2. Liver Complications

Principles

- To prevent liver disease caused by viral hepatitis, iron overload, drug toxicity or hepatocellular carcinoma.
- To monitor liver abnormalities routinely, and provide treatment for iron overload and any underlying liver disorder.

Recommendation

- Every thalassemia specialist centre should collaborate with a designated hepatologist with knowledge of liver complications in thalassemia patients.
- Liver enzymes should be monitored routinely, and abnormalities investigated for etiology, reviewed by a hepatologist if indicated, and managed accordingly.
- Liver iron concentration should be monitored routinely and chelation therapy initiated and adjusted to reduce complications of iron overload.,[288,298]
- Every effort should be made to reduce the risk of viral hepatitis by safe transfusions, hepatitis B vaccination programs and regular monitoring.
- Patients with active hepatitis B or C should be referred to the designated hepatologist and managed as per hepatology standards of care.
- Adult patients should be encouraged to avoid liver toxins including alcohol and liver-toxic drugs.
- There should be surveillance for complications in patients with cirrhosis, including for hepatocellular carcinoma.

Background

Liver disease is a common complication in older thalassemia patients. Common causes of liver disease include iron overload, transfusion-related viral hepatitis (Hepatitis B, C), drug toxicity, and biliary disease due to gallstones.

Interventions

- HFE mutation may contribute to the degree of liver iron overload in thalassemia syndromes[281].
- Liver enzymes including ALT, and bilirubin should be routinely monitored every 3 months and any abnormalities investigated[282].
- Various MRI protocols are available for liver iron quantification. The hematologist should be familiar with their institution's protocol and its limitations, and ensures it is validated[283-285]. All patients should have regular objective assessment of liver iron load by MRI. The interval between assessments should depend on the clinical situation, but in general it should be every 1 – 2 years. Iron should be appropriately chelated to reduce liver iron concentration to the normal range to avoid liver damage, fibrosis and cirrhosis.
- A target LIC of 5mg/gDW has been suggested for NTDT patients requiring chelation[286].
- Serum ferritin often dramatically underestimates LIC in NTDT[287].
- Fibroelastography has been used in a few studies for assessment of iron related liver damage in thalassemia. However a lack of validated reference range for this indication prevents widespread uptake[288-291].
- Serum hyaluronic acid (HA) has been investigated as a non-invasive marker of liver fibrosis in TM[292].
- All patients should start the full hepatitis A and B vaccination course prior to starting a transfusion program. Viral serology including HepBsAg, anti-HepB sAb, and anti-Hep C Ab should be monitored annually and if there is a two-fold rise in liver enzymes.
- Hepatitis B and C should be managed in collaboration with a designated hepatologist and as per Canadian consensus guidelines.[77,78] Thalassemia-specific complications of hepatitis treatment should be monitored for and appropriate medication adjustments made.
- Deferiprone has been shown to to be safe in regards to the liver with no progression of fibrosis[296].

- Splenectomy may contribute to the speed of iron loading in the liver[297].
- There is preliminary data to suggest Deferasirox has benefits on liver fibrosis beyond a chelating effect[166].
- Due to better overall care of thalassemia and iron overload, HCV is becoming a more common cause of morbidity and mortality, particularly in areas with high HCV prevalence[309,310].
- The magnitude of effect of HCV infection and iron on liver fibrosis and progression is controversial[298-301].
- Traditional HCV therapy used PEG IFN alone or with Ribavarin[302-307].
- Active HCV may downregulate hepcidin, contributing to increased liver iron deposition[294].
- Ribavarin therapy for HCV does not increase liver iron as much as would be expected from the increased transfusion requirements[294]. It is hypthesised that chelation is more effective when the virus is less active.
- Deferiprone should be avoided, if possible, with concomitant IFN therapy due to increased risk of significant neutropenia[295].
- Where genotype (and SNPs) permits[311,312], novel HCV therapies should be used in preference to IFN and Ribavarin treatment due to higher rates of SVR and minimal side effect profile.
- Patients with end stage liver disease and cirrhosis should be followed by a hepatologist[313].
- Patients with cirrhosis should be followed for the development of hepatocellular carcinoma with six-monthly albumin, INR, PTT and liver ultrasound[314,315].
- In the presence of elevated liver iron, liver fibrosis, and cirrhosis may be accelerated by alcohol, liver-toxic drugs, and untreated viral hepatitis. Patients should be encouraged to minimize alcohol intake and physicians should limit exposure of patients to hepatotoxic drugs.
- Management of HCC should be by a comprehensive tumour board with options including radiofrequency ablation and surgery as well as liver transplantation[316].