Approach To Jaundice

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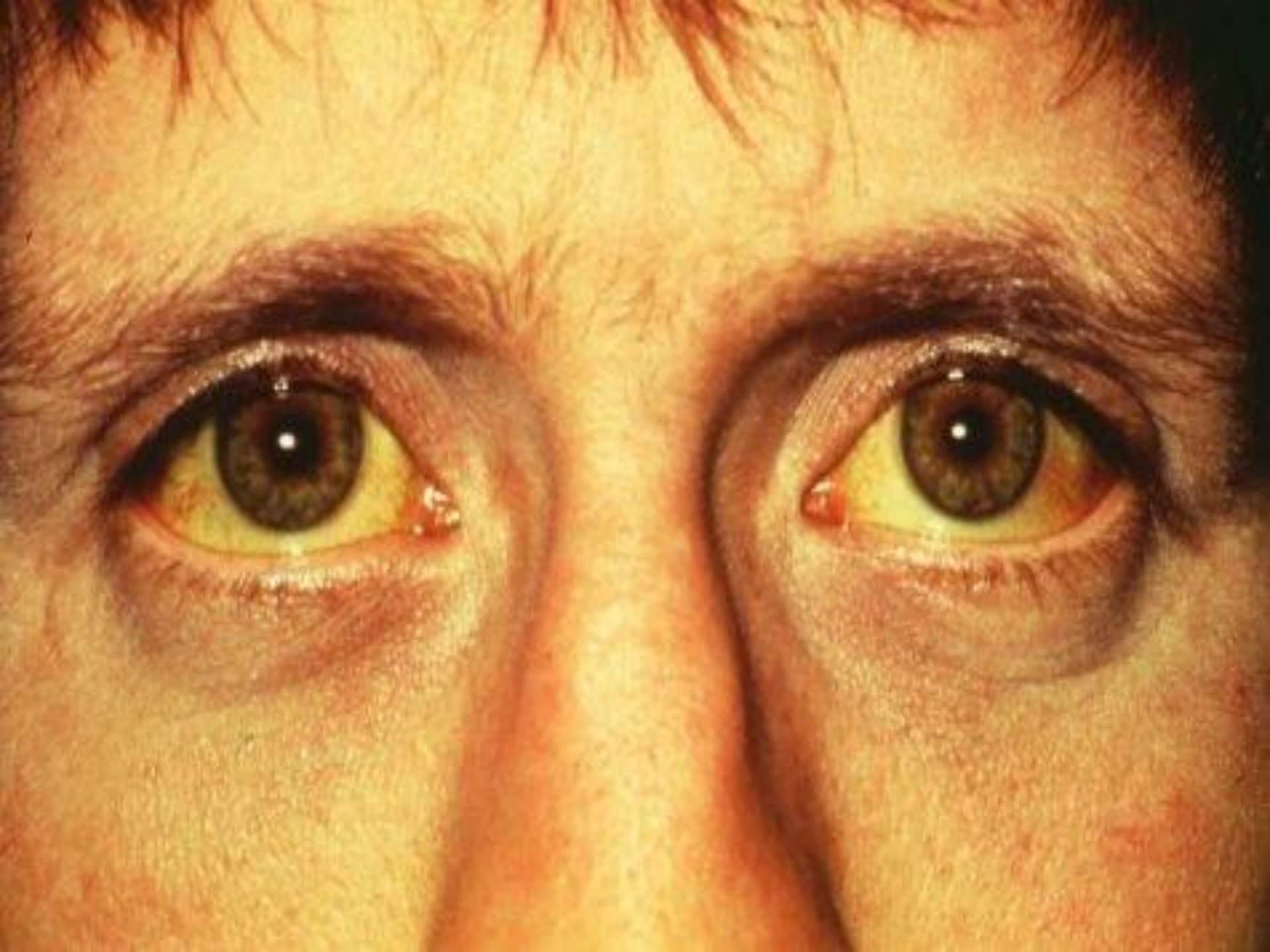


Jaundice

- Jaundice, a yellow discoloration of the sclera, skin, and mucous membranes, results from the accumulation of bilirubin, a by-product of heme metabolism.
- It must be distinguished from yellow pigmentation caused by ingesting foods rich in carotene (carrots) or drugs such as quinacrine or busulfan.

Jaundice

- Jaundice is caused by many disease processes ranging from benign to life threatening.
- History and physical examination remain important tools in evaluating the etiology of jaundice.

Bilirubin Metabolism

- Bilirubin breakdown of mature RBCs in the RES.
- 15% of bilirubin comes from the catabolism of other haem-containing proteins, such as myoglobin.
- 250 – 300 mg of bilirubin are produced daily.
- Biliverdin is formed from the haem and this is reduced to form bilirubin.
- The bilirubin produced is unconjugated and is transported to the liver attached to albumen.

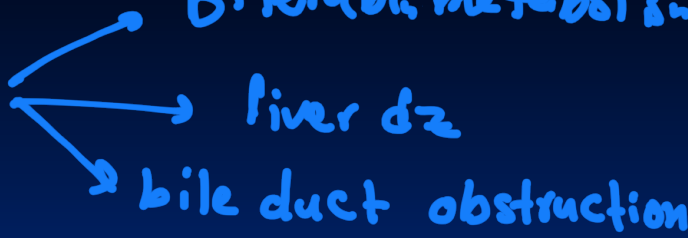
Jaundice

- Normal bilirubin levels are 0.4 ± 0.2 mg/dL, and more than 95% is unconjugated.
- Hyperbilirubinemia is defined as a total bilirubin level higher than 1.5 mg/dL, an unconjugated level higher than 1.0 mg/dL, and a conjugated level higher than 0.3 mg/dL.

Jaundice

- Generally, the serum bilirubin level must exceed 2.5 to 3.0 mg/dL for jaundice to be visible.
- Hyperbilirubinemia is separated into two classes: unconjugated (>80% of total bilirubin) and conjugated (>30% of total bilirubin).

Jaundice



- Jaundice can occur in four different ways:
  1- Increased bilirubin load as in haemolysis.
  2- Disturbance in the hepatic uptake & transport of bilirubin within the hepatocytes
  3- Defects in conjugation.
  4- Defects in the excretion of conjugated bilirubin across the canalicular cell membrane or an obstruction of the large biliary channels.

Differential Diagnosis of Jaundice and Hyperbilirubinemia

- From a practical standpoint, conditions that produce jaundice can be classified under the broad categories of isolated disorders of bilirubin metabolism, liver disease, and obstruction of the bile ducts.

Intial Evaluation

- When evaluating a patient with jaundice, initial steps include determining whether the hyperbilirubinemia is predominantly unconjugated or conjugated and whether there is any other laboratory evidence of hepatobiliary dysfunction.
- When there are associated biochemical liver abnormalities, further discrimination into a predominantly cholestatic or hepatocellular pattern is possible.

Intial Evaluation

- A hepatocellular pattern, as in this example characterized by ALT/AST elevated out of proportion to the alkaline phosphatase, should prompt a search for viral, autoimmune, toxicologic, and abnormal deposition disease.
  Acetaminophen is a common cause of mental status change, jaundice, and hepatocellular injury in the intensive care unit.

Intial Evaluation

- Liver biopsy may ultimately become necessary.
- Anatomic abnormalities are more common when there is a cholestatic pattern of injury characterized by an elevated alkaline phosphatase out of proportion to the AST/ALT.
- In those cases, ultrasound and possible other imaging may be indicated.

- Causes according to the aetiology.

Unconjugated Hyperbilirubinemia

- Increased bilirubin production (e.g., hemolysis, ineffective erythropoiesis, blood transfusion, resorption of hematomas)
- Decreased hepatocellular uptake (e.g., drugs such as rifampin, Gilbert's syndrome [secondary mechanism])
- Decreased conjugation (e.g., Gilbert's syndrome, Crigler-Najjar syndrome, physiologic jaundice of the newborn, drugs such as indinavir, atazanavir).

Conjugated or Mixed Hyperbilirubinemia

- Dubin-Johnson syndrome.
- Rotor's syndrome.

Hepatocellular Dysfunction

- Acute or subacute hepatocellular injury (e.g., viral hepatitis, hepatotoxins such as ethanol, acetaminophen; drugs such as isoniazid, phenytoin; ischemia such as in hypotension, vascular outflow obstruction, metabolic disorders such as Wilson disease, Reye's syndrome; pregnancy-related as in acute fatty liver of pregnancy, pre-eclampsia).

Hepatocellular Dysfunction

- Chronic hepatocellular disease (e.g., viral hepatitis; hepatotoxins such as autoimmune hepatitis; metabolic disorder such as hemochromatosis, Wilson disease, nonalcoholic fatty liver disease, α1-antitrypsin deficiency; celiac disease)

Hepatic Disorders with Prominent Cholestasis

- Diffuse infiltrative disorders (e.g., granulomatous diseases such as mycobacterial infections, sarcoidosis, lymphoma, Wegener's granulomatosis; amyloidosis; malignancy)
- Cholangiocyte injury (e.g., primary biliary cirrhosis; graft-versus-host disease; drugs such as erythromycin, trimethoprim-sulfamethoxazole; cystic fibrosis).

Hepatic Disorders with Prominent Cholestasis

- Miscellaneous conditions e.g., benign recurrent intrahepatic cholestasis; drugs such as estrogens, anabolic steroids; total parenteral nutrition, paraneoplastic syndromes, intrahepatic cholestasis of pregnancy; benign postoperative cholestasis.

Obstruction of the Bile Ducts

- Choledocholithiasis.
- Diseases of the Bile Ducts; Inflammation, infection (e.g., primary sclerosing cholangitis, AIDS cholangiopathy, postsurgical strictures)
  Neoplasms (e.g., cholangiocarcinoma).

Obstruction of the Bile Ducts

- Extrinsic Compression; Neoplasms (e.g., pancreatic carcinoma, metastatic lymphadenopathy, hepatocellular carcinoma, ampullary adenoma, lymphoma.
- Vascular enlargement (e.g., aneurysm, cavernous transformation of the portal vein [portal cavernoma]

History

- The onset of Jaundice in viral hepatitis is associated with a prodrome of ANV, malaise & myalgia.
- The onset of cholestasis is insidious, it is associated with pruritus.
- A history of fever with rigors, Rt upper abd. pain or a past history of biliary surgery suggest cholangitis.
- Dark urine & pale stool exclude the possibility of haemolytic jaundice.
- A history of multiple sex partners, travel, ethanol intake, drugs, bl. transfusion, needlestick exposure & tattooing is also important.

History

- Recent surgery with subsequent jaundice after one week may suggest halothane toxicity.
- Previous biliary surgery with subsequent jaundice may suggest stricture, residual stones or hepatitis.
- A family history of jaundice or liver disease suggests the possibility of hereditary hyperbilirubinaemia or genetic disorder such as Wilson disease.

Jaundice

The clinical assessment & basic biochemical parameters lead to three broad subgroups of patients:

1- Isolated elevation of s. bilirubin: when AST, ALT & ALP levels are normal.

2- Hepatocellular jaundice: when the AST & ALT levels are elevated out of proportion to the ALP levels.

3- Cholestatic jaundice: when the ALP level is elevated out of proportion to the AST & ALT levels.

Physical Examination

- The examination can assess the cause, severity, and chronicity of jaundice.
- Fever may occur with acute or chronic disease, although high fever warrants a search for a bacterial process.

Physical Examination

- Cachexia, muscle wasting, palmar erythema, a Dupuytren contracture, testicular atrophy, parotid enlargement, xanthelasma, gynecomastia, and spider angiomas suggest chronic liver disease.
- A shrunken, nodular liver with splenomegaly signals cirrhosis, whereas masses or lymphadenopathy raise the possibility of malignancy.
- A liver span of more than 15 cm suggests fatty infiltration, congestion, malignancy, or other infiltrative diseases.
- Ascites is found with cirrhosis, malignancy, and severe acute hepatitis.

Physical Examination

- A palpable, distended gallbladder suggests malignant biliary obstruction.
- Asterixis and changes in mental status are noted with advanced liver disease.

Physical Examination:

-Stigmata of CLD hepatocellular in origin.

-High fever, right upper abd. tenderness cholangitis & choledocholithiasis.

-Palpable abdominal mass Malignant obstructive Jaundice.

-Rt. upper abd. scar or palpable gallbladder Obst. J.

-Certain physical findings may suggest a particular liver disease:

*Hyperpigmentation haemochromatosis.

*Xanthoma PBC.

*Kayser-Fleischer rings Wilson disease.

Physical Examination:

- A systemic illness should be excluded e.g. distended jugular veins in constrictive pericarditis or Rt. Heart F in patient with hepatomegaly & ascites.
- Hard nodular liver 1ry or 2ry malignancy.
- Diffuse lymphadenopathy infectious mononucleosis or lymphoma.

Laboratory, Radiological & Histological Evaluation:

*Serum Biochemical Tests:

Bilirubin:

-The normal serum bilirubin is <1.5mg/dl of which <0.5% is conjugated.

-In haemolysis or genetic disorders e.g. Gilbert synd., there is unconjugated hyperbilirubinaemia (>90%).

-In hepatocellular j. >50% of bilirubin is conjugated.

-In obstructive jaundice, the circulating bilirubin is mainly conjugated.

Liver Enzymes:

- Enzymes raised in hepatocellular injury:

Aminotransferases include ALT (located in cytosol) & AST (located in mitochondria & cytosol).

- ALT is found mainly in liver while AST is also found in other tissues such as skeletal & cardiac muscle.
- ALT is more specific than AST in detecting liver dise.
- AST & ALT are released following hepatocyte necrosis.
- A marked raise in transaminases > 1000 U/L, is seen in AVH, ischaemic hepatitis & drug-induced liver disease.
- In alcoholic liver disease, the enzyme levels are rarely > 200-300 U/L, with AST:ALT ratio >2:1.

Enzymes raised in cholestasis:

- Alkaline Phosphatase (ALP), gamma-glutamyl transpeptidase (GGT) & 5'-nucleotidase (5'NT).
- ALP isoenzymes are also present in bone & placenta.
- Increase in ALP, GGT & 5'NT hepatobiliary origin.
- GGT levels are often disproportionately elevated in alcoholic liver disease.

Proteins:

- **Albumen:**

Albumen is synthesized by liver & has a half-life of 15-20 days.

Decreased level of albumen are seen in advanced hepatic cirrhosis & signify severe hepatic dysfunction.

S. albumen usually remain normal in acute hepatitis; falling values in this setting imply an unusual sever course

- **Globulins:**

Non-specific diffuse elevation is common in CLD.
There is a disproportionate elevation of IgG in autoimmune hepatitis, IgM in PBC & IgA in alcoholic liver disease.

INR & Prothrombin time (PT)

- INR/PT is a valuable index of the ability of liver to synthesize vit. K-dependent clotting factors.
- An increasing INR/PT implies relatively severe hepatocellular dysfunction.
- Exogenous administration of vitamin K will generally normalize a prolonged prothrombin time in patients with obstructive jaundice and intrahepatic cholestasis but not in patients with liver disease caused by hepatocellular injury.

Serologic Testing

- When imaging studies do not suggest biliary obstruction, jaundiced patients with biochemical evidence of hepatocellular dysfunction or cholestasis should be evaluated for underlying liver disease.

Serologic Testing

- Depending on the disorder suspected, screening laboratory studies may include viral serologies (including those for hepatitis B and C and, if the disease is acute, hepatitis A), serum levels of iron, transferrin, and ferritin (for hemochromatosis), ceruloplasmin (for Wilson disease), antimitochondrial antibodies (for primary biliary cirrhosis), antinuclear antibodies, smooth muscle antibodies, and serum protein electrophoresis or serum immunoglobulins (for autoimmune hepatitis), and tissue transglutaminase antibodies (for celiac disease).

Serologic Testing

- Confirmation of these diagnoses, as well as elucidation of diagnoses not revealed by serologic analysis, may be made by liver biopsy—and small bowel biopsy in the case of celiac disease.

Imaging for Jaundice

- RUQ Ultrasound
  - See stones, CBD diameter
- CT scan
  - Identify both type & level of obstruction
- ERCP
  - Direct visualization of biliary tree/panc ducts
  - Procedure of choice for choledocholithiasis
  - Diagnostic –AND- therapeutic (unlike MRCP)
- PTC useul of obstruction is prox to CHD
- Endoscopic Ultrasound or EUS

Imaging Procedures:

- Radiological imaging is important for the diagnosis of a focal liver mass or biliary disease. However, imaging plays little role in the evaluation of diffuse hepatocellular e.g. hepatitis.

Ultrasonography (US):

- It is a valuable but operator-dependent investigation.
- It has sensitivity of 55-91% & specificity of 82-95% for biliary obstruction.
- Although US may not detect stones in the extrahepatic bile duct, which may be obscured by overlying gas, it reliably establishes the presence of a dilated bile ducts.

Computed Tomography

- CT of the abdomen with intravenous contrast is an alternative noninvasive means of evaluating the possibility of biliary tract obstruction. Abdominal CT permits accurate measurement of the caliber of the biliary tree, with sensitivity and specificity rates of 63% to 96% and 93% to 100%, respectively, for detecting biliary obstruction; these rates are comparable with those for ultrasonography.
- Abdominal CT detects intrahepatic space-occupying lesions as small as 5 mm, is not operator-dependent, and provides technically superior images in obese persons and in those in whom the biliary tree is obscured by bowel gas.

MRCP

- Is a technical refinement of standard magnetic resonance imaging that permits rapid clear-cut delineation of the biliary tree without the need for intravenous contrast. MRCP appears to be superior to conventional ultrasound or CT for the detection of biliary tract obstruction and now plays a major role as a diagnostic test in this setting.
- Standard magnetic resonance imaging can be performed during the same examination if there is a question of a hepatobiliary or pancreatic mass or if a contrast allergy precludes CT. For detection of obstruction of the bile ducts, the sensitivity of MRCP is 82% to 100% and the specificity is 94% to 98%.

Endoscopic Ultrasonography

- EUS can detect obstruction of the bile duct and major intrahepatic bile ducts, with a sensitivity and specificity comparable with those of MRCP.
- EUS has the potential advantage of permitting biopsy of suspected malignant lesions, and under appropriate circumstances, the operator can proceed directly to ERCP for definitive biliary decompression . The risk of diagnostic EUS is comparable with that of diagnostic upper endoscopy; when needle biopsy is used, the mortality rate is approximately.
- EUS may be most useful in circumstances in which the patient is thought to be at high risk for complications of ERCP.

Endoscopic retrograde cholangiopancreatography (ERCP

- Permits direct visualization of the biliary tree. ERCP is more invasive than ultrasonography and CT. The procedure involves passage of an endoscope into the duodenum, introduction of a catheter into the ampulla of Vater, and injection of contrast medium into the bile duct; sedation and analgesia are necessary.

- ERCP is highly accurate in the diagnosis of biliary obstruction, with sensitivities of 89% to 98% and specificities of 89% to 100%.

- ERCP permits biopsy and brushings for cytology of distal biliary and periampullary lesions. Moreover, if a focal cause of biliary obstruction is identified maneuvers to relieve obstruction (e.g., sphincterotomy, stone extraction, stricture dilation, stent placement) can be performed during the same session.

- Rates of morbidity and mortality from untoward events, such as respiratory depression, aspiration, bleeding, perforation, cholangitis, and pancreatitis, are 3% and 0.2%, respectively, in patients undergoing ERCP.

Percutaneous transhepatic cholangiography: PTC

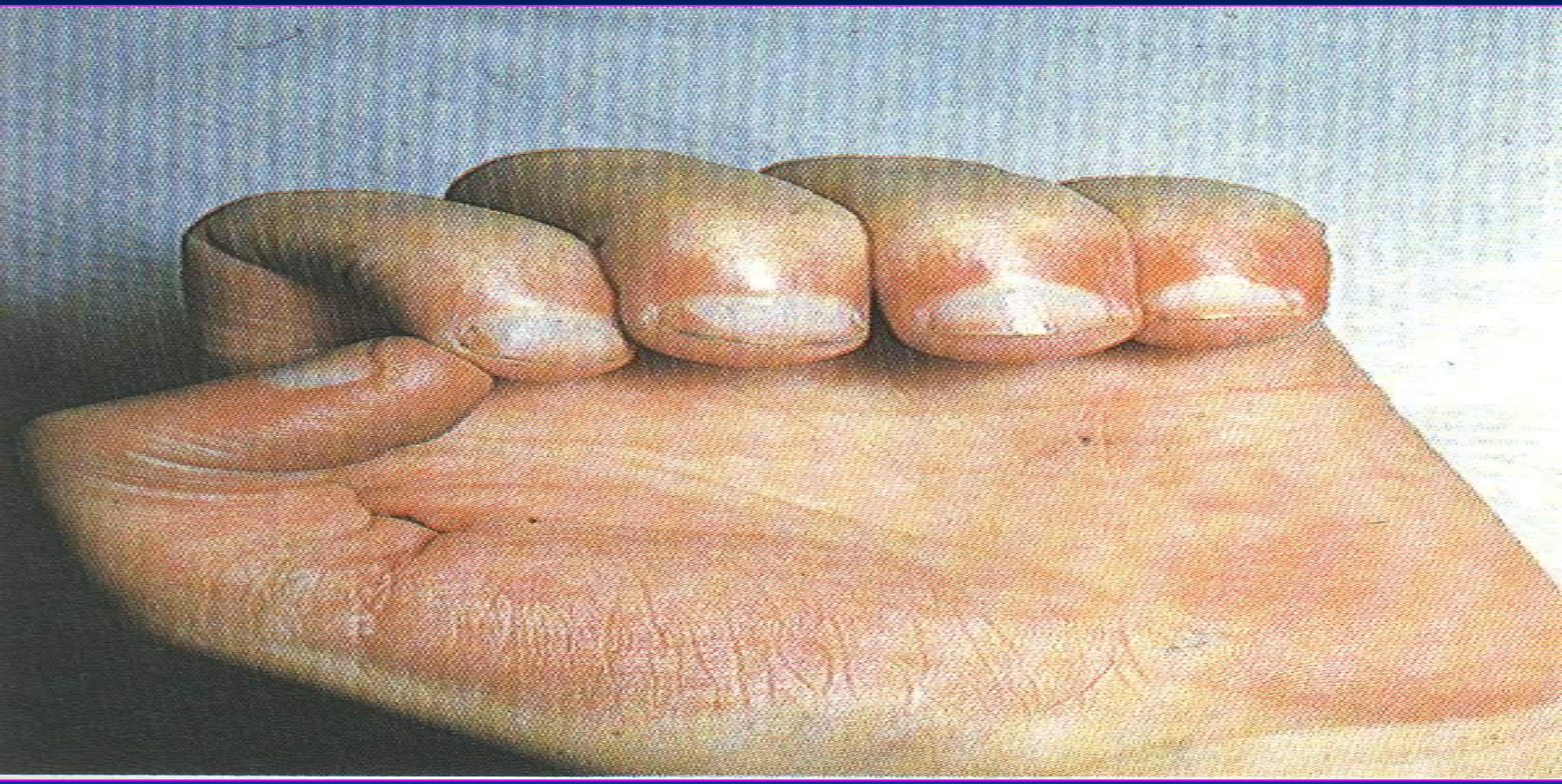
- IN PTC, direct contrast visualization of the biliary tree is obtained via a percutaneous needle puncture of the liver. It is useful if there is high biliary obstruction e.g. a tumour at the bifurcation of the hepatic ducts.
- It also permits therapeutic intervention such as stent insertion to bypass a ductal malignancy.

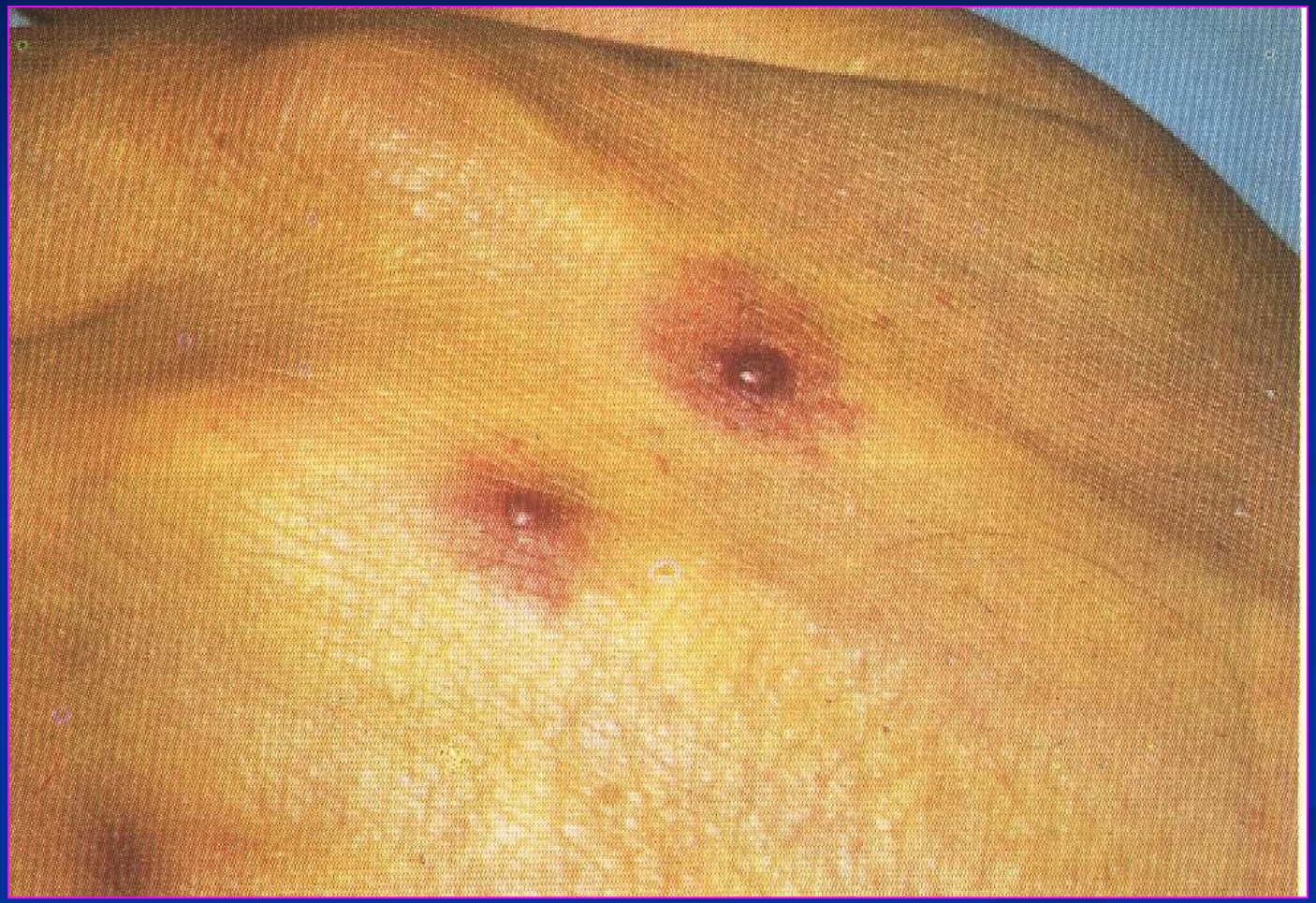
Liver Biopsy

- Liver biopsy provides precise information regarding hepatic lobular architecture and extent and pattern of fibrosis, and is most helpful for patients with persistent and undiagnosed jaundice. With special histologic stains and, if appropriate, quantification of copper or iron content, liver biopsy permits the diagnosis of viral hepatitis, fatty liver disease, hemochromatosis, Wilson disease, primary biliary cirrhosis, granulomatous hepatitis, and neoplasms.
- Liver histology may be entirely normal in acute biliary obstruction.

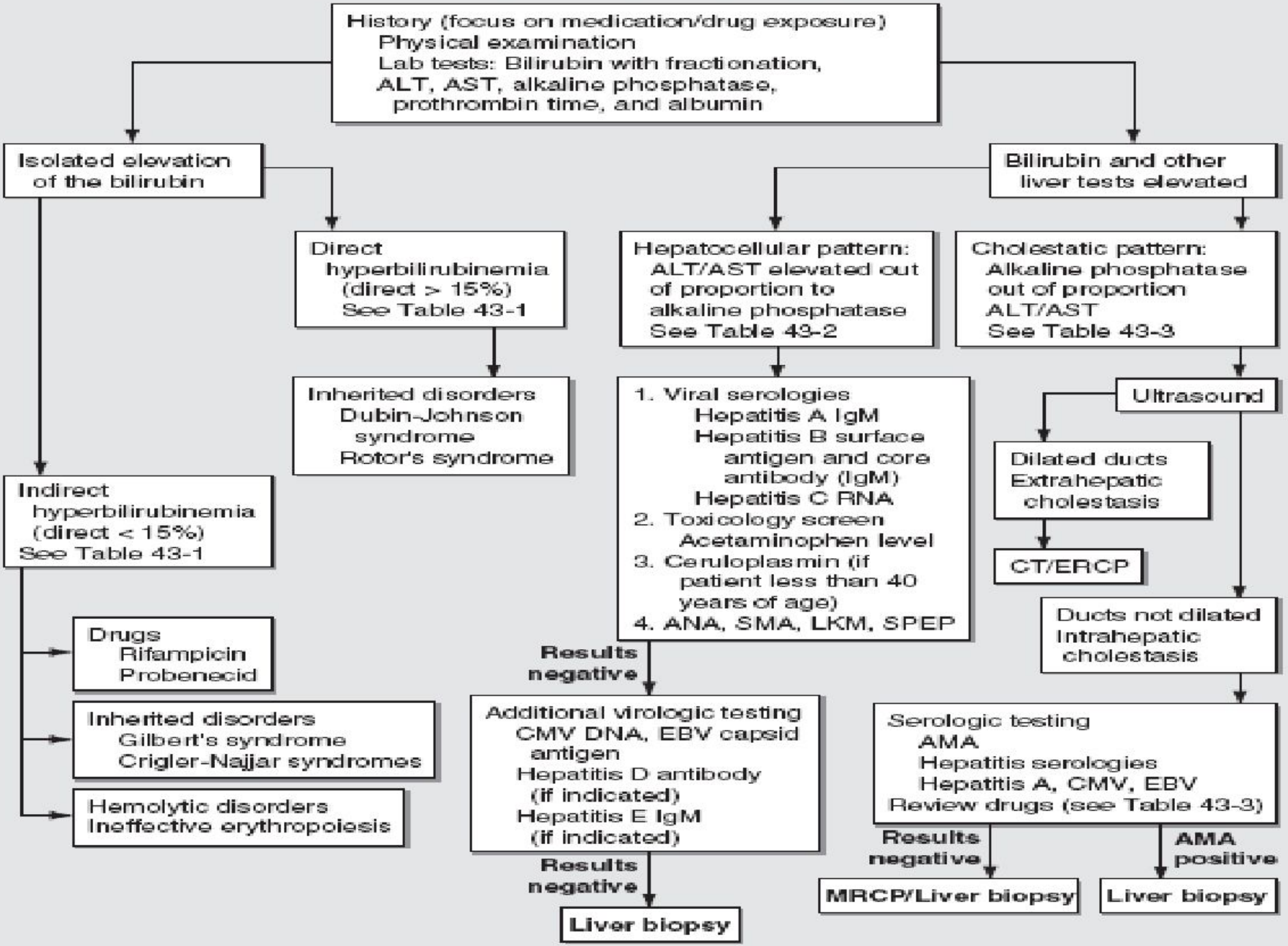
Liver Biopsy

- Liver biopsy is associated with a low but definite complication rate, predominantly from bleeding and perforation, and the need for hospitalization in 1% of cases; the mortality rate is approximately 0.01%.





Algorithm for Patient with Jaundice



THERAPEUTIC APPROACHES

- When jaundice is caused by liver disease, the optimal treatment is directed toward the underlying cause (e.g., cessation of ethanol, discontinuation of the offending drug, administration of antiviral agents, phlebotomy for hemochromatosis, immunosuppressive agents for autoimmune hepatitis).
- Therapy for hyperbilirubinemia per se is generally not necessary in adults, because the neurotoxicity of bilirubin is confined to disorders characterized by extreme elevations of unconjugated bilirubin in neonates and infants, such as physiologic jaundice of the newborn or type I Crigler-Najjar syndrome.

THERAPEUTIC APPROACHES

- The choleretic bile acid ursodeoxycholic acid (ursodiol) has been studied as a treatment for several cholestatic disorders.
- Ursodeoxycholic acid improves biochemical indices and has been suggested to slow disease progression in primary biliary cirrhosis.

THERAPEUTIC APPROACHES

- In the patient with obstruction of the bile ducts, therapy is typically directed at relieving the obstruction. Interventional endoscopic or radiologic approaches include sphincterotomy, balloon dilation of focal strictures, and placement of drains or stents; the alternatives are surgical.
- The therapeutic strategy chosen will depend, in part, on the location and likely cause of the obstructing lesion. Focal intrahepatic strictures may be amenable to an interventional radiologic approach, whereas lesions distal to the bifurcation of the hepatic ducts may be more suitably managed endoscopically (e.g., sphincterotomy for choledocholithiasis); mass lesions may require surgery.

Evaluation and Diagnosis

- *History*
- Most patients (approximately 85%) with ascites have cirrhosis.

- In about 15% of patients with ascites, there is a nonhepatic cause of fluid retention.

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