Mistakes in acute jaundice and how to avoid them

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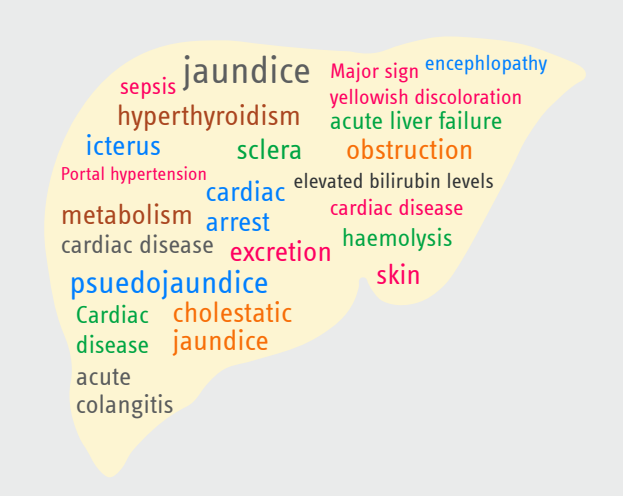

Jaundice or icterus (derived from the ancient Greek word ikteros that described the yellow-breasted oriole bird) is not a diagnosis in itself but constitutes one of the major signs in medicine. It refers to the yellowish discolouration of tissue as a consequence of the deposition of bilirubin. It is a physical manifestation of a significant increase in serum bilirubin levels. Normal serum bilirubin values are below 17 µmol/L, but for jaundice to be perceived visually, serum bilirubin levels need to be elevated above 40 µmol/L (equivalent to 2.5 mg/dL).[1]

The majority of serum bilirubin is formed by the breakdown of the heme contained in senescent red blood cells by the reticuloendothelial system. Thus, unconjugated bilirubin is released in the bloodstream, where it is bound by albumin. Then, through blood circulation, it is moved to the liver hepatocytes, where it undergoes further processing. In brief, bilirubin becomes conjugated there through glucuronidation, in order to be excreted more easily from the body, as unconjugated bilirubin is water-insoluble and cannot pass into the urine. Conjugated bilirubin forms one of the main components of bile, and most of it passes through the biliary tree to the intestine. Unconjugated and conjugated bilirubin is reported in laboratory measurements as indirect and direct bilirubin, due to their chemical properties (reaction with reagents).[1]

Jaundice can be caused by abnormalities in any of the steps comprising the formation, metabolism and excretion of bilirubin. Additionally, while these processes may function properly, jaundice can be seen due to an obstruction of the biliary tree at any level from its intrahepatic origins to its end at the ampulla of Vater. Therefore, it is understandable that a multitude of conditions may cause jaundice, and a reasonable and careful diagnostic approach is warranted to elucidate the underlying cause of this sign. The old saying may state that "Jaundice by itself never killed anyone", but it is imperative to find the cause behind this major sign as soon as possible, as in many cases, prompt intervention saves lives. Hence, the clinician facing a patient presenting with jaundice needs to be aware of the following mistakes made in approaching these patients.

Mistake 1 Failing to distinguish between pseudojaundice and jaundice

While especially rare, pseudojaundice needs to be distinguished from jaundice, as this precludes the clinician from ordering unnecessary investigations and spares the patient from unwarranted anxiety. Pseudojaundice is more frequently described in children but may also be seen in adults and is skin colour changes associated with conditions other than hyperbilirubinemia, such as carotenemia caused by excessive ingestion of beta carotene–rich foods, Addison disease, anorexia nervosa, or use of spray-tanning products. The sclerae are spared, facilitating the physician to distinguish this condition from 'true' jaundice.[2] If clinical examination is not helpful, then measuring the bilirubin levels will provide the diagnosis, as they are increased in jaundice but not in pseudojaundice.

Mistake 2 Not examining in detail the drug history of the patient and not inquiring about supplements (herbal or other)

As part of the detailed clinical interview, it is imperative to obtain a full drug and toxin history from the patient in order to identify a possible temporal relationship between recently used drugs and the onset of symptoms. This should include alcohol use (if necessary elicit information from family or partner), mushroom consumption (a rare but often fatal cause of liver failure), over-the-counter medications (ask for acetaminophen-containing analgesics and anti-inflammatories), vitamins (especially vitamin A) and all pharmaceutical substances used by the patient on a regular or sporadic basis. Specific and repeated questions should be asked regarding additional supplement consumption, as in many cultures, herbal supplements (e.g. traditional Chinese herbs) are not labelled as 'drugs'. Moreover, patients may not think that dietary supplements or vitamins can be potentially harmful and may not volunteer relevant information unless prompted. In any case, as jaundice is a potential indicator of hepatic injury, drug-induced liver injury (DILI) should be considered. DILI is a diagnosis of exclusion, so it should be revisited if more common causes of jaundice have been eliminated.

Mistake 3 Forgetting about hereditary syndromes in isolated hyperbilirubinaemia

Isolated hyperbilirubinaemia usually reflects the absence of significant liver disease. It can be either direct (conjugated) or indirect (unconjugated). Direct isolated hyperbilirubinaemia is very rare and can be seen in patients with DILI or afflicted with two familial syndromes, Rotor and Dubin-Johnson. So, a previous history of drug use is very important. If DILI is excluded, then the diagnosis of

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Rotor or Dubin-Johnson syndrome can be made in patients without severe comorbidities. These syndromes are caused by genetic mutations affecting the excretion (Dubin-Johnson) or hepatic storage (Rotor) of conjugated bilirubin[3] and can neither be nor required to be differentiated in clinical practice.

On the other hand, in indirect isolated hyperbilirubinaemia, a diagnosis not to be missed is haemolysis. A fall in haematocrit levels, without overt blood loss, should raise the suspicion of a haemolytic process that could cause jaundice by overwhelming the bilirubin metabolic pathway. Further confirmation can be obtained by ordering additional specific tests such as reticulocyte count, lactate dehydrogenase and haptoglobin levels and morphology of red blood cells by an experienced haematologist.[4] Nevertheless, a much more common scenario is the presence of Gilbert's syndrome. It is important not to overlook this benign diagnosis, as it will alleviate the need for further investigations. Gilbert's syndrome is an inherited condition found in about 5% of the general population, usually transmitted in an autosomal recessive manner. There is a defect in the conjugation of bilirubin due to mutations in the promoter of the uridine 5'-diphospho (UDP)-glucuronosyltransferase gene. Patients may present at various times during their life with a mild unconjugated hyperbilirubinaemia usually after fasting, strenuous exercise or viral illness. No treatment but reassurance is required.[5]

Mistake 4 Overlooking signs of acute liver failure

All patients with evidence of severe hepatocellular injury (high elevations of transaminases; usually above 10 times the upper limit of normal, except for alcoholic hepatitis) and jaundice should have their coagulation function checked, as elevated international normalized ratio (INR) may imply acute liver failure. Furthermore, a thorough assessment regarding the presence of hepatic encephalopathy should be performed. It is important to note that encephalopathy, especially in early stages, may be difficult to diagnose. A discussion with the family or other caregivers may be helpful about the patient's recent behaviour or other changes (e.g. in sleep pattern). If encephalopathy is detected, an investigation for precipitating factors should be initiated, and the patient should be admitted.[6] As a general principle, patients with bilirubin > 170 µmol/L, elevated INR, or mental status changes should be admitted.[7]

Mistake 5 Ignoring autoimmune hepatitis and other rarer causes

While in a jaundiced patient with a pattern of hepatocellular injury (mainly aspartate transaminase to alanine transaminase (AST/ALT) elevation), viral and alcoholic hepatitis, as well as DILI, are the most common culprits; there are cases where other conditions may be responsible. Acute autoimmune hepatitis could be the cause of jaundice in about 2-5% of these patients [8] and it should not be forgotten as part of our diagnostic workup (check for relevant serology, e.g. antinuclear antibody (ANA), anti-smooth muscle antibodies (ASMA), liver kidney microsomal type 1 antibody (anti-LKM1), soluble liver antigen/liver pancreas (anti-SLA/LP) and serum immunoglobulins and confirm with biopsy).[9] Moreover, metabolic diseases (mainly Wilson's but also haemochromatosis), although more chronic in nature, should be considered especially in adolescents or young adults.

Mistake 6 Overlooking extrahepatic, non-obstructive causes of jaundice

It is easy to become too focused on the multitude of conditions from the liver and biliary tree that cause jaundice and overlook the fact that elevated bilirubin may be a result of a more systemic affliction. A recent study showed that sepsis was the most common cause (22%) of new-onset jaundice in adult patients over a 5-year period in a community US hospital.[8] It has been suggested that sepsis and bacterial infections in general may cause intrahepatic cholestasis mainly through decreased canalicular transport of bile acids.[10] Detailed history for fever and infections is warranted as well as testing with a complete blood count that may point to the presence of sepsis.

Jaundice may also be a rare manifestation of cardiac disease.[11] It tends to be mild, and the main accompanying symptom is breathlessness. Two underlying mechanisms have been put forward: hepatic venous congestion (usually with a modest rise of alkaline phosphatase (ALP) as well) and ischaemic hepatitis due to low cardiac output (when high levels of transaminases are observed).[12]

Thyroid disorders, most frequently hyperthyroidism, can also cause jaundice. The mechanism responsible for this presentation seems to be cholestatic in origin, with a hepatocyte zone 3 injury that interferes with normal bile flow playing a key role. This endocrine-related cholestasis is usually slow to resolve, as it may take weeks to months for jaundice to disappear after proper control of thyroid function has been established.[13] Therefore, the importance of a full clinical examination and detailed system review is made evident.

Mistake 7 Forgetting that cholestatic jaundice may also be of intrahepatic origin

In a jaundiced patient with a laboratory pattern of cholestasis (mainly alkaline phosphatase and gamma-glutamyl transferase (GGT) elevation), most clinicians may first consider extrahepatic obstructive aetiologies (choledocholithiasis, extrinsic compression of the biliary tree, disease of the large bile ducts) as the most probable causes. Nonetheless, this cholestatic pattern may be due to pathology originating from the liver parenchyma, such as diffuse infiltrative disorders (amyloidosis, lymphoma, hepatocellular carcinoma (HCC), sarcoidosis) and diseases of the small intrahepatic bile ducts (primary biliary cholangitis, DILI, intrahepatic primary sclerosing cholangitis, etc.) or even parasitic intracellular disease. If no concrete diagnostic evidence is obtained from appropriate imaging, and particularly if there is no bile duct dilatation in a patient without clinical suspicion of acute bile duct obstruction, then these intrahepatic conditions may provide a viable alternative, and specific serological tests along with a liver biopsy may be necessary to establish the correct diagnosis.

Mistake 8 Forgetting that cholangitis may present without abdominal pain or with transaminase levels compatible with acute hepatitis

Acute cholangitis is another diagnosis that should be promptly made, as early administration of an appropriate antibiotic regimen is associated with better disease outcomes. The classical presentation of acute cholangitis is the combination of signs known as Charcot's triad (jaundice, fever and right upper quadrant tenderness) but this applies only to 50-75% of patients with cholangitis.[14] Atypical presentations are usually found in the elderly and the immunocompromised. Therefore, even in the absence of the full constellation of symptoms, a high degree of clinical suspicion should be upheld in all cases of jaundiced patients with concurrent fever.[15] Furthermore, acute cholangitis is a condition with considerable mortality and urgent decompression may be needed (usually via endoscopic retrograde cholangiopancreatography (ERCP) or in specific cases with percutaneous transhepatic cholangiography (PTC)) to reduce the risk of sepsis secondary to cholestasis.[15]

Acute cholangitis may occasionally present with very elevated transaminase levels (>10-20 times the upper limit of normal) and then can be misdiagnosed as acute hepatitis. A detailed medical history and ultrasonographic findings are crucial for the correct diagnosis, which leads to prompt initiation of the necessary antibiotic regimen.

Mistake 9 Failing to recognise promptly acute alcoholic hepatitis as a diagnosis

Acute alcoholic hepatitis has been described as one of the most common aetiologies of new-onset jaundice.[8] The appearance of jaundice as a sign

of alcoholic hepatitis usually reflects significant impairment of liver function (along with other findings, e.g. coagulopathy) and represents a severe form of the disease, associated with substantial mortality. A probable diagnosis can be made in patients with less than 2 months of jaundice and a history of alcohol excess less than 2 months before presentation, in the absence of sepsis or other causes of hepatic injury.[16] Further diagnostic clues are provided by AST values of >50 IU/L, usually <200-300 IU/L, with an AST: ALT ratio >1.5-2, while increased values of gamma-glutamyltransferase (γGT) coupled with macrocytosis point with a high degree of probability to alcohol dependency.[17] Rapid diagnosis is important for a) prompt assessment of disease severity after application of the Glasgow Alcoholic Hepatitis Score and/or the Maddrey Discriminant Function Index, b) exclusion of underlying infection and c) possible initiation of appropriate treatment with steroids in severe cases.

Mistake 10 Failing to consider acute jaundice as a sign of acute-on-chronic liver failure

Decompensation of chronic liver disease accounts for about 1 in 5 cases of jaundice of recent onset in a recent study.[8] As a marker of the hepatic excretory function, it can be used as an indicator of progression in the evolution of chronic liver disease (a cut-off value of 205 µmol/L has been proposed for acute on chronic liver failure).[18] Its potential as a prognostic biomarker in this challenging subset of patients has been widely accepted, and bilirubin values have been incorporated in the MELD 3.0 and Child-Pugh scores that are used for liver transplantation allocation and prediction of survival correspondingly.[19,20] Therefore, a new onset of jaundice in the cirrhotic patient should necessitate early investigation for causes of decompensation and consideration for appropriate management and/or referral for transplantation, if applicable.

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Standards and Guidelines

- Fawaz R, et al. Guideline for the evaluation of cholestatic jaundice in infants: Joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr* 2017; 64: 154–168 [https://onlinelibrary.wiley.com/doi/10.1097/MPG.0000000000001334]

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