Canadian Cystic Fibrosis Conference

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CF related liver disease (CFLD) – clinical guidelines

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Cystic Fibrosis Canada | w/o limits

Conflicts of Interest

None to declare

Case

- 45yoF, DoB: 1980/07/14
- Homozygous F508del, Dx age 3.5yrs
- **PMHx**: P.I., CFRD (age 20), non-smoker, pneumothorax (VATS bullectomy), low bone density, hypothyroid, genital herpes
- Colonized with B cepacia & S marcessans
- Transferred to adult care on Aldactone
- CT 2011: macronodular liver + splenomegaly
- Hepatology 2012 – “long standing nodular liver & low platelets. ? Ascites in 2001”
- Follow up – system issues
- Passed away in 2018 with advanced lung + liver disease, poorly controlled DM, low BMI (despite G Tube) & recurrent chest infections

Objectives

1. Understand background of CFLD
2. CFF liver guidelines 2024 & Canadian draft guidelines
3. Review Halifax clinic data – to date
4. Address questions on screening

Background of CFLD

- Prevalence not fully known – possible 30% in pediatrics, 40% in adults
- 3rd leading cause of death in CF
- "Classic" CFLD:
  - Multifocal biliary cirrhosis in those P.I.
  - Biliary cirrhosis usually identified by age 10
  - Results in portal hypertension
- CFLD is not a single condition

Canadian DRAFT guidelines, 2025

Observational Study > Liver Int. 2023 Apr;43(4):878-887. doi: 10.1111/liv.15544. Epub 2023 Feb 28.

Increase of liver stiffness and altered bile acid metabolism after triple CFTR modulator initiation in

▸ Eur J Nutr. 2025 Jun 21;64(5):224. doi: 10.1007/s00394-025-03745-3

Adding salt to foods and risk of metabolic dysfunction-associated steatotic liver disease and other chronic liver diseases

Shunming Zhang [1,2,✉], Zhenyu Huo [3], Yan Borné [2], Emily Sonestedt [2], Lu Qi [4,5,✉]

Background of CFLD - terminology

CFHBI: CF hepatobiliary involvement

- ≥1, *without* aCFLD: hepatomegaly, <F4 fibrosis, increased liver stiffness by elastography (<F4), hepatic steatosis, focal biliary cirrhosis, cholestasis, persistent (>3-6mos) elevated liver function testing, abnormal liver imaging, cholelithiasis, sclerosing cholangitis or hepatolithiasis

aCFLD: advanced CF liver disease

- ≥1 of: nodular liver, advanced cirrhosis (F4), multi-lobular cirrhosis (with or without portal HTN) or non-cirrhotic portal HTN

Hepatology, 2024; 79: 1220-1238

SPECIAL ARTICLE

OPEN

Cystic fibrosis screening, evaluation, and management of hepat

Zachary
Meghana
Dominiq[11]
Julio Le
Rebeca
Stacy Al[22]

We anticipate that these new guidelines will improve early diagnosis and care for children and adults with CF-associated hepatobiliary disease and ultimately improve the morbidity and mortality of PwCF

Hepatology, 2024; 79: 1220-1238

Screening & Monitoring recommendations

1. Blood work (at time of clinical stability):

- All patients, annually: T bili, AST, ALT, ALP, GGT, platelets (if aCFLD then q6months)
    - APRI: AST to platelet ratio (most studied in CF)
    - GPR: GGT to platelet ratio
    - Fib4: used at our clinic
    - Forms index

High sensitivity, low specificity

- aCFLD, q6months: AST, ALT, GGT, ALP, conjugated (or direct) bilirubin, albumin, platelets, INR

2. Annual exam to assess for hepatosplenomagally
3. Ultrasound:
    1. Pediatric: q2 yrs from age 3-18yrs
    2. Adults: CFF repeat q2yrs if abnormalities (Canadian – every few years)
    3. Canadian, test for reversal of portal venous flow: q2yrs (CFHBI), q6mos (aCFLD), annually in pediatrics

Canadian DRAFT guidelines, 2025
Hepatology, 2024; 79: 1220-1238

Screening & monitoring recommendations

4. Elastography: abnormal blood work, P/E or U/S. If advanced dz, repeat annually
5. If liver disease: ensure work up for differential diagnoses are performed
6. MRI cholangiopancreatography: if elevated GGT, ALP, D. bili if inconclusive U/S
7. EGD to assess for varices if platelets<150 &/or liver stiffness >20kpa on elastography (adults, unable to comment for children)
8. **Cirrhosis** (or suspected):
   - U/S (assess for HCC): CFF q6months (adults)/annually (children). Canadian: annual for both
   - serum alpha feto protein (AFP): CFF annually for both. Canadian: annually in pediatrics, q6mos in adults
9. aCFLD + varices: monitor according to current published guidelines

Canadian DRAFT guidelines, 2025
Hepatology, 2024; 79: 1220-1238

Treatment recommendations

1. Ursodiol:
   - CFF: No routine use of ursodiol
   - Candian: use long term to decrease liver enzymes
2. **Modulators**:
   1. Use in those with CFHBI with close monitoring (lung benefit felt to outweigh liver risk)
   2. Unsure if aCFLD with portal HTN, but no decompensation
   3. Do not use if aCFLD + decompensation (expert opinion)
   4. Recommend modulator therapy in those with liver transplant with close monitoring
3. Choly for those with symptomatic gallbladder disease
4. ERCP for those with symptomatic biliary tract disease
5. B-blockers should be used for 1^0 & 2^0 prevention of variceal bleeding (adults)
6. Consider portosystemic shunt (TIPS) or transplant if aCFLD (consider lung+liver if FEV1 ≤40%)

Canadian DRAFT guidelines, 2025
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Treatment recommendations

7. **Pharmacy** consultation q6months: CFHBI or aCFLD
- Review high risk medications, polypharmacy, herbals, EtOH, therapy modifications
- Hep A & B vaccinations

8. **Dietitian** review q6months: deficiencies in liver specific macro & micro nutrients
9. If aCFLD screen for **diabetes** annually (even if <10yrs of age)
10. Multi-disciplinary care: those with aCFLD should follow with:
- Respirology, GI/Hepatology, endocrinology, +/- transplant team
- +/-: social work, physiotherapy, psychology

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Protocol for liver disease – Pediatrics

Blood Work: All patients, annually: ☐ T bili, AST, ALT, ALP, GGT, platelets ☐ Fib 4 score or APRI aCFLD, q6 months: ☐ AST, ALT, GGT, ALP, conjugated (or direct) bili, albumin, platelets, INR	**Varices:** ☐ Upper endoscopy if platelets <150 &/or liver stiffness >20kpa on elastography ☐ B Blockers for 1^0 & 2^0 bleeding prevention
Ultrasound: ☐ Baseline at age 3yrs, or at diagnosis ☐ Repeat q2years	**DM**: ☐ Screen annually if aCFLD
Elastography: ☐ Baseline (if abnormalities) ☐ Repeat annually (aCFLD)	**Cirrhosis**: ☐ Ultrasound qyearly ☐ Alpha fetoprotein yearly
Modulators: ☐ ok if CFHBI (close monitoring) ☐ Maybe if aCFLD with portal HTN & no decompensation	If aCFLD, perform **work up**: ☐ Hep A, B, C, potentially E ☐ Cholestatic & auto immune disease ☐ EtOH associated

Halifax Clinic results

- All screened with yearly blood work and calculated Fib4 score
- >90% have had baseline ultrasound
- ~70% have had fibroscan
- Very few have normal scans – some have had abnormal scans despite normal blood work and Fib4 scores

Why screen?

- Identify those with liver disease with the goal of:
- Preventing further injury/disease progression:
  - Avoid hepatotoxic medications – including certain antibiotics
  - Dosing of modulator therapy & monitoring schedule
  - Counselling on weight loss, Omega-3, caffeine, ? Reducing salt intake
- Monitoring for disease progression & complications (hepatocellular carcinoma)
- Planning for liver transplant as appropriate

Specific questions

1. Who is responsible for managing CF liver disease screening and management?
    - Screening – CF centres
    - Management – multi disciplinary
2. What screening protocols should be implemented?
    - Blood work & calculated score (Fib4 or APRI?)
    - Baseline ultrasound
3. How is our clinic adapting to screening for liver disease?
    - Fib4 score, U/S (unsure frequency), fibroscans
4. What role should primary care physicians play in screening for liver disease?
    - None?
5. How has Trikafta changed the landscape?
    - Unsure, will weight gain/steatosis/MASH result in cirrhosis in aging patients
6. Are there new risks or protective strategies emerging from modulator use?
    - Protective or potential harmful – monitoring and data required

Specific questions

6. What are the most pressing unanswered research questions?
    - How early do we screen?
    - How often do we screen?
    - Do we screen all patients on a regular basis, or can we identify those at risk?
    - Are modulators protective?
7. Where are the biggest gaps in clinical knowledge or practice? See #6
8. What opportunities exist for collaborative research across disciplines?
9. What are the main challenges in integrating aging-related care into CF models?
10. What should CF Canada prioritize to support aging individuals with CF?
11. How can we better engage family physicians & community care providers?

References

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Thank You.

Calculations

TABLE 1 Noninvasive determinants of liver fibrosis in CF

Index	Formula	Thresholds for aCFLD	Hepatitis B threshold for F3-F4 fibrosis[a]
Liver fibrosis indices			
APRI	[(AST/ULN AST)/PLT] × 100	≥ 0.545[b]	< 0.5 normal, > 1.5 fibrosis[c]
GPR	[(GGT/ULN GGT)/PLT] × 100	≥ 0.545[b]	≥ 0.32[c]
FIB-4	(Age in years × AST)/(PLT × $\sqrt{}$ALT)	Insufficient data	Insufficient data
Forns Index	[(7.811–3.131 × ln(PLT)] + [(0.781 × ln(GGT)] + [(3.467 × ln(Age)) – (0.014 × cholesterol)]	Insufficient data	Insufficient data

Liver stiffness measurement	Thresholds for CFHBI	Thresholds for aCFLD (F3-F4 fibrosis)	Hepatitis B threshold for F3-F4 fibrosis
Transient elastography[d]	> 5.95 kPa[e]	> 8.7 kPa[f]	> 8.8 kPa[g]
2D shear wave	> 1.45 m/s[h]	> 1.84 m/s[h]	> 8.9 kPa [i,j]
Elastography	> 6.85 kPa[k]	> 9.05 kPa[k]	—

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