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

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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

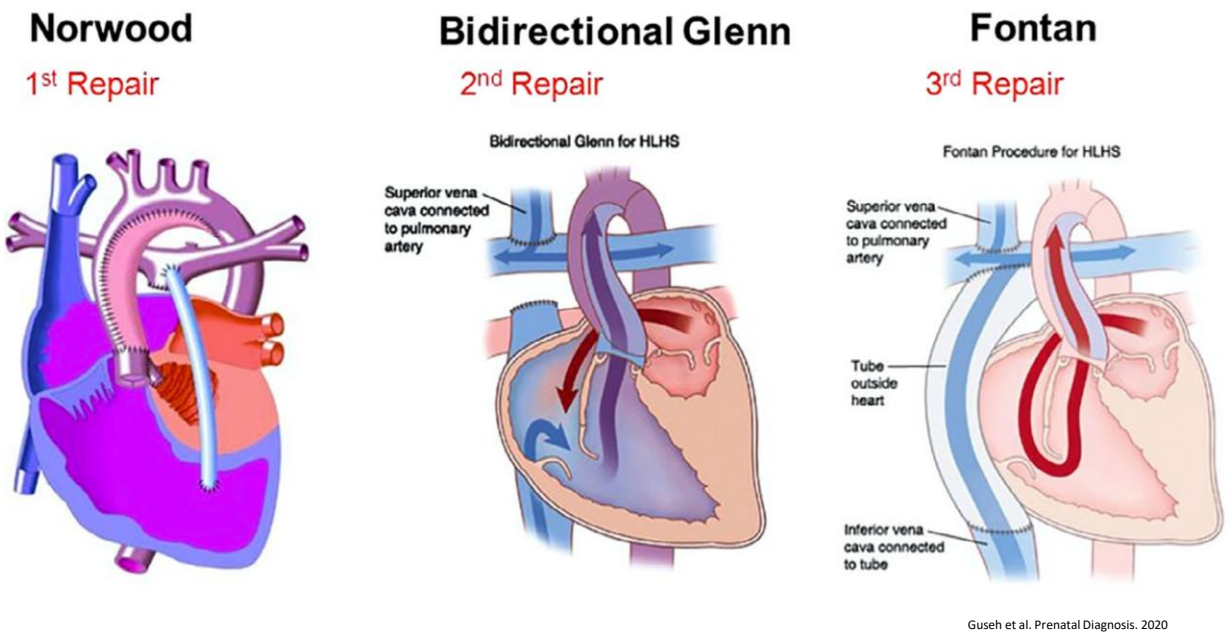
Procedure

- 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

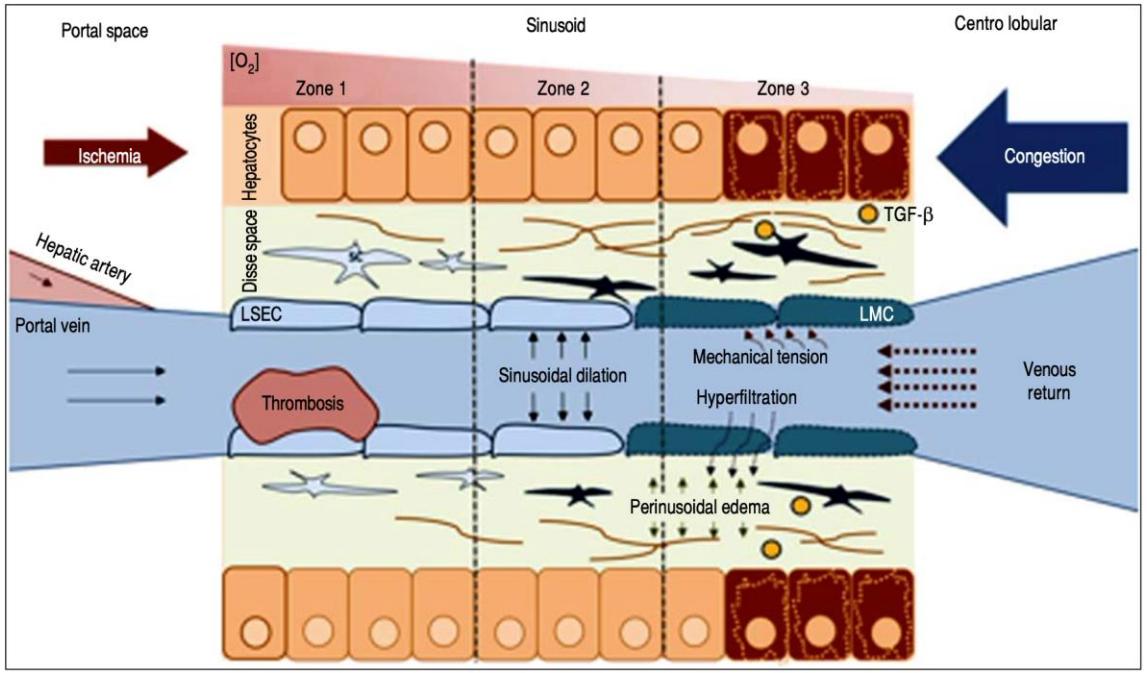
Physiology

- Total cavopulmonary connection → high CVP, low CO, and low O2 saturation
- Passive, non-pulsatile pulmonary flow → liver congestion → shear stress on hepatic vasculature → sinusoidal fibrosis
- Reduced CO with hypoxia → centrilobular ischemia → further fibrosis
- Unclear if hemodynamics are related to progression of fibrosis

- **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**



Guseh et al. Prenatal Diagnosis. 2020

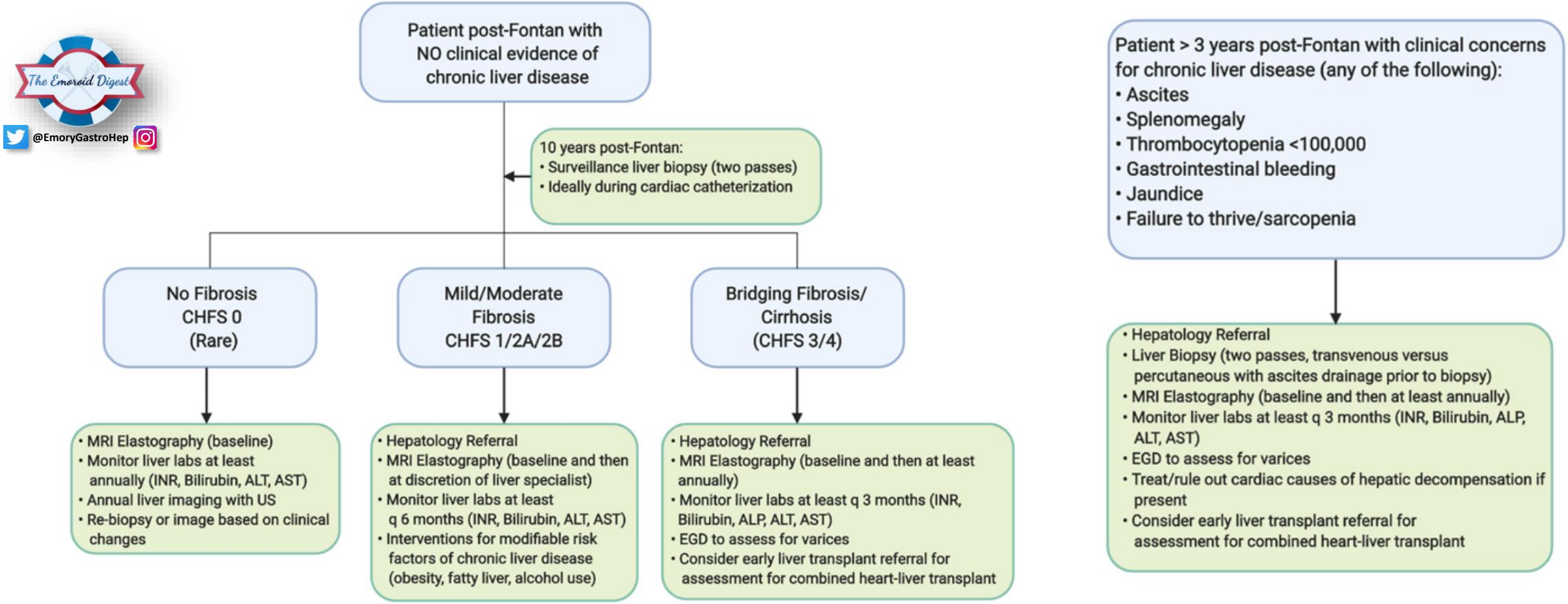


Tellez et al. Annals of Hepatology. March 2018.

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

Diagnosis and Monitoring

- Serum biomarkers
  - AST, ALT, ALP, bili, 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



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