Jaundice as a Diagnostic and Therapeutic Problem: A General Practitioner's Approach

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Abstract

Background: Jaundice is a common clinical finding in clinical practice of hepatologists and general practitioners. It occurs when serum bilirubin levels exceed 3 mg/dL. **Summary:** In this review, we summarize the pathophysiological mechanism of jaundice, clinical approach to the patient with jaundice, and laboratory and imaging techniques. Clinical presentation of jaundice manifests through yellow skin and sclera coloration. Evaluation of every patient includes detailed medical history and examination. In the laboratory, evaluation of enzymes of hepatic inflammation as well as cholestatic enzymes with serum bilirubin must be included. Additional laboratory analysis and imaging modalities are needed in order to differentiate jaundice etiology. Moreover, imaging is available and needed in further evaluation, and treatment is dependent on the underlying cause. **Key Messages:** In this review, we will outline the pathophysiological mechanism of jaundice, clinical approach to the patient with jaundice, and diagnostic and treatment approach to these patients.

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Introduction

Jaundice is a clinical manifestation of elevated serum bilirubin. Accumulation of elevated serum bilirubin leads to yellow discoloration of the skin, sclera, and other mucous membranes known as jaundice or icterus. When serum bilirubin level exceeds 3 mg per dL, jaundice becomes clinically apparent. From general practitioners' (GPs') point of view, timely and adequate assessment of the patient with jaundice is of great importance [1]. A general approach to the patient with jaundice should include detailed medical history, careful clinical examination, and appropriate laboratory and imaging techniques (Fig. 1) [2]. Epidemiology data suggest that incidence of jaundice varies depending on the underlying cause, and it is more common in certain age groups. Namely, jaundice affects approximately 6 out of 10 otherwise healthy newborns, mainly due to immature hepatic conjugation and uptake [3]. Jaundice due to alcoholic liver disease, as well as nonalcoholic liver disease, is more common in men, while primary biliary cholangitis as an underlying cause of jaundice is dominantly seen in women [4]. In this review article, we aim to provide a systematic approach to the patient with jaundice, especially in terms of diagnosis and therapy.

Fig. 1. Approach to the patient with jaundice. AST, aspartate aminotransferase; ALP, alkaline phosphatase; US, ultrasound.

Bilirubin Metabolism and Pathophysiology of Jaundice

Degradation of heme is responsible for bilirubin formation. The majority of hem derives from hemoglobin of erythrocytes, whereas small parts originate from ineffective erythropoiesis and degradation of other hem-containing proteins such as myoglobin, catalases, and cytochrome P450 isoenzymes [5]. Bilirubin formation is a 2-phase process, where in the first phase, heme transforms to biliverdin, and in the second phase through reductase, biliverdin is transformed to unconjugated bilirubin [6]. Unconjugated bilirubin is water insoluble and as such is transported with albumin to the liver, where conjugation occurs. The process of conjugation in the liver is intermediated by uridine diphosphate (UDP)-glucuronyltransferases. Conjugated bilirubin from liver cells is transferred to the biliary system and through bile it enters the intestines. Intestinal cells predominantly absorb conjugated bilirubin, which is later evacuated via urine as urobilinogen, while unabsorbed part is evacuated through stool as stercobilinogen. Elevation of unconjugated or conjugated bilirubin as a result of an alteration of bilirubin metabolism leads to jaundice [7]. Bearing in mind the

pathophysiological mechanism of bilirubin, etiology of jaundice could be divided into prehepatic, hepatic, and posthepatic causes (Table 1).

Prehepatic jaundice occurs earlier than bilirubin enters the hepatocytes, and it is caused by increased bilirubin production or may be the result of interference of hepatocyte uptake by certain medications. A wide range of extrahepatic disorders may be the underlying cause of prehepatic jaundice such as hemolysis, ineffective erythropoiesis, blood transfusions, or hematoma absorption [8]. Hemolysis may be inborn or acquired, with a wide range of defect mechanisms such as atypical structure of hemoglobin, defects of erythrocyte membrane or enzymes, immune or mechanical deterioration of erythrocytes, or hypersplenism [9]. Additionally, hemolysis develops due to extravascular or intravascular degradation of erythrocytes. Drugs which may interfere with hepatocyte bilirubin uptake and further contribute to prehepatic jaundice are antivirals, antibiotics, and immunosuppressives [10].

Hepatic causes leading to hyperbilirubinemia are multiple. Several disorders of hepatocyte enzymatic activity have influence on conjugation processes, with the Gilbert syndrome as the most common in general population [11]. The affected gene in this benign condition is *UGT1A1* with a metabolic defect of decreased bilirubin conjugation. Interestingly, different mutations of the same gene *UGT1A1* lead to development of the very rare Crigler-Najjar syndrome, with severely decreased bilirubin conjugation in type II or even complete absence of conjugation in type I [12]. Dubin Johnson syndrome and Rotor syndrome are benign familial metabolic defects, autosomally recessive inherited, characterized by impaired export of conjugated bilirubin [13]. Different liver diseases are accompanied by hyperbilirubinemia and jaundice with additional impairment of other liver function tests. Hepatocellular injury and cholestatic disorders are commonly seen in patients with various liver disorders. Conditions that manifest in acute or chronic hepatocellular dysfunction are viral hepatitis, autoimmune liver disease, metabolic liver diseases, toxic liver injury, or ischemic hepatitis. Additionally, intrahepatic cholestatic disorders include infiltrative diseases, primary biliary cholangitis, familial disorders, and certain drugs.

The etiopathogenesis of posthepatic jaundice is obstruction of biliary drainage. Posthepatic jaundice may be caused by bile duct obstruction due to choledocholithiasis, diseases of the bile duct including infectious, inflammatory, and malignant diseases, or compression outside the bile duct [14].

Table 1. Differential diagnosis of jaundice

Prehepatic causes of jaundice	Hepatic causes of jaundice	Posthepatic causes of jaundice
Hemolysis	Drug-induced liver injury	Surgical strictures
Hemolytic reactions	Alcoholic hepatitis	Bile stones
Hematoma	Autoimmune hepatitis	Bile duct cancers
Pulmonary infarction	Hemochromatosis Ischemic hepatitis	Compression of the bile ducts
Drugs	Nonalcoholic fatty liver disease Alpha-1 antitrypsin deficiency Viral hepatitis	Tumors Pancreatitis

Table 2. Symptoms and signs associated with liver disease and biliary obstruction

	Liver disorder	Biliary obstruction
History	Viral exposure Hepatotoxin exposure Alcohol exposure Familial history	Pain in right upper quadrant Fever, chills Previous surgery
Laboratory analysis	Elevation of AST and ALT Prolonged PT and INR Low platelet count	Elevated ALP Elevated white blood cell count
Physical examination	Spider naevi Dupuytren contractures Hepatomegaly Splenomegaly Ascites	Palpable abdominal mass Abdominal tenderness

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase.

Medical History

When approaching the patient with jaundice, detailed medical history is needed. Association with other symptoms can be extremely helpful in establishing the differential diagnosis of jaundice (Table 2). Namely, associated fever could indicate the presence of viral hepatitis but also could point to parasitic or bacterial infections [15]. Furthermore, if the patient is reporting symptoms such as loss of appetite, malaise, and muscle aches, clinical suspicion on viral hepatitis is on the rise. Additionally, thorough history of eventual risk factors for viral hepatitis is very useful in diagnosis establishment. Moreover, nausea and vomiting preceding jaundice may also suggest viral hepatitis or acute gallstone biliary obstruction, whereas prolongation of these symptoms may suggest chronic

hepatitis or biliary obstruction. Also, if the chills are present alongside with fever, it could indicate possible biliary obstruction. Significant weight loss as well as loss of appetite could be a sign of underlying malignancy. Pruritus could be a manifestation of biliary obstruction or if the case of long lasting pruritus, primary biliary cholangitis [16]. In the medical history of jaundice patients, data regarding onset of the symptoms could also imply etiology of jaundice. Namely, abrupt onset may suggest hepatitis and infectious or drug-related disorder, while jaundice slowly appearing in weeks might indicate chronic hepatitis or some kind of obstruction of biliary drainage. Moreover, previous episodes of jaundice are characteristic for liver cirrhosis or familial disorder of bilirubin metabolism. Data regarding the potential use of alcohol or drugs should be noted, as well as previous surgeries or other ill-

Table 3. Laboratory analysis in patients with jaundice

Laboratory analysis	Prehepatic jaundice	Intrahepatic jaundice	Posthepatic jaundice
Unconjugated bilirubin	↑↑	↑	↑
Conjugated bilirubin	–	↑↑	↑↑
AST and ALT	–	↑↑	↑
ALP	–	–	↑↑↑
γ-GGT	–	↑	↑↑
Albumins	–	↓	–
Prothrombin time	–	Prolonged in hepatic insufficiency	Prolonged in obstruction and responded to vitamin K
LDH	↑↑↑	–	↑
Haptoglobin	↓↓↓	↓	–

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, glutamyltransferase; LDH, lactate dehydrogenase.

nesses. Family history is needed in order to evaluate possible inborn and familial conditions.

In the majority of the patients with viral hepatitis, jaundice is painless, where in some cases, patients report dull pain in the right hemiabdomen, while pain in upper quadrants of the abdomen with irradiation to upper right parts of the thorax may suggest gallstone disease [17]. Heavy pain in the upper abdomen with irradiation to the back might be a sign of pancreatitis.

Physical Examination

Physical examination of the patient with jaundice reveals yellow coloration of the skin and sclera and other tissues. If the patient is conscious, well oriented, and without any neurological disturbances, it may be assumed that cause of jaundice is probably not hepatocellular injury, and additional investigation may be oriented to obstruction. Further examination of the skin may show hematomas, which could solely be the underlying cause of jaundice or point to defects in the coagulation cascade. If the cause of the jaundice is chronic liver disorder, physical examination may be useful in detecting spider naevi, palmar erythema, Dupuytren contractures, hepatomegaly, splenomegaly, or ascites. Spider naevi are usually seen on the upper parts of the body, thorax, neck, arms, and face. Palmar erythema and Dupuytren contractures are usually seen on hands, where in Dupuytren, one or more fingers is permanently in a flexion. Physical examination is very important to determine the size of the liver, bearing in mind that it is dependable on the height and weight of the patient. Small liver, alongside with jaundice, may

suggest liver failure due to various conditions, while enlarged liver may be seen in nonalcoholic liver disease, amyloidosis, and neoplasm. Furthermore, palpation of the abdomen may reveal enlarged tender gallbladder or tumors. Splenomegaly is commonly seen in patients with liver cirrhosis, due to portal hypertension, and also it may be seen in various hematological disorders, such as hemolytic disease. Ascites is a sign of decompensated cirrhosis or a portal vein occlusion. Sometimes in patients with primary biliary cholangitis, typical xanthomas or xanthelasma may be seen on the skin and further contribute to diagnosis establishment. Detailed examination of all organ systems is necessary in every individual patient with jaundice.

Laboratory Analysis in Assessment of Jaundice

Laboratory investigations are necessary in order to establish the etiology of jaundice, and they must include bilirubin with its fractions, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyltransferase (GGT), proteins, albumins, prothrombin time, and complete blood count as well as haptoglobin and lactate dehydrogenase (LDH) (Table 3). LDH elevation is commonly seen in patients with hemolysis; however, this enzyme is nonspecific. Namely, there are several LDH isoenzymes, of which LDH-1 is found dominantly in the red blood cells and heart, LDH-2 is found in the reticuloendothelial system, LDH-3 is seen in the lungs, while LDH-4 is commonly found in the kidneys and pancreas, and LDH-5 is found in the liver and muscle cells [18]. Additionally, LDH is a

nonspecific parameter of various malignancies. Haptoglobin is a protein, synthesized by the liver, which binds to free hemoglobin to later be deposited in the reticulo-endothelial system. In the condition of intravascular hemolysis, hemoglobin in circulation will bind to haptoglobin, which will reflect in its low levels. Like ferritin, haptoglobin is an acute phase reactant; hence, it could be elevated in various inflammatory conditions. Patients with hemolysis, aside low haptoglobin and elevated LDH, will have also changes in CBC and bilirubin fractions.

Bilirubin fractions are needed in order to distinguish conjugated from unconjugated bilirubin, where conjugated bilirubin usually refers to hepatobiliary disease. Elevation of unconjugated bilirubin is a characteristic for hemolysis; however, it also may be seen in Gilbert syndrome and impaired hepatic function. In cases of mixed hyperbilirubinemia, both fractions are elevated, and it can be seen in patients with familial conditions or hepatitis.

Elevated AST and ALT may suggest hepatocellular inflammation and necrosis, bearing in mind that they are predominately found in the liver, although they could be found in the muscles and heart and in smaller part in the red blood cells, kidneys, and pancreas [19]. ALT is principally found in the liver, so in comparison with AST, it is more specific in determining liver inflammation.

Elevated levels of ALP and γ -GGT may suggest cholestasis. ALP is mostly found in liver cells, but can also be found in the bones and in lesser amount in the intestines, kidneys, and white blood cells. When the serum values are elevated, usually patients present with cholestasis, biliary obstruction due to neoplasm, or infiltrative process. When elevation is mild to moderate, except liver disorders, cause of elevation may be bone infiltrations, malignancies, other processes or diseases of bones such as osteomyelitis, and systemic infections and hematological diseases. Low levels of ALP are commonly seen in patients with Wilson disease. γ -GGT synthesis is widespread through the different organs and organ systems. It is predominantly synthesized in the liver and has a role in the processes of detoxification. Besides the liver, small amount may be found in the kidneys, lymphocytes, and lungs. Elevated levels may suggest hepatobiliary disease and also a drug-induced liver injury among other conditions and diseases [20]. Previous findings have suggested that γ -GGT levels may also predict metabolic syndrome as well as cardiovascular risks bearing in mind that γ -GGT has a role in cholesterol metabolism [21]. In the assessment of patients with jaundice, low levels of albumins and prolonged prothrombin time could point to hepatic in-

sufficiency. Additionally, thrombocytopenia in complete blood count may suggest advanced liver disease with portal hypertension and hypersplenism [22].

Liver Biopsy and Transient Elastography

Liver biopsy in the majority of European countries is performed only in specialized centers, bearing in mind its costs, invasiveness, and possible complications [23]. In patients with hepatocellular inflammation, liver biopsy is the preferred method for histological severity of liver damage. When focal masses are seen in the liver, biopsy is ultrasound (US) guided. In patients with disturbed coagulation status, liver biopsy could be performed through the transjugular route. In the last decades, liver biopsy has been replaced with the noninvasive method for the assessment of liver fibrosis – transient elastography [24]. Transient elastography is based on shear wave velocity measurement, which is later converted to liver stiffness and is expressed in kilopascals. It is easy to perform, cost-effective in comparison with liver biopsy, complications have not been noted, and results are immediate and simple for interpretation. Moreover, it can be used in monitoring the patients on antiviral and other therapies [25].

Imaging

From GP point of view, in the majority of European countries, the approach to various imaging methods is applicable. Namely, >70% of GPs had open access to various imaging methods including endoscopy [1]. Imaging methods are needed in every patient with jaundice. Different imaging methods may be useful in order to establish the underlying etiology of jaundice adequately. Abdominal US is the most frequently used imaging technique and usually the first method in assessment of jaundice patients, especially in the context of suspected biliary obstruction. It is a noninvasive, portable, safe, and inexpensive method. The limitations of the method are operator dependency and performance difficulties in obese or flatulent patients. Color Doppler ultrasonography is available in addition to ultrasonography as well as contrast-enhanced sonography, in providing additional information about portal hypertension and small neoplasms. CT with contrast is an everyday used technique in assessment of patients with suspected hepatobiliary-pancreatic disease. This method is operator independent; however, it is expensive and with ionizing radiation.

Magnetic resonance may be useful in detection of focal liver lesions and differentiation of benign focal changes from carcinomas [26]. Magnetic resonance cholangiopancreatography (MRCP) has a significant role in detection of bile duct changes [27]. MRCP is superior in comparison with CT and US in investigation of the biliary tract. Also, MR can be performed in the same act as MRCP, which provides additional information. Endoscopic ultrasonography can also detect lesions in the biliary system with similar sensitivity as MRCP with possibility of potential biopsy of the suspected lesion; however, as any upper endoscopy, it has a mortality risk. Endoscopy is necessary when underlying diagnosis of jaundice is cirrhosis, in order to assess the presence of complications including esophageal and gastric varices [28].

Unconjugated Hyperbilirubinemia

The underlying cause of unconjugated hyperbilirubinemia could be due to increased bilirubin production, altered bilirubin uptake, or altered bilirubin conjugation [29]. Increased bilirubin production is usually unrelated to liver disorders and is seen in different hematological conditions, such as hemolysis or hematomas, blood transfusions, or pulmonary infarctions. Hemolysis develops due to destruction of red blood cells because of intrinsic or extrinsic causes, when the bone marrow is incapable of further compensation of the red blood cell loss. The most common cause of unconjugated hyperbilirubinemia is hemolysis, where usually values of serum bilirubin do not surpass >5 mg/dL. Additionally, laboratory analysis in these patients aside unconjugated hyperbilirubinemia shows anemia, reticulocytosis, elevated serum LDH, and low haptoglobin levels. A list of conditions or diseases with increased bilirubin production is shown in Table 2. Altered bilirubin uptake by the liver may be due to heart failure, different shunts, or drugs. Drug-induced hyperbilirubinemia is usually self-resolving after drug discontinuation. Gilbert syndrome and Crigler-Najjar syndrome are conditions of inherited defect in bilirubin conjugation. UDP-glucuronosyltransferase mutations that lead to reduced enzymatic activity are responsible for Gilbert syndrome. Namely, Gilbert syndrome manifests as occasional episodes precipitated by fasting, stress, menstrual cycle, or other illness. This benign condition is very common in general population with the prevalence up to 7% [30]. Except for jaundice, patients appear without any other symptoms. Usually, there is a male preponderance due to generally lower synthesis of bilirubin in women.

Bearing that in mind, Gilbert syndrome is frequently diagnosed in puberty due to higher concentration of sex steroid hormones. Diagnosis is made after the fasting test or the phenobarbitone test. Treatment is unnecessary due to benign characteristics of this condition. Crigler-Najjar is an autosomal recessive inherited disorder due to mutations in the gene for UDP-glucuronosyltransferase which results in decreased or absent enzyme activity. It is an extremely rare disease affecting 1 per 1 million worldwide. Two types have been identified, type 1 autosomal recessive disorder related with kernicterus and type 2 with still undefined type of inheritance, which respond to treatment with phenobarbitone [12].

Mixed Hyperbilirubinemia

Two autosomally inherited syndromes Dubin Johnson syndrome and Rotor syndrome are benign familial metabolic defects that are characterized by impaired export of conjugated bilirubin. Different molecular defects are responsible for development of these 2 syndromes. In Dubin Johnson syndrome, defect is on the MRP2 that leads to damage in the process of bilirubin secretion, whereas in Rotor syndrome, defect is on the transport proteins OATPB1 and OATPB3. In the mid of the twentieth century, such condition, Rotor syndrome, was firstly described. Rotor syndrome is an autosomal recessive benign condition characterized by conjugated hyperbilirubinemia with good prognosis and no need for treatment [30]. In the majority of adult patients with conjugated hyperbilirubinemia, there is either hepatocellular or cholestatic damage. Liver biopsy is not necessary in confirming these syndromes, bearing in mind that neither leads to progressive liver impairment.

Conjugated Hyperbilirubinemia

Commonly, viral hepatitis may be the cause of conjugated hyperbilirubinemia with hepatocellular inflammation. That further emphasizes the need for additional serologic tests, imaging methods, and eventually even a liver biopsy in order to establish a definite diagnosis. In differential diagnosis of conjugated hyperbilirubinemia with hepatocellular inflammation, we must include autoimmune, metabolic, inherited, alcoholic, and drug-related liver injuries (Table 3). Intrahepatic cholestasis with conjugated hyperbilirubinemia may suggest primary biliary cholangitis, primary sclerosing cholangitis, veno-oc-

clusive disease, and graft versus host disease. Additionally, infiltrative diseases such as granulomatous diseases or malignancy may be the cause of intrahepatic cholestasis [31]. Also, many drugs may affect bilirubin biliary secretion [32]. Extrahepatic obstruction remains still one of the frequent causes of cholestasis, and bearing that in mind, imaging modalities such as EUS, ERCP, and MRCP are extremely useful in diagnosis establishment [33]. Choledocholithiasis is one of the most common causes of jaundice worldwide. Jaundice occurs when bile stone blocks the common bile duct (CBD), and bilirubin excess enters the circulation. Occurrence of gallstone in general population goes up to 15% [34]. Factors involved in the gallstone formation in CBD include bile stasis, bacteria, imbalance in pH, and others. Typical symptoms of patients with CBD obstruction include light-colored stool, dark urine, and pain in the abdomen, and if the patient has fever and altered mental status, we may conclude that the patient has Charcot triad or Reynolds pentad. In much lesser percent, obstruction of the CBD may be precipitated by biliary strictures after cholecystectomy, or jaundice may be caused by some surgical procedures with formation of choledochojejunal anastomosis. Malignancies additionally may be the cause of obstructive icterus. A list of the causes that are related to extrahepatic obstruction is shown in Table 1.

Pseudojaundice

Patients may have skin discoloration similar to jaundice in various medical conditions such as Addison disease or due to skin tanning lotions or other skin-coloring agents. Pseudojaundice is commonly seen in individuals or infants consuming carotene-rich foods. Carotene is a molecule that gives yellow color to the skin. In order to distinguish pseudojaundice from jaundice, careful clinical examination is needed, since pseudojaundice does not affect the sclera. Furthermore, serum bilirubin levels in this condition are within the reference range. There have been cases of pseudojaundice due to side effects of certain drugs, such as rifabutin [35].

Treatment

Treatment is fully dependent on the cause. In the management of clinical disorders across Europe, there are significant differences among countries [1]. Namely, treatment of pseudojaundice in cases of skin-coloring agents

is not necessary. Treatment of prehepatic cause of jaundice is actually a treatment of the underlying disease. In the majority of previously described syndromes such as Gilbert syndrome, Rotor syndrome, and Dubin Johnson syndrome, treatment is not necessary. In cases of liver dysfunction, treatment of liver disease will affect bilirubin levels. Namely, in the cases of alcoholic hepatitis, treatment will firstly be directed to cessation of alcohol usage. In the cases of drug-induced hepatitis, treatment will firstly focus on withdrawal of the suspected drug. For viral hepatitis, nowadays, antivirals are the method of choice. In primary biliary cholangitis, treatment of choice remains UDCA. In patients with end-stage liver disease, liver transplantation is the only method of choice.

In patients with obstructive jaundice, endoscopic procedures as well as surgery remain the backbone of the therapy. Namely, the goal is to remove or relieve the obstruction, and ERCP is one of the preferred methods. This method relies on sphincterotomy, balloon dilatation, and stent placement. One of the life-threatening complications of this method is pancreatitis. In cases of malignant obstruction, surgery remains the method of choice.

Conclusion

In every patient with suspected jaundice, detailed clinical, laboratory, and imaging examinations are needed in order to establish the etiology and accordingly determine the adequate treatment. Detailed history and physical examination will at the very beginning give sufficient clinical suspicion and further direct laboratory and imaging modalities. Laboratory investigation will provide additional information if the jaundice is due to disorder of bilirubin metabolism, liver disease, or biliary obstruction. Imaging modalities will be especially significant in suspicion on hepatobiliary obstruction, so further treatment can adequately be performed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Pavlovic Markovic A. and Stojkovic Lalosevic M. wrote the manuscript; Mijac D.D. and Dragasevic S. were included in the literature review and contributed to manuscript drafting; Sokic Milutinovic A., Pavlovic Markovic A., and Stojkovic Lalosevic M.

contributed to study conception and design; Milovanovic T. and Krstic M. contributed to the review of the literature and final draft of the manuscript and were responsible for the revision of the manuscript for important intellectual content; all authors issued final approval for the version to be submitted.

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