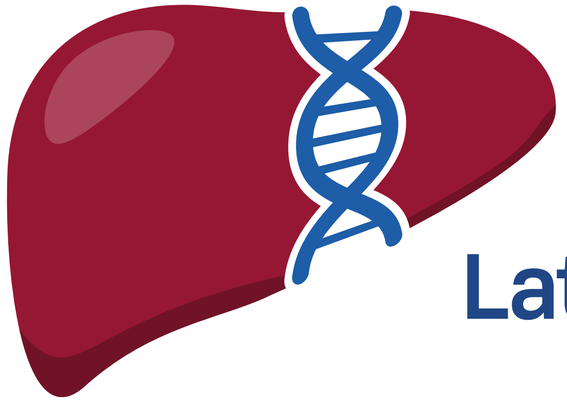

Unveiling the Spectrum: A Deep Dive into **Late-Onset Genetic Cholestasis**

SLIDE SUMMARY

Unmet needs in late-onset genetic cholestasis

An expert discussion with Verena Keitel-Anselmino, featuring Silvia Vilarinho and Deepak Joshi

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Clinical presentation and diagnosis of late-onset genetic cholestasis

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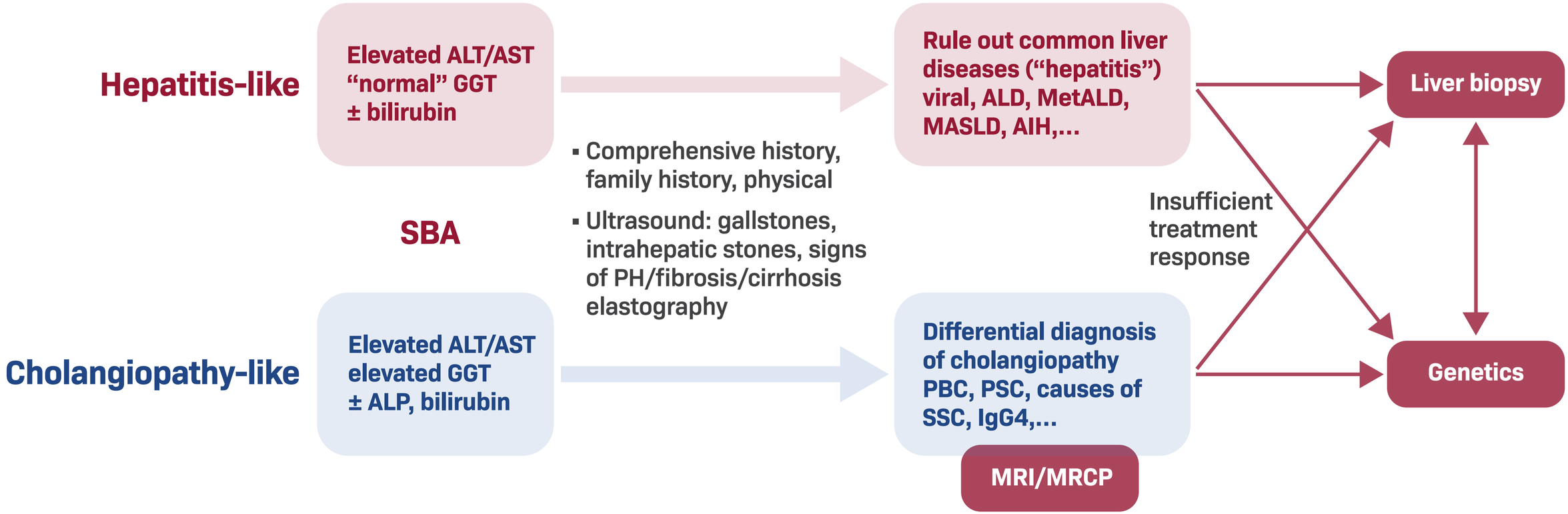
Clinical presentation of late-onset genetic cholestasis

- 14–30% of adult liver diseases remain of unidentified etiology despite comprehensive diagnostic workups.
- Genetic analysis can clarify clinical phenotypes in 30–50% of such cases.

	Serum BA	ALT & AST	Bilirubin	GGT	Associated genes
Hepatitis-like presentation Reflects hepatocyte damage due to bile acid accumulation (e.g., *ABCB11* mutations affecting bile salt export pump BSEP).	↑	↑	↗	=	***ABCB11*** **(BSEP)** *ATP8B1 (FIC1), TJP2* *NR1H4 (FXR), MYO5B* *USP53, SEM7A, etc*
Cholangiopathy-like presentation Reflects cholangiocyte injury due to reduced phospholipid secretion (e.g., *ABCB4* mutations affecting MDR3).	↗	↑	↗	↑	***ABCB4*** **(MDR3)** *KIF12, ZFYVE19* *DCDC2*

ALT, alanine transaminase; AST, aspartate transferase; BA, bile acid; GGT, gamma-glutamyl transferase.

Diagnostic workup



AIH, autoimmune hepatitis; ALD, alcohol-associated liver disease; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate transferase; GGT, gamma-glutamyl transferase; IgG4, immunoglobulin G4; MASLD, metabolic dysfunction-associated steatotic liver disease; MetALD, metabolic dysfunction-associated alcohol-related liver disease; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PBC, primary biliary cholangitis; PH, portal hypertension; PSC, primary sclerosing cholangitis; SBA, serum bile acid; SSC, secondary sclerosing cholangitis.

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Example phenotypic/genotypic presentations

Drug-induced cholestatic liver injury (DILI)

- Can present with prolonged/severe jaundice and pruritus.
- Consider genetic testing in anabolic steroid-induced DILI and high serum bile acids and/or prolonged jaundice.
- *ABCB11* gene shown to be significantly enriched in anabolic steroid-induced DILI.

Low phospholipid-associated cholelithiasis (LPAC) syndrome

- 45% of LPAC cases carry a *ABCB4* disease-associated variant.
- *ABCB4* variants are significantly associated with chronic GGT elevation, CBD stones, and CCA in personal/family medical history.

Diagnostic criteria for LPAC (at least 2 out of 3):

- Age at symptom onset (biliary colic) <40 years.
- Recurrence of symptoms after cholecystectomy.
- Intrahepatic micro- or macrolithiasis.

Intrahepatic cholestasis of pregnancy

- Characterized by pruritus and an elevation in serum bile acid concentrations, typically developing in the late second and/or third trimester and rapidly resolving after delivery.
- Associated with the *ABCB4* gene.

Benign recurrent intrahepatic cholestasis (BRIC)

- Can present with pruritus, jaundice, elevated serum bile acids.
- Common triggers are viral infections, certain medication.
- Associated with the *ABCB11* or *ATP8B1* genes.

CBD, common bile duct; CCA, cholangiocarcinomas; GGT, gamma-glutamylaminotransferase.

Dong C, et al. *JHEP Rep*. 2020;3(2):100201; de Vries E, et al. *Liver Int* 2020;40(12):3042–3050. Van Mil S, et al., *Gastroenterology*. 2004; 127(2):379–84, Klomp LE, et al. *Hepatology* 2004;40(1):27–38; Nayagam et al. *Aliment Pharmacol Ther*. 2020;52(11-12):1628–1639.

Genetic testing for late-onset genetic cholestasis

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The role of genetic testing in late-onset genetic cholestasis

- Human genome sequencing and cost reductions in next-generation sequencing have facilitated the discovery of genes associated with liver diseases.
- Initially focused on pediatric cases (e.g., PFIC1, PFIC2, PFIC3), genetic testing is now revealing that these disorders also present in adulthood.
- Whole exome sequencing allows for ongoing reanalysis of genetic data, providing new insights as clinical and research data evolve.

When to perform genetic testing?

Persistent, unexplained cholestasis with:

- Atypical or progressive disease course.
- Family history of gallstones, ICP, or hepatobiliary malignancies.
- Recurrent cholestasis (e.g., ICP, biliary colic).

If you do not receive a satisfactory answer from genetic testing, reach out for more information and/or consider re-analysis every 1–2 years.

ICP, intrahepatic cholestasis of pregnancy; PFIC, progressive familial intrahepatic cholestasis.

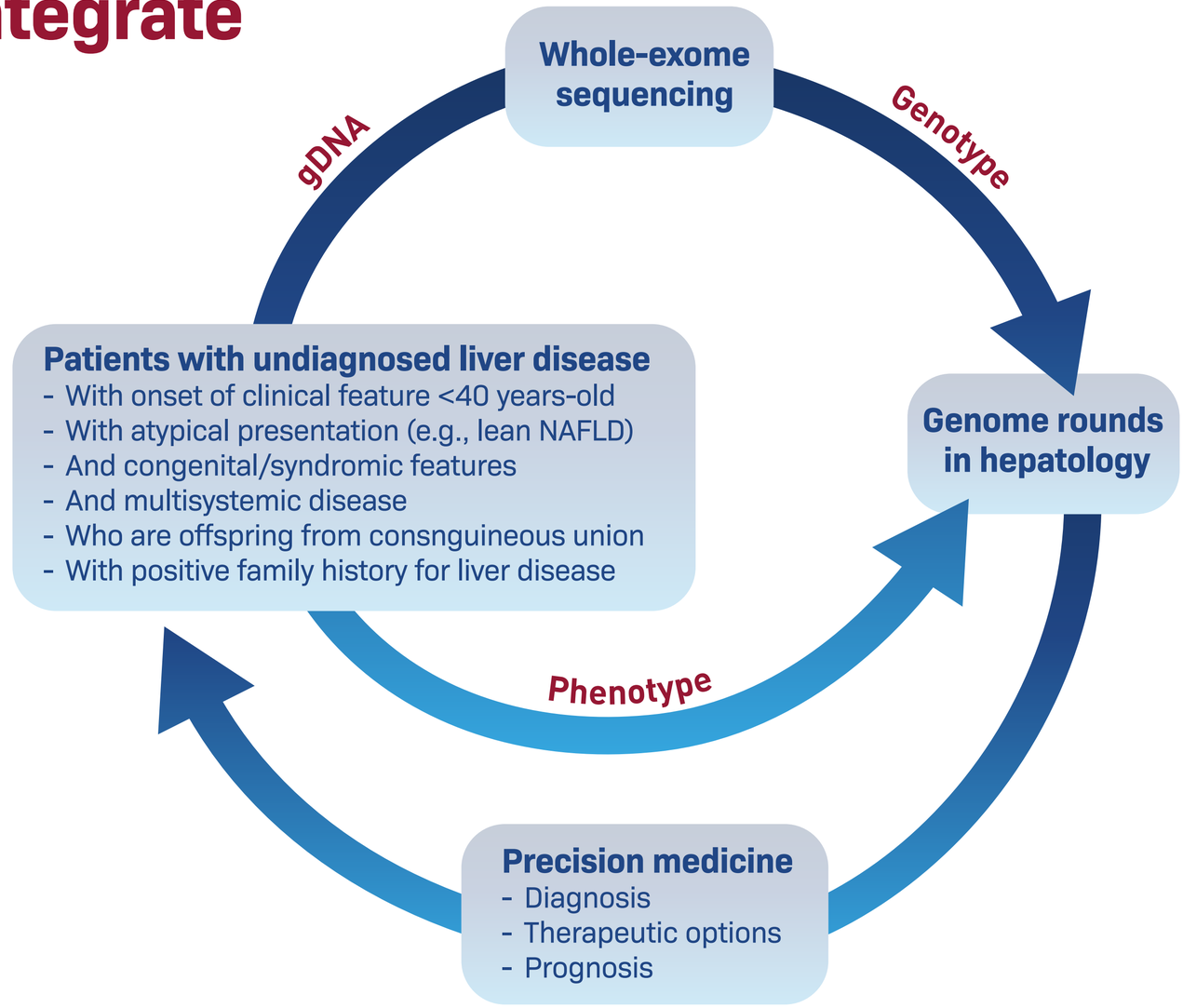
Interdisciplinary approach to integrate genetics into clinical practice

Collaboration

Bringing together hepatologists, clinical geneticists, and pathologists ensures more accurate genotype-phenotype correlations.

Revisiting Data

- Genetic findings should be reinterpreted over time as clinical presentations evolve and as new research emerges.
- Emergent data suggests that patients with mild phenotypes and mono-allelic mutations in *ABCB4* should continue follow-up with a hepatologist to ensure ongoing prospective data is obtained to accurately assess their progression risk.



gDNA, genomic DNA; NAFLD, non-alcoholic fatty liver disease.

Challenges, benefits, and future directions

Challenges

- Variants of Uncertain Significance (VUS) are common.
- Interpretation requires a multidisciplinary approach (e.g., hepatologist, geneticist, pathologist).

Benefits

- Timely diagnosis enables appropriate management and helps to identify disease risk in family members.

Future directions

- Establish centralized databases for liver gene variants.
  - Genotype-phenotype correlation of *ABCB4*-related disease(s) is an evolving field, and careful monitoring is recommended.
- Incorporate genomic data into clinical trials and longitudinal studies.
- Prospective data is key to establishing screening guidelines for malignancy risk (e.g., hepatobiliary malignancies in *ABCB4* carriers).

The integration of genetic findings with novel treatments offers new hope for patients, underscoring the critical role of genetic medicine in hepatology.

Key management considerations for late-onset genetic cholestasis

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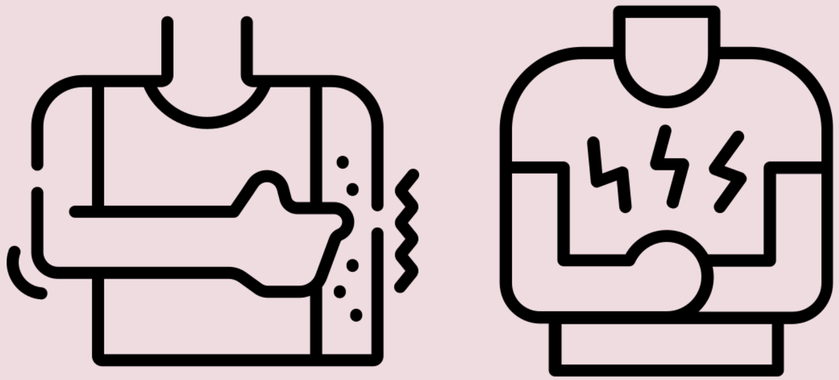
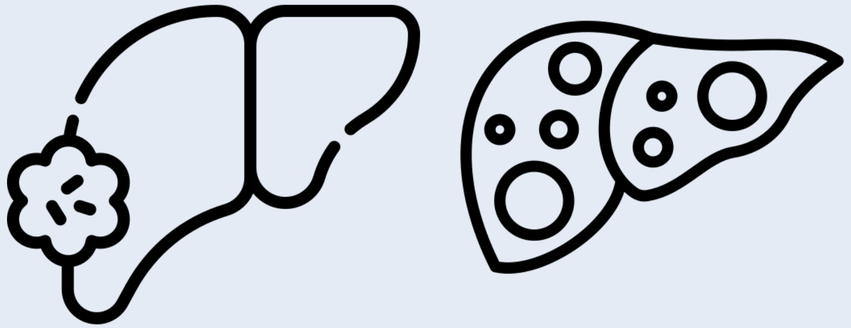
Management priorities



Symptom control

- Address pruritus, abdominal pain, and other debilitating symptoms.



Disease progression prevention

- Prevent complications such as fibrosis and cirrhosis.
- Surveillance for hepatobiliary malignancies.

Management strategies

Symptom management

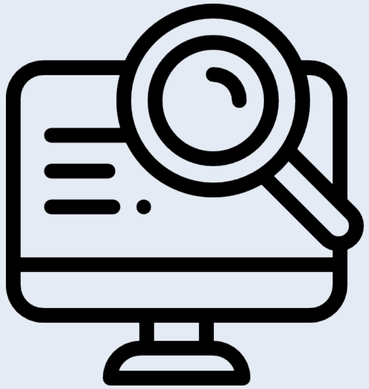
Pruritus is a debilitating symptom affecting quality of life.

Initial options include conservative measures and pharmacotherapy:

- Fibrates: Effective for cholestatic pruritus.
- UDCA: Often used but variably effective in non-pregnancy-related cholestasis.
- Rifampicin: Considered for resistant pruritus.
- IBAT inhibitors: Effective for pruritus and reducing bile acid levels, particularly in PFIC and BRIC.

Advanced options:

- Opioid antagonists, SSRIs, and bile acid sequestrants (e.g., cholestyramine) may be prescribed but have lower efficacy.
- In refractory cases, experimental therapies or surgical interruption of enterohepatic circulation may be considered.



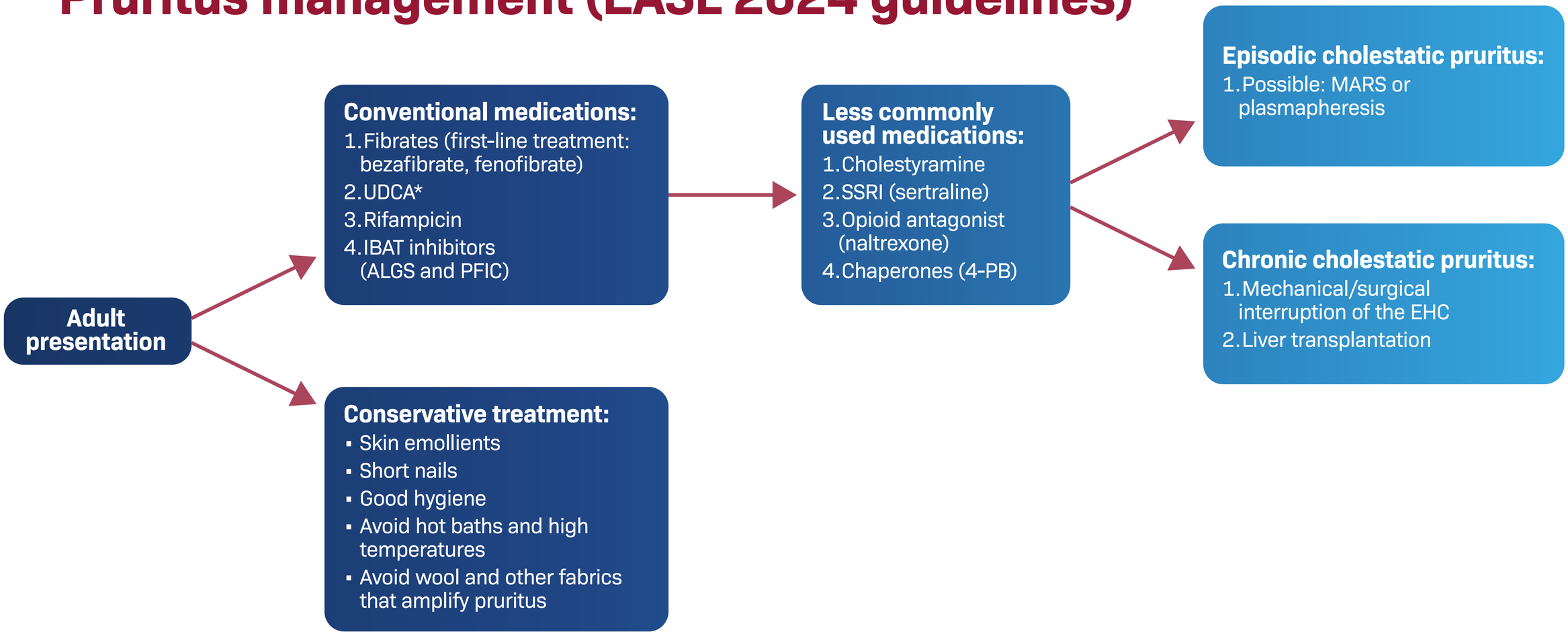
Long-term surveillance

Monitoring fibrosis and malignancy:

- Regular ultrasound and fibroscan assessments (e.g., annually) to monitor for fibrosis and hepatocellular carcinoma, especially in truncating *ABCB11* mutations.
- Prospective data and registries are needed to optimize surveillance intervals and identify risk factors.

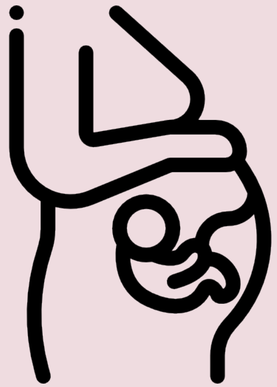
IBAT, ileal bile acid transporter; PFIC, progressive familial intrahepatic cholestasis; SSRI, selective serotonin reuptake inhibitor; UDCA, ursodeoxycholic acid; 4-PB, 4-phenylbutyric acid.

Pruritus management (EASL 2024 guidelines)



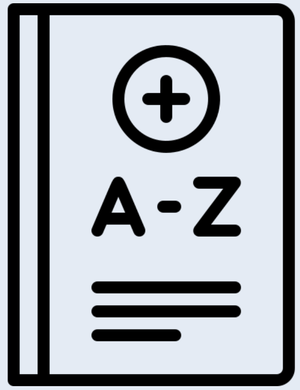
*UDCA is not generally considered a first-line treatment due to lack of evidence, however, because of its low risk profile, it is often tried as one of the first options in the management of cholestatic pruritus.
ALGS, Alagille syndrome; EHC, enterohepatic circulation; IBAT, ileal bile acid transporter; MARS, molecular adsorbent recirculating system; PFIC, progressive familial intrahepatic cholestasis; SSRI, selective serotonin reuptake inhibitor; UDCA, ursodeoxycholic acid; 4-PB, 4-phenylbutyric acid. Images reproduced with permission from Verkade HJ, et al. *J Hepatol* 2024;81(2):303–325.

Special considerations



Pregnancy and genetic cholestasis

- High serum bile acids in late pregnancy pose risks to both mother and fetus.
- IBAT inhibitors are being explored as treatments for severe intrahepatic cholestasis of pregnancy (ICP).
- Nasobiliary drainage has also been used in severe cases but carries significant risks.



Nomenclature of BRIC

- The term "benign" recurrent intrahepatic cholestasis (BRIC) is misleading, as bile acid accumulation over time may lead to inflammation and fibrosis.
- Suggestion to revise terminology to reflect disease progression risk and the need for ongoing surveillance.

IBAT, ileal bile acid transporter.

Advances in management strategies

IBAT inhibitors

- Demonstrated efficacy in pediatric cohorts for PFIC and Alagille syndrome, with emerging use in adult patients.
- Show promise in improving symptoms, quality of life, and potentially delaying disease progression.
- Initial data show they are safe in pregnancy and for those on combined oral contraceptives.

Expanding role of hepatology

- With improved therapies and native liver survival, more patients are transitioning from pediatric to adult hepatology care, requiring hepatologists to manage genetic cholestasis across the lifespan.
- A "genetic hepatology" subfield is emerging to address the complexities of diagnosing and treating these conditions.

Future innovations

- Advances in mRNA technologies, small molecule therapies, and gene editing (e.g., CRISPR) may offer direct correction of genetic defects in diseases like *ABCB11*- and *ABCB4*-related cholestasis.

IBAT, ileal bile acid transporter; PFIC, progressive familial intrahepatic cholestasis.

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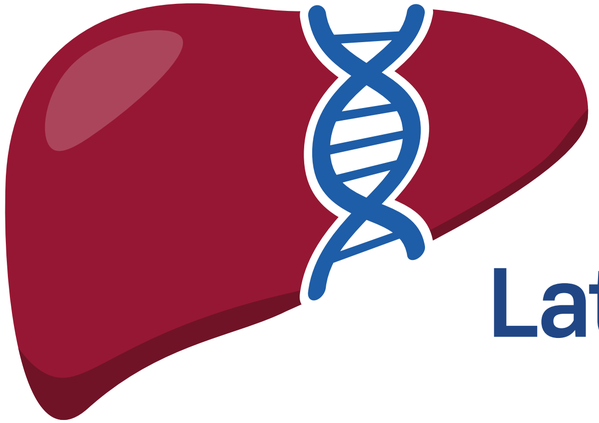
AASLD abstracts of interest

Whilst the panel could not cover all in detail, the below posters/abstracts from AASLD 2024 informed their discussion:

- Abstract 4367: Identification and in vitro characterization of a novel BSEP and *ABCB4* dual-acting positive functional modulator targeting the treatment of a broad range of hepatobiliary diseases.
- Poster 2463/Abstract 1253: The pivotal role of *ABCB11* on genetic susceptibility to drug-induced liver injury from anabolic steroids.
- Poster 4280/Abstract 2351: A phase I, open-label, fixed-sequence, crossover study to evaluate the potential interaction of multiple-dose odevixibat with the pharmacokinetics of single-dose combined oral contraceptive steroids in healthy female participants.
- Abstract 2377: Whole exome sequencing for the diagnosis of genetic cholestasis in adults.
- Poster 4277/Abstract 2348: Effects of odevixibat vs placebo on hepatic biochemical parameters and liver adverse events with PFIC: Data from the PEDFIC 1 study.
- Poster 4400/Abstract 2470: Impact of maralixibat on caregiver burden for patients with Alagille syndrome and progressive familial intrahepatic cholestasis.
- Poster 4436/Abstract 2504: Bile acid subspecies are correlated with pruritus and bilirubin improvement in PFIC patients treated with maralixibat: Data from MARCH and MARCH-ON.
- Oral session 0161: Clinical status and liver histology at liver transplantation in progressive familial intrahepatic cholestasis – experiences from the Childhood Liver Disease Research Network.

Accessible at: https://www.aasld.org/the-liver-meeting/liver-meeting-2024-abstracts



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This activity is made possible thanks to an independent educational grant from Ipsen.

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