Navigating Cholestasis

When might you consider Progressive Familial Intrahepatic Cholestasis (PFIC) in the adult cholestatic patient?

IPSEN

While initially characterized in pediatric patients, PFIC can manifest **later in life** after a specific trigger or patients may remain undiagnosed into adulthood[1–3]

PFIC can be difficult to diagnose in adults due to **variable genotypes and phenotypes** that often differ from patients with pediatric-onset PFIC[4–6]

Certain **patient presentations of progressive cholestatic liver disease** may signal the need for **further assessment**[7]

Explore the algorithm below to learn more about the patient presentations that may benefit from reassessment for PFIC

SYMPTOMS OF CHOLESTASIS

- Pruritus
- Jaundice
- Fatigue

Elevated ALP + GGT and/or bilirubin

Detailed history & physical examination

No likely cause identified

Ultrasound

Normal

AMA + ANA (sp100, gp210)

Negative

MRCP, FibroScan

Negative

Positive

Liver biopsy

Positive

Inconsistent with any known cause of cholestasis

POTENTIAL DIAGNOSIS

DILI, ICP, hormone-induced cholestasis

Recent history of DILI, ICP, hormone use[9,10]

History of complicated gallstones, LPAC, family history of gallstones[11]

Family history of liver disease, ICP, HCC, DILI, or episodic PFIC[9]

Dilated ducts, stone, tumor

PBC

PSC

SSC

MASLD[12]

MASH[12]

Parenchymal or biliary disease

COULD IT BE PFIC?

Click on the buttons below to find out more about presentations that may indicate PFIC

- **Cholestatic pruritus following recent liver issue**
- **History of complicated gallstones/LPAC**
- **Family history of liver disease/ liver issue**
- **Insufficient response to treatment despite compliance**
- **AMA negative PBC**
- **Small duct PSC**
- **Lean MASLD without metabolomic syndrome**[12]
- **MASLD with pruritus**[12]
- **MASH with pruritus and without metabolic syndrome**[12]
- **Idiopathic cholestasis**

MAKING A DIAGNOSIS

Click on the buttons below to learn more about diagnostic tests for suspected PFIC

- **Biochemical tests**
  Serum bile acids
- **Supportive genetic analysis**
  ATP8B1, ABCB11, ABCB4 and others

Want to learn more?

For more information on **PFIC**, visit: https://www.omim.org/entry/211600

For more information on **adult-onset PFIC**, read: Nayagam JS et al. *Hepatol Commun* 2022;6:2654–2664

Adapted from Dröge C et al, 2023;[7] Alkhouri N, 2023;[3] EASL, 2009.[8]

ALP, alkaline phosphatase; **AMA**, antimitochondrial antibodies; **ANA**, antinuclear antibodies; **DILI**, drug-induced liver injury; **GGT,** gamma-glutamyl transferase; **gp210**; glycoprotein 210; **HCC**, hepatocellular carcinoma; **ICP**, idiopathic cholestasis of pregnancy; **LPAC**, low phospholipid-associated cholelithiasis; **MASLD**, metabolic dysfunction-associated steatotic liver disease; **MASH**, metabolic dysfunction-associated steatohepatitis; **MRCP**, magnetic resonance cholangiopancreatography; **PBC**, primary biliary cholangitis; **PSC**, primary sclerosing cholangitis; **sp100**, speckled protein 100; **SSC**, secondary sclerosing cholangitis.

1. Vitale G et al. *Cancers* 2022;14:3421; **2.** Althwanay A et al. *Am J Gastroenterol* 2022;117:p e2058; **3.** Alkhouri N. Presented at AASLD 2023, Boston, US; 10–14 November; **4.** Vitale G et al. *J Gastroenterol* 2018;53:945–958; **5.** Nayagam JS et al. *Hepatol Commun* 2022;6:2654–2664; **6.** Schatz SB et al. *Hepatol Comms* 2018;2:504–514; **7.** Dröge C et al. *Explor Dig Dis* 2023;2:34–43; **8.** EASL. *J Hepatol* 2009;51:237–267; **9.** Vitale G et al. *Dig Liver Dis* 2019;51:922–933; **10.** Ganne-Carrie N et al. *J Hepatol* 2003;8:693–697; **11.** Mirza N et al. *J Child Sci* 2020;10:e134–e136; **12.** Boehlig A et al. *Biomedicines* 2022;10:451.

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CHOLESTATIC PRURITUS FOLLOWING RECENT LIVER ISSUE

Secondary cholestasis triggered by a liver issue can be a sign of PFIC.[1]

Consider reassessing your patient for PFIC if they present with cholestatic pruritus following a recent liver issue, including:

- Intrahepatic cholestasis of pregnancy[2]
- Drug-induced cholestasis[3]
- Hormone-induced cholestasis (cholestasis triggered by birth control, menopause, etc.)[4,5]

PFIC, progressive familial intrahepatic cholestasis.

1. Alkhouri N. Presented at AASLD 2023, Boston, US; 10–14 November; **2.** Hardikar W et al. *World J Gastroenterol* 2009;15:1126–1129; **3.** Vitale G et al. *Dig Liv Dis* 2019;51:922–933; **4.** Ganne-Carrie N et al. *J Hepatol* 2003;8:693–697; **5.** Zu Y et al. *Front Pharmacol* 2021;12:761255.

Adapted from Dröge C et al, 2023;[7] Alkhouri N, 2023;[3] EASL, 2009.[8]

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Inconsistent with any known cause of cholestasis

Idiopathic cholestasis

OSIS

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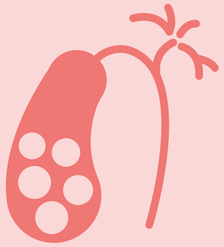
ABCB4

nore?

FIC, visit:
v/211600

-onset PFIC,
read: Nayagam JS et al. *Hepatol Commun* 2022;6:2654–2664

HISTORY OF COMPLICATED GALLSTONES, LPAC OR FAMILY HISTORY OF GALLSTONES



Gallstones are a known complication of PFIC[1] and low phospholipid-associated cholelithiasis (LPAC) is linked to mutations in the *ABCB4* gene,[2] which is one of the genes most associated with PFIC.[3]

Consider reassessing your patient for PFIC if they have:[2,4]

- A history of intrahepatic gallstones
- Strong family history of gallstones and incident at a young age
- LPAC leading to stones in the gallbladder or liver

PFIC, progressive familial intrahepatic cholestasis.

1. Jankowska I and Socha P. *Clin Res Hepatol Gastroenterol* 2012;36:271–274; **2.** Vitale G et al. *Cancers* 2022;14:3421; **3.** Nayagam JS et al. *Hepatol Commun* 2022;6:2654–2664; **4.** Mirza N et al. *J Child Sci* 2020;10:e134–e136.

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Inconsistent with any known cause of cholestasis

Idiopathic cholestasis

FAMILY HISTORY OF LIVER DISEASE OR LIVER ISSUE

PFIC is a hereditary condition caused by mutations in at least 12 genes, including *ATP8B1*, *ABCB11* or *ABCB4*.[1]

As these genes have also been implicated in other liver diseases, you might consider reassessing your patient for PFIC if they have a family history of:

- Intrahepatic cholestasis of pregnancy[2,3]
- Drug-induced liver injury[2]
- Hepatocellular carcinoma[2]
- Episodic PFIC[2]

PFIC, progressive familial intrahepatic cholestasis.

1. OMIM. PS211600. Available at: https://www.omim.org/clinicalSynopsis/table?mimNumber=601847,619484,619658,602347,615878,619662,617049,619849,619874,620010,619868,211600&from=PS211600. Accessed January 2024; **2.** Vitale G et al. *Dig Liv Dis* 2019;51:922–933; **3.** Hardikar W et al. *World J Gastroenterol* 2009;15:1126–1129.

Adapted from Dröge C et al, 2023;[7] Alkhouri N, 2023;[3] EASL, 2009.[8]

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INSUFFICIENT RESPONSE TO CHOLESTATIC/CHOLANGIOPATHIC LIVER DISEASE TREATMENT DESPITE COMPLIANCE

For patients diagnosed with a cholestatic/cholangiopathic liver disease other than PFIC, poor treatment response could indicate an incorrect diagnosis.

Consider reassessing for PFIC in your patients with insufficient response to therapy for a different cholestatic/cholangiopathic liver disease despite good compliance.

PFIC, progressive familial intrahepatic cholestasis.
Dröge C et al. *Explor Dig Dis* 2023;2:34–43.

Inconsistent with any known cause of cholestasis

Idiopathic cholestasis

Adapted from Dröge C et al, 2023;[7] Alkhouri N, 2023;[3] EASL, 2009.[8]

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CHOLESTASIS WITH UNUSUAL PRESENTATION

If your patient is receiving care for another liver disease but has unusual symptoms, it could be a sign of PFIC.[1]

Consider reassessing for PFIC in patients with:

- Small duct PSC[2,3]
- AMA-negative PBC[4–6]
- MASLD with pruritus[7]
- Lean MASLD without metabolic syndrome[7,8]
- Lean MASH with pruritus and without metabolic syndrome[7,8]

AMA, antimitochondrial antibody; **MASLD**, metabolic dysfunction-associated steatotic liver disease; **MASH**, metabolic dysfunction-associated steatohepatitis; **PBC**, primary biliary cholangitis; **PFIC**, progressive familial intrahepatic cholestasis; **PSC**, primary sclerosing cholangitis.

1. Alkhouri N. Presented at AASLD 2023, Boston, US;10–14 November; **2.** Hilscher MB et al. *Mayo Clin Proc* 2020;95:2263-2279; **3.** Oliveira HM et al. *Eur J Case Rep Intern Med* 2017;10.12890/2016_000537; **4.** Chascsa DM and Lindor KD. *Clin Liver Dis* 2018;22:589-601; **5.** Zen Y et al. In: Burt AD et al, eds. MacSween's Pathology of the Liver. 7th ed. 2018:515–593; **6.** Nalbantoglu I and Jain D. *Semin Diagn Pathol* 2019; 10.1053/j.semdp.2019.07.003; **7.** Boehlig A et al. *Biomedicines* 2022;10:451; **8.** Nayagam JS et al. *Hepatol Commun* 2022;6:2654–2664.

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IDIOPATHIC CHOLESTASIS

Variations in the genes responsible for PFIC have been identified in a number of patients with idiopathic cholestasis.[1,2]

Consider reassessing your patient if signs of cholestasis manifest without an apparent or identified cause, especially in the presence of pruritus.[1,2]

PFIC, progressive familial intrahepatic cholestasis.

1. Vitale G et al. *J Gastroenterol* 2018;53:945–958; **2.** Aamann L et al. *Scand J Gastroenterol* 2018;53:305–311.

Idiopathic cholestasis

Adapted from Dröge C et al, 2023;[7] Alkhouri N, 2023;[3] EASL, 2009.[8]

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BIOCHEMICAL TESTS

A range of biochemical abnormalities may indicate PFIC, including elevated serum bile acid levels, elevated bilirubin levels and abnormal transaminase levels.[1,2]

	PFIC type 1	PFIC type 2	PFIC type 3
Serum bile acids	↑↑	↑↑↑	↑
Serum GGT	-	-	↑
Serum bilirubin	↑	↑	↑
Serum ALP	↑	↑	↑
Serum ALT	↑	↑	↑

Table adapted from Gunaydin et al, 2018[1]
This table only includes PFIC types 1, 2 and 3. Please see www.omim.org/entry/211600 for more information on other PFIC types.

If PFIC is suspected, assessment of these measures can help confirm a diagnosis.[2]

↑, mild elevation; ↑↑, moderate elevation; ↑↑↑, large elevation.
ALP, alkaline phosphatase; **ALT**, alanine transferase; **GGT**, gamma-glutamyl transferase; **PFIC**, progressive familial intrahepatic cholestasis.
1. Gunaydin M et al. *Hepat Med* 2018;10:95–104; **2.** McKiernan P et al. *JHEP Reports* 2024;6:100949.

GENETIC ANALYSIS

So far, variations in at least 12 genes have been associated with PFIC.[1] These include:[1,2]

- *ATP8B1*, encoding FIC1 – PFIC type 1
- *ABCB11*, encoding BSEP – PFIC type 2
- *ABCB4*, encoding MDR3 – PFIC type 3
- *TJP2*, encoding TJP2 – PFIC type 4
- *NR1H4*, encoding FXR – PFIC type 5
- *MYO5B*, encoding MYO5B – PFIC type 10

Genetic testing can be useful to reinforce a suspected diagnosis of PFIC.[3] A lower threshold for genetic testing could lead to earlier diagnosis of PFIC, allow screening for family members,[4] and be key to facilitating individualized treatment.[3]

However, genetic testing for PFIC has certain limitations, including:

- Difficulty in predicting pathogenicity of new variants[5]
- Inconsistency in genotype-phenotype relationships[5,6]
- Mutations may reside in as-yet-undiscovered causative genes or regions of genes that are not evaluated in genetic assays, meaning testing can be inconclusive[2,6,7]

Genetic testing is not essential for a positive diagnosis of PFIC and should not delay treatment initiation. In the absence of genetic confirmation, information obtained by probing the patient's family history may support a clinical diagnosis of PFIC.[6,8,9]

BSEP, bile salt export pump; **FIC1**, familial intrahepatic cholestasis 1; **FXR**, farnesoid X receptor; **MDR3**, multidrug resistance protein 3; **MYO5B**, myosin VB; **PFIC**, progressive familial intrahepatic cholestasis; **TJP2**, tight junction protein 2.

1. OMIM. PS211600. Available at: https://www.omim.org/clinicalSynopsis/table?mimNumber=601847,619484,619658,602347,615878,619662,617049,619849,619874,620010,619868,211600&from=PS211600. Accessed January 2024; **2.** Bull L and Thompson RJ. *Clin Liver Dis* 2018;22:657–669; **3.** Vitale G et al. *J Gastroenterol* 2018;53:945–958; **4.** Althwanay A et al. *Am J Gastroenterol* 2022;117:p e2058; **5.** McKiernan P et al. *JHEP Reports* 2024;6:100949; **6.** Davit-Spraul A et al. *Hepatology* 2010;51:1645-1655; **7.** Bakir A et al. *Ann Hum Genet* 2021;10.1111/ahg.12456; **8.** Vitale G et al. *Dig Liv Dis* 2019;51:922–933; **9.** Mirza N et al. *J Child Sci* 2020;10:e134–e136.