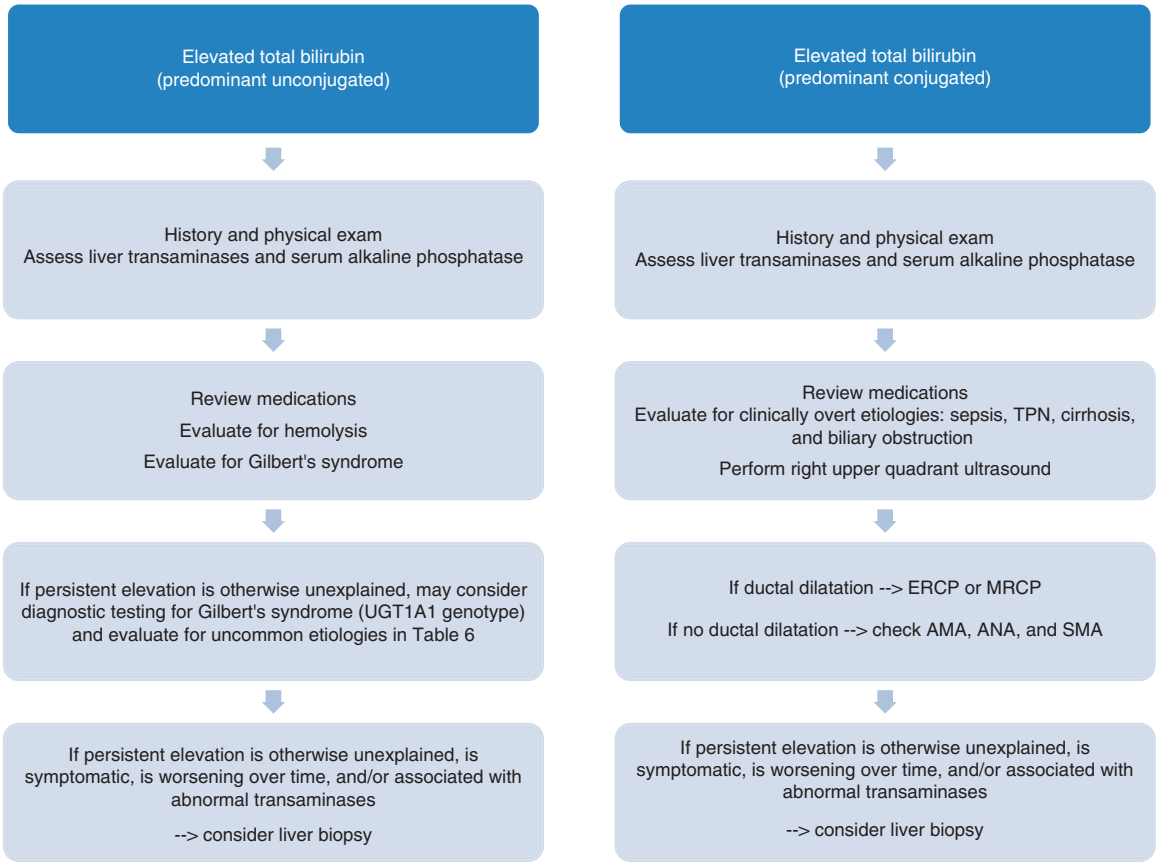

Figure 5. Algorithm for evaluation of elevated serum total bilirubin.

In contrast to indirect hyperbilirubinemia, conjugated (direct) hyperbilirubinemia generally implies the presence of parenchymal liver damage or biliary obstruction. This is associated with a number of hepatic disorders which result in decreased excretion of bilirubin into the bile ductules, and leakage of bilirubin from hepatocytes into serum. Total serum bilirubin levels may exceed 30 mg/dl in cases of severe liver damage, including alcoholic hepatitis with cirrhosis, and may be seen in advanced cirrhosis patients with sepsis and/or renal failure (51,96,97). In addition, an isolated hyperbilirubinemia may be seen after major surgery and typically resolves (98). The approach to elevated bilirubin is shown in **Figure 5**.

There are two rare inherited conditions associated with direct hyperbilirubinemia: Dubin–Johnson syndrome and Rotor syndrome where the direct bilirubin is ~50% of the total with all other liver tests being normal including alkaline phosphatase and GGT levels. It is not necessary to distinguish the two disorders. Dubin-Johnson syndrome occurs due to a defect in the multidrug resistance canalicular enzyme while Rotor syndrome appears to be related to defective bilirubin storage by hepatocytes (99). Causes of elevated bilirubin are listed in **Table 6**.

In summary, clinicians often encounter elevated liver chemistries in practice. The evaluation of elevations of AST and ALT levels are guided by the clinical presentation and the degree of elevation. A normal ALT should be <29–33 IU/l in males and 19–25 IU/l in females. Minimal elevations may be approached by a history and examination, discontinuation of hepatotoxic medicines and all alcohol consumption, in addition to an evaluation for hemochromatosis, fatty liver and viral hepatitis. An evaluation for autoimmune liver disease, Wilson's disease, and alpha-1antitrypsin deficiency is also warranted if the above tests are normal. Higher degrees of elevation (5–15 times the upper limit is normal) should be approached with an evaluation for viral hepatitis A, B, and C, iron panel, ceruloplasmin, alpha-1 antitrypsin phenotype, and autoimmune markers. If there are signs of acute liver failure, urgent hepatology consultation with referral to a liver transplant center should be undertaken immediately. Those who present with an elevation in alkaline phosphatase with normal AST, ALT, and bilirubin levels should have their alkaline phosphatase elevation confirmed with a GGT level and if elevated an ultrasound of the liver should be ordered. If the imaging is normal, autoimmune markers should be ordered. A liver biopsy may ultimately be required to obtain a diagnosis. An elevated bilirubin should be evaluated by determining conjugated and unconjugated fractions of bilirubin. An elevated conjugated bilirubin implies parenchymal liver damage or biliary obstruction. Extrahepatic causes such as hemolysis should also be assessed. Right upper quadrant ultrasound should be performed in patients