

Jaundice (Non-Neonatal)

1. Background

Jaundice is a yellowish discolouration of the skin, sclera, and mucous membranes due to elevated bilirubin as result of abnormal bilirubin metabolism and/or excretion. The bilirubin can either be unconjugated (indirect bilirubin) or conjugated (direct bilirubin). Unconjugated bilirubin is poorly soluble in water; while bilirubin conjugated to glucuronic acid makes it soluble in water. Unconjugated bilirubin disorders are much more common in children and are usually distinct from disorders of conjugated bilirubin.

Total serum bilirubin is normally less than 17 $\mu\text{mol/L}$ and jaundice can be readily detected when serum total bilirubin is greater than 85 $\mu\text{mol/L}$.

- Unconjugated hyperbilirubinemia = increased total serum bilirubin level with <15% in the conjugated form
- Conjugated hyperbilirubinemia = increased total serum bilirubin level with >20% in the conjugated form

It is critically important to identify the underlying cause of jaundice so that appropriate treatment can be initiated as soon as possible, if required. Jaundice occurs in all age groups but is much more common in neonates and infants. The differential diagnosis in older children and adolescents however, is very different from infants and neonates and thus will be explored here. Although the presence of jaundice suggests pathology, it is non-specific; thus this topic write-up explores bilirubin metabolism as well as common causes of jaundice in the older child and adolescent.

2. Bilirubin Metabolism

Bilirubin is a pigmented breakdown product of heme metabolism.

- 70-80% of total body bilirubin is stored in senescent red blood cells (RBCs)
- 20-30% is from prematurely destroyed erythroid cells in the bone marrow and from turnover of hemoproteins (ie: myoglobin and cytochrome)

RBCs travel intravascularly to cells of the reticuloendothelial system (spleen and liver primarily) where they are phagocytosed by macrophages that contain catabolic enzymes and heme oxygenase (HO). HO catalyzes the reaction that cleaves the heme (porphyrin) ring thus releasing end products biliverdin, carbon monoxide, and iron. A second reaction catalyzed by biliverdin reductase converts biliverdin to unconjugated bilirubin. This bilirubin is insoluble in water and thus is bound to albumin and transferred to the liver. Unconjugated bilirubin is taken up

by carrier-mediated membrane transport soon to be made soluble through conjugation.

Within the hepatocyte, unconjugated bilirubin is bound to ligandin, which traps it inside the cell. Processing occurs in the endoplasmic reticulum (ER) of the hepatocyte where the bilirubin is conjugated to glucuronic acid. This reaction solubilizes the bilirubin. Conjugated bilirubin products, bilirubin monoglucuronides and bilirubin diglucuronides, are generated in disproportionate amounts (80% bilirubin diglucuronides) and diffuse from the ER before being actively transported into bile canaliculi, and eventually into the general pool of bile.

Conjugated bilirubin flows in bile into the small intestine via the major duodenal papilla. Once it reaches the distal ileum and proximal colon it is hydrolyzed to unconjugated bilirubin by bacterial beta-glucuronidases. Unconjugated bilirubin is then reduced further by normal gut bacteria to colourless urobilinogen and stercobilin that will face one of three fates:

1. 80-90% will be excreted in feces as is or in its oxidized orange form, urobilin
2. 10-20% is recycled (passively absorbed, secreted into venous blood and re-secreted by the liver)
3. A minimal amount is excreted in urine.

3. **Questions to Ask:**

- Age at first presentation
- Ethnic origin
- Jaundice – usually becomes apparent when the serum bilirubin concentration is >32 $\mu\text{mol/L}$
- Any history of dark, tea coloured urine or acholic (pale) stools?
- Any yellowing of the whites of the eyes?
- Abdominal pain? Pruritus?
- Family history of jaundice or consanguinity – may suggest inherited disorder
- Risk factors for viral hepatitis – including maternal-infant transmission, blood transfusions, IV drug abuse, high risk sexual activities
- Medications/toxic exposures
 - o Especially acetaminophen abuse or misuse
- Dietary history – appetite, carotene intake, fava bean ingestion if G6PD suspected
 - o Sclera are NOT discoloured with carotenemia
- Recent travel

4. **Differential Diagnosis:**

The differential diagnosis of jaundice in a child is extensive and one must first classify the hyperbilirubinemia as unconjugated or conjugated. One may also classify jaundice into prehepatic, hepatic and post-hepatic causes. In this review,

we will discuss the differential diagnosis in terms of unconjugated and conjugated hyperbilirubinemia. It is important to remember that the acute onset of jaundice may in fact be the first clinical manifestation of unrecognized chronic liver disease.

Unconjugated Hyperbilirubinemia:

- Hemolytic Anemias (Excessive hemolysis)
 - RBC membrane disorders (ie. hereditary spherocytosis)
 - Enzyme defects (ie. Glucose-6-phosphate dehydrogenase (G6PD) deficiency, pyruvate kinase deficiency)
 - Hemoglobinopathies (ie. sickle cell, alpha and beta thalassemia)
- Inherited Disorders:
 - Gilbert's syndrome – autosomal recessive disorder seen in 5% population
 - Mild unconjugated hyperbilirubinemia as a result of a mutation in UGT1 that impairs the function of UDP glucuronosyl transferase enzyme (thus unable to conjugate bilirubin effectively)
 - Triggered with intercurrent infection, exercise, stress
 - Criglar-Najjar – very rare autosomal recessive disorder
 - Complete absence or limited activity of UDP glucuronosyl transferase enzyme
 - Usually presents in first few days of life

Conjugated Hyperbilirubinemia:

- Infections (result from intrahepatic cholestasis)
 - Hepatitis A, B, C, D and E
 - Epstein Barr Virus (EBV)
 - Cytomegalovirus (CMV)
 - Herpes Simplex Virus (HSV)
 - Gram negative bacterial infections and sepsis
- Metabolic Liver Disease
 - Wilson's Disease – autosomal recessive disorder of copper metabolism
 - Alpha-1 Antitrypsin Deficiency – autosomal codominantly inherited disease
 - Cystic Fibrosis – autosomal recessive disease; hepatobiliary dysfunction develops in up to 2/3rds of patients with CF
- Biliary Tract Disorders (Extra- or posthepatic biliary tract disorders that cause obstructive type of jaundice with icterus, dark urine, acholic stools and pruritus)
 - Cholelithiasis
 - Cholecystitis
 - Choledocal Cyst – congenital cystic dilatations of the intra- or extrahepatic bile ducts

- Sclerosing Cholangitis – chronic fibro-obliterative disease, often associated with inflammatory bowel disease
- Autoimmune Liver Disease
 - Type 1 – associated with anti-smooth muscle antibodies
 - Type 2 – associated with anti-liver kidney microsomal antibodies
- Hepatotoxins
 - Acetaminophen – ****leading cause of fulminant hepatic failure in older children and adolescents****
 - Alcohol
 - Anticonvulsants
 - Anesthetics
 - Chemotherapeutic agents
 - Antibiotics
 - Oral Contraceptives
- Vascular Causes
 - Budd Chiari syndrome – clinical picture of abdominal pain, ascites and hepatomegaly caused by obstruction of the hepatic veins
 - Veno-occlusive disease

5. Procedures for Investigation:

- Physical Examination (Always including vital signs and growth parameters)
 - General appearance → jaundice, sclera icterus, pallor, malnutrition
 - Signs of chronic liver disease → palmar erythema, spider nevi on chest/upper extremities, etc
 - Generalized lymphadenopathy, pharyngitis (EBV infection)
 - Eyes – Kayser-Fleischer (KF) rings (Wilson's disease)
 - Liver – careful palpation and percussion to assess texture and size
 - Nodular shrunken liver suggests cirrhosis
 - Tender, hepatomegaly suggests acute hepatitis
 - Spleen – splenomegaly (hemolysis, EBV infection)
 - Abdomen – distension, ascites
 - Neurologic – confusion, asterixis, hyperreflexia may all be features of hepatic encephalopathy
- Investigations
 - Bilirubin fractionation
 - Unconjugated hyperbilirubinemia → most often due to hemolytic disease in this age group
 - CBC, reticulocytes, direct and indirect Coombs test, haptoglobin, and Hb electrophoresis (if suspecting hemolytic disease)
 - Conjugated hyperbilirubinemia → suggests hepatobiliary disease
 - CBC, liver enzymes (ALT, ALT, GGT, ALP), albumin, total protein, coagulation factors (INR, PT and PTT)

- Liver function tests include glucose, coagulation profile (PT is the most sensitive), albumin, cholesterol and ammonia (not liver enzymes)
- Predominant elevation of ALT/AST suggests hepatocellular injury; whereas predominant elevation of ALP/GGT suggests biliary tract disease
- Further lab investigations are directed toward finding a diagnosis and may include:
 - Abdominal ultrasound – to establish hepatic architecture and rule out biliary tract disease
 - Abdominal CT, Endoscopic Retrograde Cholangiopancreatography (ERCP)
 - Hepatitis serologies
 - EBV serology and/or Monospot
 - Serum alpha-1 antitrypsin levels
 - Immunoglobulins, ANA, ASMA, anti-liver kidney microsomal Ab
 - Serum ceruloplasmin, 24 hr urinary copper excretion

6. Conclusion

Jaundice is a non-specific indicator of possible pathology. A thorough history and physical examination coupled with appropriate laboratory tests can assist with accurate diagnosis. Supplementary radiological imaging is often indicated. The underlying etiology of jaundice in the older child and adolescent varies greatly from infants and neonates and thus, a good approach to and knowledge of your differential diagnosis (unconjugated versus conjugated hyperbilirubinemia) is essential. Due to the wide spectrum of potential causes of jaundice; its treatment and prognosis varies accordingly.

7. References:

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