JAUNDICE

Jaundice, or icterus, refers to the yellow pigmentation of the skin, sclera or urine by bilirubin. Normal serum bilirubin levels range from 0.3 to 1.0 mg/dl. The level at which jaundice can usually be recognised is 2 to 2.5 mg/dl but this varies.

The sclera contains a lot of elastin which has a special affinity for bilirubin, hence its pigmentation. Jaundice must be distinguished from carotenaemia, due to carotenoid pigments in the blood stream, which causes yellowish discolouration of the skin, but not the sclera.

80 to 85 percent of bilirubin is derived from the catabolism of haemoglobin present in senescent red blood cells. The other 15 to 20 percent comes either from the destruction of maturing erythroid cells in the bone marrow or from non-erythroid compounds, especially in the liver, involving the turnover of haeme and haeme proteins such as cytochrome, myoglobin and haeme-containing enzymes.

Unconjugated bilirubin is transported in the plasma tightly bound to albumin. Some conjugated bilirubin is loosely and reversibly bound and some is bound very tightly and irreversibly. Conjugated bilirubin appears in the serum when there is cholestasis. Tightly bound bilirubin does not appear in the urine.

Bilirubin is found in body fluids such as the cerebrospinal fluid, joint effusions and cysts in proportion to the albumin content of the fluids and is absent from true secretions such as tears, saliva and pancreatic juice.

Hepatic metabolism of bilirubin involves uptake, conjugation and excretion.

In conjugation, the water-insoluble unconjugated bilirubin is converted to water-soluble bilirubin glucuronide which can be excreted by the liver cell into bile.

Secretion of conjugated bilirubin is the energy dependent rate limiting step, and the one most susceptible to impairment when the liver cell is damaged. Impairment leads to a decreased excretion of bilirubin into the bile, and re-entry of conjugated bilirubin into the blood stream.

The Intestinal phase

The bilirubin glucuronide excreted into the intestinal lumen, may be excreted in the stool or metabolised to urobilinogen and related products by the action of bacteria in the lower part of the small intestine and the colon. Conjugated bilirubin is not reabsorbed.

Urobilinogen is reabsorbed from the small intestine into the portal blood. Some urobilinogen is re-excreted by the liver into the bile (enterohepatic circulation). The rest is excreted in the urine. In hepatocellular disease (hepatic excretory mechanism becomes impaired) and in haemolytic anaemia (greatly increased production of bilirubin), the urinary urobilinogen may increase considerably.

Renal excretion of bilirubin

Normally, the urine contains undetectable levels of bilirubin. Unconjugated bilirubin is not filtered or excreted by the kidneys because it is tightly bound to albumin. The unbound fraction of conjugated bilirubin is dialysable and is filtered by the renal glomeruli.

Elevated levels of plasma bile salts may explain the increased renal excretion of conjugated bilirubin, leading to a plateau at 30 to 40mg/dl, while with severe hepatocellular injury, where there are no bile salts in the plasma, the levels may be much higher.

Test for bile pigments

The van den Berg reaction in an aqueous medium measures the water soluble fraction of bilirubin. In methanol the total bilirubin level is measured. The total minus direct gives the amount of indirect (unconjugated) bilirubin in the serum.

Table. Differences between conjugated and unconjugated bilirubin

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<thead>
<tr>
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<th>Unconjugated</th>
<th>Conjugated</th>
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<tbody>
<tr>
<td>Water solubility</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Affinity for lipids</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Renal excretion</td>
<td>-</td>
<td>+</td>
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<tr>
<td>van den Bergh reaction</td>
<td>Indirect</td>
<td>Direct</td>
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<tr>
<td>Binding to serum albumin (reversible)</td>
<td>+++</td>
<td>+</td>
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<tr>
<td>Formation of bilirubin albumin</td>
<td>Complex (Irreversible)</td>
<td>-</td>
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Types of jaundice

A simple anatomical classification into three predominant types, Prehepatic, hepatic and cholestatic helps clinical diagnosis and management.

Pre-hepatic: This group is marked by an increase in total and unconjugated bilirubin levels with normal hepatic enzyme values. Billirubin cannot be detected in the urine. The cause may be haemolysis or a familial disturbance of billirubin uptake or conjugation.

Hepatic: The jaundice usually comes on rapidly. Fatigue and malaise are conspicuous. Varying degrees of liver failure-personality change, flapping tremor, coma, may be manifested. There may be fluid retention in the form of oedema and ascites. Serum biochemistry reveals elevated enzymes. (eg. viral hepatitis, drug induced hepatitis) With time peripheral stigmata of chronic liver disease, eg. spider naevi, palmar erythema, gynaecomastia, etc may develop.

Cholestatic: This presents because adequate amounts of bile do not reach the duodenum. The patient remains relatively well in the initial phases, for cholestasis per se is compatible with reasonably good health. Pruritus is prominent. With time, the patient becomes increasingly pigmented. The serum shows an elevation of conjugated bilirubin, alkaline phosphatase and cholesterol. Steatorrhoea is responsible for weight loss and there is malabsorption of fat soluble vitamin A, D and K and of calcium.

Approach to a patient with jaundice

A careful history and physical examination is essential. Nausea, fatigue and fever suggest type A viral hepatitis. A history of injections, blood transfusion and a prodrome of arthralgia suggest a type B viral hepatitis. Contact with jaundice patients in camps, hospitals, schools or communities should be noted. Take a drug history to identify and remove offending agents. An alcoholic who presents with jaundice probably has alcoholic liver disease. Progressive deterioration in health and weight loss suggests and underlying carcinoma. A family history is helpful to diagnose conditions like Wilson’s disease, haemolytic jaundice and congenital hyperbilirubinemia.

On examination, the presence of asterixis indicates severe liver disease and impending coma. Skin change include purpuric spots and easy bruising. Cutaneous manifestations of cirrhosis include spider naevi, palmar erythema, white nails and loss of secondary sexual characteristics. In severe cholestasis, scratch marks, melanin pigmentation, xanthomas on the eyelids and clubbing may be seen. Malignant nodules may be present in the skin. Dilated peri-umbilical veins indicate a portal collateral circulation. Ascites may be due to cirrhosis or malignant disease of the peritoneum. A very large nodular liver suggests cancer. The liver may be enlarged and tender in hepatitis and in CCF, small and shrunken in cirrhosis. A bruist over the liver indicates acute alcoholic hepatitis or primary liver cancer. In obstructive jaundice due to cholelithiasis, the gall bladder may be tender and Murphy’s sign positive. A palpable gall bladder suggests malignant growth obstructing the common bile duct. The abdomen must be carefully examined for any primary tumour. A rectal examination may pick up an unsuspected carcinoma or unsuspected GI bleeding.

Investigations

Examination of the urine and faeces is often helpful. Bilirubinuria is an early sign in hepatic jaundice. Persistent absence of urobilinogen suggest total obstruction of the common bile duct. Persistent excess of urobilinogen with a negative billirubin test supports the diagnosis of haemolytic jaundice.

Significant occult blood in the stools suggests an ampullary carcinoma or portal hypertension.

The serum bilirubin level confirms jaundice. Clinically evident jaundice reflects a serum bilirubin value over 2.5mg/dl. SGOT (AST) and SGPT (ALT) are markedly elevated in hepatitis. A disproportionately low ALT in the presence of an elevated AST suggests alcoholic/ hepatitis. A markedly raised alkaline phosphatase suggests biliary obstruction and cholestasis. A low serum albumin with a reversal of the A/G ratio is found in hepatic cirrhosis.

Investigations for haemolysis include haemoglobin, blood film including reticulocyte count, and Coombs test. If the prothrombin time is prolonged, vitamin K 10 mg given intravenously for three days tends to return to normal in cholestasis while in patients with hepatocellular disease it shows little change.

An upper GI endoscopy helps to identify varices and looks for malignant growth in the stomach and the periampullary region. A chest x-ray may help pick up secondaries in the lung or an elevated diaphragm due to liver enlargement.
Ultrasonography is a very valuable investigation if a patient has cholestatic jaundice.

For a tissue diagnosis, do a needle biopsy of the liver provided the haemoglobin is normal, the clotting factors are adequate (platelets > 80,000 patient prothrombin time within 4 seconds of control prothromin time) blood is available, and the patient is cooperative.

Treatment: will depend on the cause of the jaundice. In hepatic jaundice an offending cause like a drug should be withdrawn immediately. For viral hepatits, rest and good nutrition should be ensured, early signs of impending coma should be looked for and treated if present. Patients with cholestatic jaundice need surgery if they have an obstructive lesions. Those with intra-hepatic cholestasis should be managed conservatively. In patients with 'pre-hepatic' jaundice, the cause for the hemolysis should be identified and managed. The familial non-nemolytic hyperbilirubinemias have an excellent prognosis and once the diagnosis is made on the basis of a family history, duration, absence of stigmata of hepatocellular disease and normal hepatic histology, the patient can be reassured.