Cholestatic Diseases

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Conflict of Interest Disclosure – Saumya Jayakumar
(over the past 24 months)

No relevant relationships with any commercial or non-profit organizations

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CanMEDS Roles Covered

X	**Medical Expert** (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
	Communicator (as *Communicators*, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
X	**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
	Leader (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
	Health Advocate (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
X	**Scholar** (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
	Professional (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of

Case: 16 yr old girl

- Transferred for evaluation of possible acute liver failure
- HPI:
  - Jaundice and severe itching, dark urine, acholic stools ~2 weeks prior to admission
  - Jehovah's Witness
  - Initially presented to children's hospital ➔ transferred for ALF/transplant evaluation
  - No bleeding, no alteration in mental status (although pt c/o "tired", sleeping more than normal per mother)
  - No RF for viral hepatitis, no sick contacts, no prior similar sx
  - Patient traveled to Mexico for 1 month, returned ~ 3 weeks prior to presentation at hospital

Case continued

- Meds:
  - "Vitamin shots" in Mexico and at home (x3, last one 1 month ago) – no documented features of pernicious anemia, not vegetarian
  - No new meds/herbals/OTC
- PMHx:
  - Nil significant
- Family Hx:
  - Nil significant
  - Non-consanguinous parents

Case: Physical exam

- Deeply jaundiced, extensive excoriations
- VS normal
- C/o fatigue, but A&O x 3, no asterixis, no significant neurological findings
- No features of chronic liver disease
- No dysmorphic facial features suggestive of chromosomal disorders (e.g. Alagille)

Labs

Labs	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
AST	47	58	54	53	48	52	44	60	52	53	63
ALT	30	33	34	32	29	29	25	30	28	29	34
ALP	315	351	376	332	331	360	332	344	289	280	282
GGT	4	3	5	4	6	4	8	4	3	5	6
Tbili	350	380	429	380	404	458	378	381	284	264	246
DBili	318	274	350	310	354	324	307	303	215	188	174
INR	1.4	1.6	1.8	1.6	1.2	1.1	1.2	1.0	1.1	1.2	1.0

Case: Investigations

- Labs
  - Normal CBC, renal function, albumin
  - Negative AMA, ASMA, anti LKM, ANCA
  - Normal IgG, A1AT
  - Negative HAV, HBV, HCV, HEV, Dengue, HIV, Zika, adenovirus
  - Positive IgG for CMV and EBV, but negative EBV PCR
  - Normal ceruloplasmin, Increased serum copper (40.19)
  - Negative βHCG

- Imaging
  - AXR = calcifications in liver, thought to be granulomas
  - MRCP = normal bile ducts, no obstruction, no features of cirrhosis/portal HTN

Liver Biopsy

- "Cholestatic Hepatitis"
  - Canalicular cholestasis with rare hepatic necrosis
  - Mild portal lymphohistiocytic inflammation
  - No significant bile duct damage/ductopenia/bile plugs
  - No concentric periductal fibrosis or florid BD lesions/granulomas
  - **No fibrosis**
  - No steatosis/steatohepatitis, negative iron stains, PAS, copper

Hospital Course

- Patient started on Ursodiol (15mg/kg) – minimal change in labs
- On day 3 after admission, patient reports that fatigue has improved, but still very itchy
- Patient started on Cholestyramine, but no improvement in pruritus

Thinking pause

- Is this acute liver failure?
  - No → no evidence of hepatic synthetic dysfunction (normal INR) or Hepatic Encephatopathy
- Why is serum copper high?
  - Serum copper is increased in cholestatic diseases
- Why is GGT normal/low?

- What to do next?

Genetic Testing Results

EGL Genetic Cholestasis Panel

SUMMARY

Five variants of unknown significance detected.

RESULTS AND INTERPRETATION

Disclaimer: This patient's result is listed above. An example report may have been provided with the ordering information for this test. The exampl report may **NOT** match the results for this individual. The example report **MUST NOT** be included in or incorporated into this individual's medical record.

Sequence analysis of the targeted regions of genes included in this test (see methodology) detected the following:

Gene	MIM#	Disease (Inheritance)	Variant	Zygosity	Type
ABCB11	603201	Progressive familial intrahepatic cholestasis 2 (AR); Benign recurrent intrahepatic cholestasis 2 (AR)	NM_003742.2:c.404A>C (p.E135A)	Apparently Homozygous	VOUS
			NM_003742.2:c.2125G>A (p.E709K)	Heterozygous	VOUS
ALDOB	612724	Hereditary fructose intolerance (AR)	NM_000035.3:c.-82-132G>A	Heterozygous	VOUS
CYP7B1	603711	Congenital bile acid synthesis defect 3 (AR); Spastic paraplegia 5A (AR)	NM_004820.4:c.463G>A (p.E155K)	Heterozygous	VOUS
PEX26	608666	Peroxisome biogenesis disorder 7A/7B (AR)	NM_017929.5:c.200A>G (p.N67S)	Heterozygous	VOUS

Abbreviations: AR - autosomal recessive; VOUS - Variant of unknown significance

Please note, this assay cannot differentiate the presence of this variant in both parental copies of the gene from the presence of the variant in one

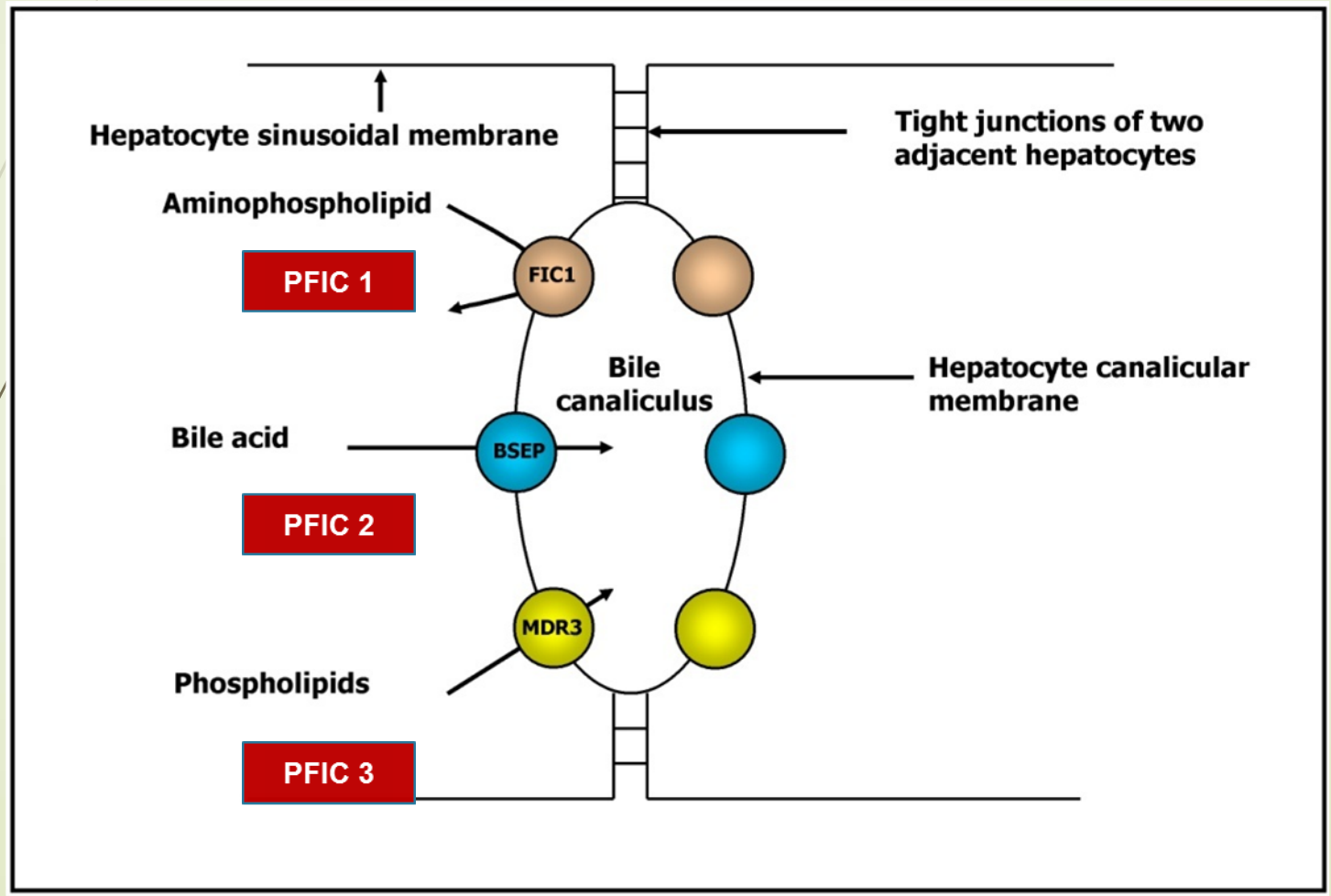
- Help! What does this mean??
  - Time to reach out to your Pediatric colleagues!

Spectrum of genetic disease

- PFIC (progressive familial intrahepatic cholestasis)

- BRIC (benign recurrent intrahepatic cholestasis)
- ICP (intrahepatic cholestasis of pregnancy)

Progressive Familial Intrahepatic Cholestasis (PFIC)



	PFIC 1	PFIC 2	PFIC 3
Transmission	Autosomal recessive	Autosomal recessive	Autosomal recessive
Protein	FIC 1	BSEP	MDR3
Function	Phospholipid flippase	Bile acid transport	Phosphatidyl-choline floppase
GGT	↓	↓	↑
Serum bile acids	↑↑	↑↑	↑
Bile	↓ 1° bile acids	↓↓ 1° bile acids	↓ phospholipids
Liver phenotype	Progressive cholestasis, severe pruritus	Progressive cholestasis, severe pruritus, risk of HCC	Cholestasis presents later, moderate pruritus
Other sites of expression	Intestine, pancreas, kidney	None	None
Extrahepatic symptoms	Chronic diarrhea, pancreatitis, growth failure	None	None
Spectrum	BRIC 1, ICP	BRIC 2, ICP	ICP

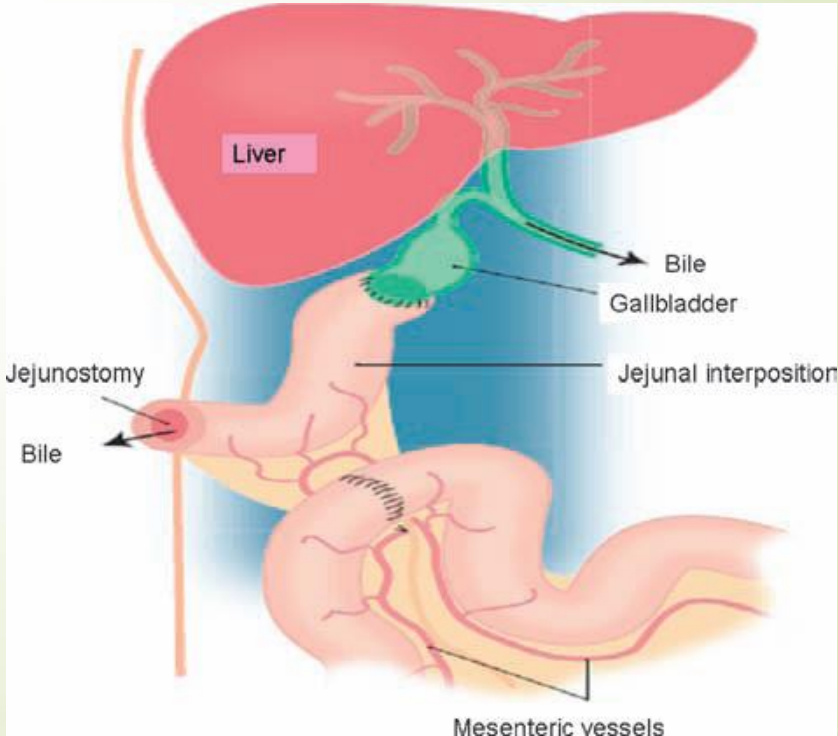
Pediatric presentation of disease (PFIC 1 & 2)

- Jaundice in infancy ➔ progressive cholestasis
- Pruritus, hepatosplenomegaly
- Portal hypertension
- Failure to thrive (fat malabsorption)
- PFIC 1: diarrhea, SN deafness, pancreatic insufficiency
- PFIC 2: HCC, CCA risk (15%)

Expanding etiology of progressive familial intrahepatic cholestasis *World J Hep* 2019

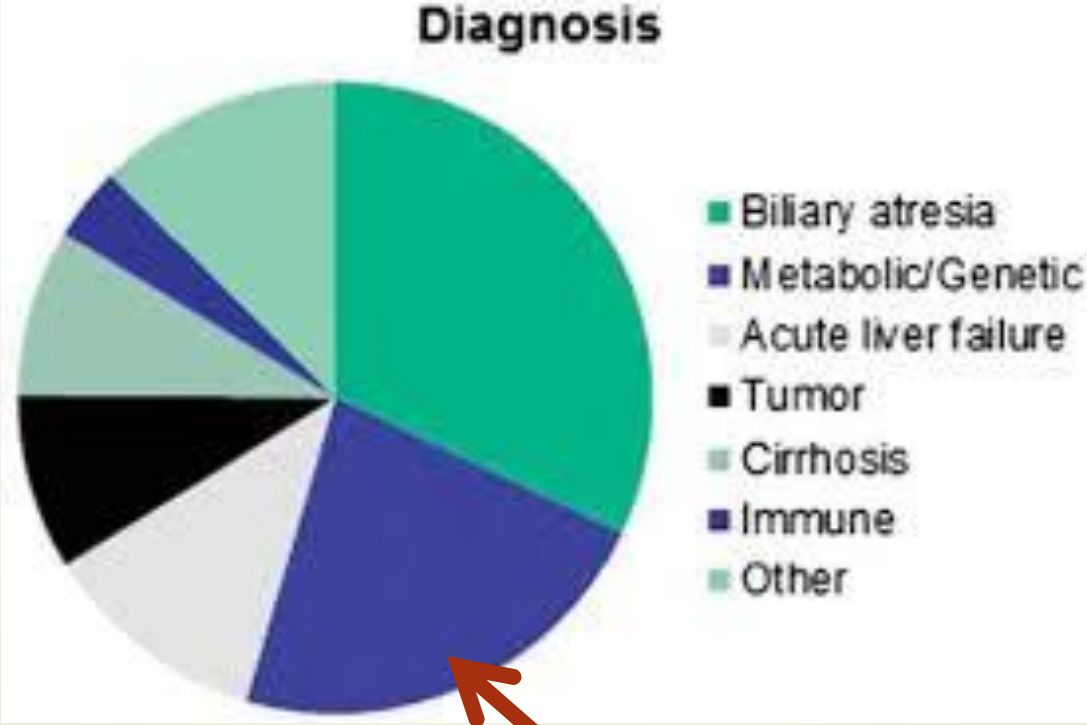
PFIC: management

- Biliary diversion
- Mechanism of effect?
  - ↓ enterohepatic circulation of bile acids
  - Change in composition of bile acid pool



PFIC 1&2: management

- Under investigation: inhibitors of ileal bile acid transporter
- Liver transplant



Squires et al. *Hepatology* 2014

Adult: Benign Recurrent Intrahepatic Cholestasis (BRIC 1 & 2)

- Clinical presentation:
  - Episodic jaundice & intense pruritus +/- steatorrhea x weeks
    - Variable severity
  - Symptom-free intervals of weeks – years
  - Onset often within 1st 2 decades of life
  - Benign course
- Labs: ↑conj bili, ↑bile acids, ↓GGT during episodes
- Triggers:
  - Unclear. Viral infection, OCP, pregnancy implicated
- Genetics: Phenotypic continuum
  - BRIC 1: mutations in ATP8B1 (missense)
  - BRIC 2: specific mutations in ABCB11

Expanding etiology of progressive familial intrahepatic cholestasis *World J Hep* 2019

Intrahepatic cholestasis of pregnancy

- 1% of pregnancies
- Clinical presentation
  - Intense pruritus, palms/soles, particularly at night
  - Present in 3rd trimester, worsens until delivery
  - Jaundice absent
  - Serum bile acids ↑
  - ALT, ALP ↑ 2-10x normal; GGT normal

Familial cholestasis: PFIC, BRIC and ICP. *Best Pract Res Clin Gastro* 2010

Intrahepatic cholestasis of pregnancy - mechanisms

- Genetics
  - 10-15% first degree relatives affected
  - Geographic variability
  - Mutations in ATP8B, ABCB11, ABCB4 (genes associated with PFIC 1-3)
- Hormonal milieu
  - Starts in 3rd trimester
  - More common in twin pregnancy
- Role of hormones in cholestasis
  - Inhibiting influence on major bile acid uptake transporter as well as bile salt export via BSEP

Familial cholestasis: PFIC, BRIC and ICP. *Best Pract Res Clin Gastro* 2010

Summary

- Patient homozygous for mutations in ABCB11
- BRIC 2
- Supportive care until symptoms resolution

- BRIC, ICP and PFIC represent a continuum of disease arising from mutations in genes involved in bile acid handling