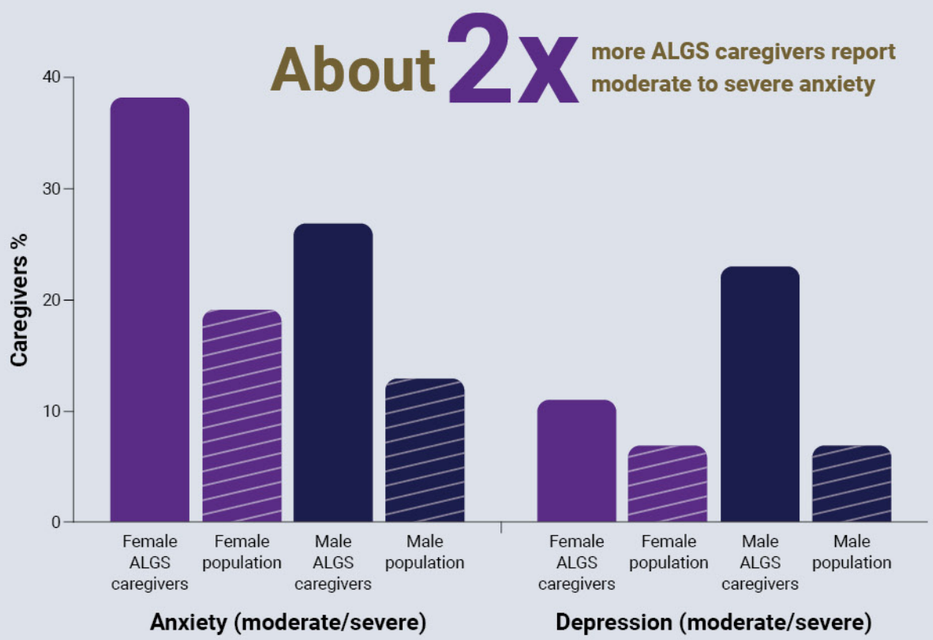
*Missing an average of 2.8 years of employment.
ChLD=cholestatic liver diseases.

Caring for someone with ALGS can take a toll on caregivers

Compared to caregivers within a general population, ALGS caregivers report[23]

- Limitations of personal time
- Increased stress
- Interruption of family activities

A higher proportion of caregivers of children with ALGS report anxiety and depression compared to UK population norms[24]



The goals of treatment are clear, but an unmet need still remains in ChLD

The treatment and care of ChLD focuses on 3 main areas[21]

Provide relief from cholestatic pruritus (itch)[19,27]

Improve nutrition[19,27]

Manage disease complications and help delay liver transplantation[5,10,27,35]

Palliative options and supplemental nutrition are often the first steps for treating pruritus

Palliative treatment of cholestatic pruritus[10,35]

- Cold, short baths
- Moisturizers
- Local, topical steroids (corticosteroid creams)
- Antihistamines and sedatives

The key areas of focus for supplemental nutrition are[10,19,35,36]

- Caloric intake
- Dietary fat
- Water-soluble vitamins
- FSVs
- Sunlight and dietary calcium

The use of these palliative approaches may help keep skin healthy but they may not sufficiently address pruritus in all patients[37]

ChLD=cholestatic liver diseases.

While the use of several drugs aim to treat cholestasis and pruritus in ChLD, they are not approved for PFIC or ALGS

Drugs frequently used to treat pruritus in PFIC and ALGS are listed below[21]

Proposed mechanism or intended use	Approved for pruritus in PFIC or ALGS?
Hydrophilic bile acid used to treat primary biliary cirrhosis and gallstones is frequently used as initial pharmacologic treatment in PFIC and ALGS[19,27,38,39]	✗ [38,39]*
An antibiotic used to treat bacterial infections, such as tuberculosis[40]	✗ [40,42]
A resin used to lower cholesterol levels in the blood[41]	✗ [41,43]

Untreated ChLD may result in surgery and these treatments may not provide relief from cholestatic pruritus[7,8,10,14]

*Hydrophilic bile acid is approved for PFIC 3 in France.[44]

Surgical intervention in PFIC and ALGS may be associated with serious risks

The goal of surgical intervention in ChLD is to reduce unbearable pruritus and delay disease progression[2,10]

Surgical biliary diversion

The first main type of surgery used in ChLD is surgical biliary diversion (SBD). SBD aims to interrupt enterohepatic circulation by reducing the size of the bile acid pool. Common types of SBD include partial biliary diversion, and ileal bypass.[18,19]

Partial biliary diversion

- Although partial biliary diversion (PBD) may delay liver transplantation, in addition to complications, many patients still go on to require transplantation[10,18]

Ileal bypass

- Although ileal bypass avoids the external stoma of partial external biliary diversion and its associated complications, ileal adaptation occurs over time and symptoms return in about half of PFIC patients within a year[19]
- In ALGS, ileal bypass may not fully resolve xanthomas or severe pruritus in all patients[18]

ChLD=cholestatic liver diseases.

ChLD often leads to end-stage liver disease and the need for life-saving liver transplantation

Liver transplantation

A liver transplantation is the second main type of surgery used in PFIC and ALGS. Even when liver function is satisfactory, the debilitating nature of cholestatic pruritus may necessitate transplantation.[18,19,45] Other indications for liver transplantation include end-stage liver disease and hepatocellular carcinoma.[2]

In patients with PFIC from a large, worldwide, natural history cohort[11,46]

- At age 10, **33%-59% of patients with PFIC 1 and 53% of patients with PFIC 2** had a liver transplantation[11,46]
- The mortality rate following liver transplantation **in PFIC 1 and PFIC 2 patients was 16%,** according to one study[47]*

In patients with ALGS from a large, worldwide, natural history cohort[15]

- At age 10, **37.8% of patients with ALGS** had a liver transplantation[15]
- The mortality rate following liver transplantation in ALGS patients was **13% after 1 year and 14% after 5 years,** according to one study[48]

Liver transplantation has considerable risks, including graft rejection, vascular and CNS complications, disease recurrence, and the need for lifelong immunosuppression[10,48]

*Based on a retrospective analysis of 62 children who were admitted to the hospital between 1978 and 2007. Liver transplantation was performed in 25 patients directly before the routine administration of UDCA in 1990 and use of biliary diversion in 1995, or after failure of UDCA treatment with or without biliary diversion.[47]
CNS=central nervous system; UDCA=ursodeoxycholic acid.

There are no approved treatment options in ChLD that help patients delay disease progression and surgical intervention[2]

It’s time to see the deeper danger of cholestatic liver diseases (ChLD)

PFIC and ALGS are chronic, progressive conditions that require urgent attention

- When left untreated, they can progress to liver fibrosis, cirrhosis, liver failure, and even death[2,5,6,8]
- Elevated sBA, pruritus, and failure to thrive are several common signals of ChLD, severely impacting activities of daily living for both patients and caregivers[2,8,10,19,22-24]

For patients,
these symptoms affect quality of sleep, overall mood, school performance, and growth and development[2,7,8,19-21,32,33]

For caregivers,
sharing the burden of ChLD affects their quality of sleep, personal relationships, career development, and mental and physical health[22-24,34]

An unmet need still remains in ChLD

- Use of palliative approaches may help keep skin healthy but may not sufficiently address pruritus in all patients[37]
- Surgical intervention in PFIC and ALGS is associated with serious risks, and delaying liver transplantation for as long as possible is beneficial to patients[10,18,19,48]

There are no approved treatment options in ChLD that help delay disease progression and the need for surgical intervention[2]

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It's time to change the approach for patients with PFIC and ALGS

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