Fontan-Associated Liver Disease: Screening, Management, and Transplant Consideration

Epidemiology
- Fontan-associated liver disease (FALD) describes spectrum of fibrosis and cirrhosis resulting from Fontan circulation
- Operation performed in congenital univentricular physiology (ex. hypoplastic left heart, tricuspid atresia, etc.)
- >900 Fontans performed/year in US in children ages 2-5
- 70,000 worldwide have undergone Fontan
- Only 1/3 of adult Fontan patients are with acceptable cardiac function and no end organ disease

Procedure
- 3 Stages: Norwood, Glenn, and Fontan
  - Norwood 1) creates new aorta that connects to the RV, 2) creates shunt between PA and RV (or aorta), 3) closes PDA, and 4) opens ASD
  - Glenn connects SVC to PA and removes BT shunt
  - Fontan connects IVC to PA
- Blood from SVC and IVC are diverted directly to pulmonary arteries, achieving total cavopulmonary connection

Physiology
- Time since Fontan is the most important predictor of advanced FALD
- 100% of patients have histologic evidence of fibrosis.
- 40% have bridging fibrosis at 10 years post-Fontan

Citation: Emamaullee J et al. Fontan-Associated Liver Disease Screening, Management, and Transplant Considerations. Circulation. 2020 August. PMID: 32776846

Reviewed by: Andrew Yu
### Diagnosis and Monitoring

#### Serum biomarkers
- AST, ALT, ALP, bilirubin, GGT rarely elevated
- INR only biomarker associated with high-grade fibrosis (F3-F4)
- MELD-Na does not correlate with disease severity and is rarely elevated
- MELD-XI (excludes INR) correlated with biopsy-proven fibrosis

#### Imaging Modalities
- US, CT, or MRI to assess liver morphology and signs of portal hypertension
- Nodularity does not necessarily = cirrhosis
- Elastography can assess stiffness but unable to distinguish between passive congestion and fibrosis

#### Liver biopsy
- Gold standard
- Use METAVIR or Congestive Hepatic Fibrosis Score (CHFS)
- Obtain at 10 years post-Fontan

#### Liver Lesions
- Often have hypervascular nodules, large regenerative nodules, and focal nodular hyperplasia
- 3-15% of post Fontan develop HCC
- MRI helpful but diagnosing true HCC with LIRADS is challenging as congestive hepatopathy may affect contrast washout in delayed venous phase
- Liver biopsy usually necessary

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**Patient post-Fontan with NO clinical evidence of chronic liver disease**

10 years post-Fontan: Surveillance liver biopsy (two passes)
- Ideally during cardiac catheterization

**Patient > 3 years post-Fontan with clinical concerns for chronic liver disease (any of the following):**
- Ascites
- Splenomegaly
- Thrombocytopenia <100,000
- Gastrointestinal bleeding
- Jaundice
- Failure to thrive/sarcopenia

**Liver biopsy referral and management**
- Liver biopsy (two passes, transvenous versus percutaneous with ascites drainage prior to biopsy)
- MRI elastography (baseline and then at least annually)
- Monitor liver labs at least q 3 months (INR, Bilirubin, ALP, ALT, AST)
- EGD to assess for varices
- Treat/rule out cardiac causes of hepatic decompensation if present
- Consider early liver transplant referral for assessment for combined heart-liver transplant

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**Patient with Fibrosis**

**No Fibrosis**
- CHFS 0 (Rare)
- MRI Elastography (baseline)
- Monitor liver labs at least annually (INR, Bilirubin, ALT, AST)
- Annual liver imaging with US
- Re-biopsy or image based on clinical changes

**Mild/Moderate Fibrosis**
- CHFS 1/2A/2B
- Hepatology referral
- MRI Elastography (baseline and then at discretion of liver specialist)
- Monitor liver labs at least q 6 months (INR, Bilirubin, ALT, AST)
- Interventions for modifiable risk factors of chronic liver disease (obesity, fatty liver, alcohol use)

**Bridging Fibrosis/Cirrhosis**
- CHFS 3/4
- Hepatology referral
- MRI Elastography (baseline and then at least annually)
- Monitor liver labs at least q 3 months (INR, Bilirubin, ALP, ALT, AST)
- EGD to assess for varices
- Consider early liver transplant referral for assessment for combined heart-liver transplant

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*The Emerald Digial*

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When does FALD require liver transplant?

- No guideline exists for when to do heart transplant vs combined heart-liver transplantation (CHLT).
- Heart transplant is pursued in setting of failing Fontan.
- Liver transplant alone is not advised.
- If high grade fibrosis seen, would 1st try implementing strategies to lower R sided heart pressures and improve hepatic venous outflow.

Considerations and Key Unknowns

- Degree of liver fibrosis does not correlate with risk of progression to decompensated cirrhosis and need for transplant.
- We cannot predict who with FALD, after heart transplant alone, may stabilize or regress their hepatic fibrosis vs who may decompensate.
- Long-term risk of developing HCC is unknown.
- There is reported discordance between explant liver histology and pretransplantation liver biopsy.
  - ~30% with more advanced fibrosis on explant
  - Can determine at time of transplantation if CHLT is needed with direct visualization of native liver

Heart Transplant Alone vs CHLT

- Overall survival is similar
- CHLT experience less rejection compared to heart alone
  - 20% of patients with congenital heart have allosensitization due to prior transfusion requirements and CHLT can overcome rejection
  - Heart transplant recipients subsequently placed on liver transplant waiting list have high mortality