

# Mistakes in acute jaundice and how to avoid them

Spyros Siakavellas and George Papatheodoridis

**J**aundice 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. Jaundice refers to the yellowish discoloration of tissue that occurs as a consequence of the deposition of bilirubin. This discoloration is a physical manifestation of a marked increase in serum bilirubin levels. Normal serum bilirubin values are  $<17 \mu\text{mol/L}$ ; for jaundice to be perceived visually serum bilirubin levels need to be elevated to  $>40 \mu\text{mol/L}$  (equivalent to  $2.5 \text{ mg/dL}$ ).<sup>1</sup>

Most serum bilirubin is formed from the breakdown of the haem contained in senescent red blood cells by the reticuloendothelial system. Thus, unconjugated bilirubin is released in the bloodstream, where it is bound by albumin. Through the blood circulation bilirubin is moved to liver hepatocytes, where it undergoes further processing. In brief, bilirubin becomes conjugated in the hepatocytes through glucuronidation, which allows it to be excreted from the body (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 are reported in laboratory measurements as indirect and direct bilirubin, according to their chemical properties (i.e. reaction with reagents).<sup>1</sup>

Jaundice can be caused by abnormalities in any of the steps comprising the formation, metabolism and excretion of bilirubin. In addition, these processes may be functioning properly, but jaundice can be seen because of an obstruction of the biliary tree at any point, from its intrahepatic origins to its end at the ampulla of Vater. For this reason, it is clear that numerous conditions can result in jaundice. When faced with a patient presenting with jaundice a reasonable and careful diagnostic approach is, therefore, warranted to elucidate the underlying cause of this sign. Conventional wisdom may be that “jaundice by itself never killed anyone,” but it is imperative to find the cause as soon as possible, as prompt intervention saves lives in many cases.

Here, we outline several of the mistakes made when approaching a patient presenting with acute jaundice based on our clinical experience and published data.

## Mistake 1 Failing to distinguish between pseudojaundice and jaundice

Although especially rare, pseudojaundice needs to be distinguished from jaundice, as this prevents the clinician from ordering unnecessary investigations and spares the patient unwarranted anxiety. Pseudojaundice is most frequently described in children but may be also seen in adults. The skin colour changes seen in patients with pseudojaundice are associated with conditions other than hyperbilirubinaemia, such as carotenaemia (caused by excessive ingestion of foods rich in beta carotene), Addison disease, anorexia nervosa, or the use of spray-tanning products. The sclerae are spared, helping the physician



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to distinguish pseudojaundice from ‘true’ jaundice.<sup>2</sup> If clinical examination is not helpful, then measuring the bilirubin levels will provide the diagnosis, as they are increased in patients with jaundice but not in those with pseudojaundice.

## Mistake 2 Not obtaining a detailed drug history and not inquiring about supplement use

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. The history should include alcohol use (if necessary, eliciting information from the patient’s family or partner), mushroom consumption (a rare but often fatal cause of liver failure), over-the-counter medications (particularly acetaminophen-containing analgesics and anti-inflammatory drugs), vitamins (especially vitamin A) and all other pharmaceutical substances used by the patient on a regular or sporadic basis.

Specific and repeated questions should be asked regarding additional supplement consumption, as herbal supplements (e.g. traditional Chinese herbs) are not labelled as drugs in many cultures. Moreover, patients may not realise 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 frequent causes of jaundice have been eliminated.

## Mistake 3 Forgetting about hereditary syndromes in patients with isolated hyperbilirubinaemia

Isolated hyperbilirubinaemia usually reflects the absence of significant liver disease. It can be either direct (conjugated bilirubin) or indirect (unconjugated bilirubin). Direct isolated hyperbilirubinaemia is very rare and can be seen in patients who have DILI or are afflicted with one of two familial syndromes, Rotor or Dubin–Johnson. Previous history of drug use is, therefore, extremely important—if DILI is excluded, then the diagnosis of Rotor

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Spyros Siakavellas is a Gastroenterology Fellow and George Papatheodoridis is Professor of Medicine and Gastroenterology in the Academic Department of Gastroenterology, Medical School of National and Kapodistrian University of Athens, General Hospital of Athens “Laiko”, Athens, Greece.

Correspondence to: s.siakavellas@gmail.com

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or Dubin–Johnson syndrome can be made in those patients who do not have severe comorbidities. These syndromes are caused by genetic mutations affecting the excretion (Dubin–Johnson) or hepatic storage (Rotor) of conjugated bilirubin;<sup>3</sup> they can neither be, nor are required to be, differentiated in clinical practice.

In patients who have 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. Confirmation can be obtained by ordering additional specific tests, such as reticulocyte count, LDH (lactate dehydrogenase) and haptoglobin levels, and morphologic assessment of red blood cells by an experienced haematologist.<sup>4</sup>

A much more frequent scenario in patients with indirect isolated hyperbilirubinaemia is the presence of Gilbert's syndrome. This benign diagnosis should not be overlooked, as it alleviates the need for further investigations. Gilbert's syndrome is an inherited condition found in about 5% of the general population and is usually transmitted in an autosomal recessive manner. Patients have a defect in the conjugation of bilirubin due to mutations in the promoter of the UDP-glucuronosyltransferase gene. Patients who have Gilbert's syndrome may present at various times during their life with a mild unconjugated hyperbilirubinaemia, usually after fasting, strenuous exercise or viral illness. No treatment other than reassurance is required.<sup>5</sup>

#### **Mistake 4 Overlooking signs of acute liver failure**

If there is evidence of severe hepatocellular injury (i.e. high elevations of transaminase levels; usually >10 times the upper limit of normal [ULN], except for alcoholic hepatitis) and jaundice, coagulation function should be checked because an elevated INR (international normalized ratio) may indicate 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 to determine the patient's recent behaviour and any other changes they may have been experiencing (e.g. in sleep pattern). If encephalopathy is detected, an investigation for precipitating factors should be initiated and the patient admitted.<sup>6</sup> As a general principle, patients who have a bilirubin

level >170 µmol/L, an elevated INR or mental status changes should be admitted.<sup>7</sup>

#### **Mistake 5 Ignoring autoimmune hepatitis and other rarer causes of acute jaundice**

In a jaundiced patient with a pattern of hepatocellular injury (mainly aspartate transaminase [AST]/alanine transaminase [ALT] elevation) viral and alcoholic hepatitis, as well as DILI, are the most frequent culprits, but there are other conditions that may be responsible. Acute autoimmune hepatitis could be the cause of jaundice in about 2–5% of such patients<sup>8</sup> and should not be forgotten as part of the diagnostic workup—check for relevant serology (e.g. antinuclear antibodies [ANA], anti-smooth-muscle antibodies [ASMA] and serum immunoglobulins) and confirm with a biopsy sample.<sup>9</sup> Although more chronic in nature, metabolic diseases (mainly Wilson's disease, but also haemochromatosis) should also be considered, especially in adolescents or young adults.

#### **Mistake 6 Overlooking extrahepatic, nonobstructive causes of jaundice**

It is easy to become too focused on the multitude of liver and biliary tree conditions that cause jaundice and overlook the fact that elevated bilirubin may be a result of a more systemic disorder.

A US 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 hospital.<sup>8</sup> The suggestion has been made that sepsis and bacterial infections in general can cause intrahepatic cholestasis, mainly through decreased canalicular transport of bile acids.<sup>10</sup> Taking a detailed history for fever and infections is, therefore, warranted, as is performing a complete blood count that may point to the presence of sepsis.

Jaundice may also be a rare (found in 5% of patients with heart failure) manifestation of cardiac disease.<sup>11</sup> In such cases, jaundice tends to be mild and the main accompanying symptom is breathlessness. Two underlying mechanisms have been put forward to explain the presence of jaundice in patients with cardiac disease: hepatic venous congestion (usually with a modest rise of alkaline phosphatase [ALP]) and ischaemic hepatitis due to low cardiac output (when high levels of transaminases are observed).<sup>12</sup>

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 having 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.<sup>13</sup> The importance of a full clinical examination and detailed system review in this situation is, therefore, evident.

#### **Mistake 7 Forgetting that cholestatic jaundice may be of intrahepatic origin**

With a jaundiced patient who has a laboratory pattern of cholestasis (mainly alkaline phosphatase and gamma-glutamyltransferase [GGT] elevation), most clinicians may first consider the most probable cause to be an extrahepatic obstructive aetiology (e.g. choledocholithiasis, extrinsic compression of the biliary tree, disease of the large bile ducts). Nonetheless, this cholestatic pattern may be due to pathology originating from the liver parenchyma, such as diffuse infiltrative disorders (e.g. amyloidosis, lymphoma, hepatocellular carcinoma [HCC], sarcoidosis) and diseases of the small intrahepatic bile ducts (e.g. primary biliary cholangitis [PBC], DILI, intrahepatic primary sclerosing cholangitis [PSC], etc.) or even parasitic intracellular disease. If no concrete diagnostic evidence is obtained by using the appropriate imaging modality, 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. Specific serological tests along with a liver biopsy sample 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 associated with considerable morbidity and even mortality and should be diagnosed promptly, as early administration of an appropriate antibiotic regimen is associated with better disease outcomes. The classic 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 acute cholangitis.<sup>14</sup> As atypical presentations of acute cholangitis can be found, usually in the elderly and the immunocompromised, 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 who have concurrent fever.<sup>15</sup>

Acute cholangitis may occasionally present with very elevated transaminase levels (>10–20 times the ULN) 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 Not promptly recognizing acute alcoholic hepatitis as a diagnosis

Acute alcoholic hepatitis has been described as one of the most frequent aetiologies of new-onset jaundice.<sup>8</sup> The appearance of jaundice as a sign of acute alcoholic hepatitis usually reflects considerable impairment of liver function (along with other findings, such as coagulopathy) and represents a severe form of the disease, associated with substantial mortality. A probable diagnosis can be made in patients who have had jaundice for less than 2 months and a history of alcohol excess less than 2 months before presentation, in the absence of sepsis or other causes of hepatic injury.<sup>16</sup> 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 GGT coupled with macrocytosis point to alcohol dependency with a high degree of probability.<sup>17</sup>

Rapid diagnosis of acute alcoholic hepatitis is important for several reasons. First, for the prompt assessment of disease severity after application of the Glasgow Alcoholic Hepatitis Score and/or the Maddrey Discriminant Function Index. Second, for the exclusion of underlying infection. Third, for the 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 reportedly accounts for about 1 in 5 cases of jaundice of recent onset.<sup>9</sup> As a marker of the hepatic excretory function, serum bilirubin levels 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 the diagnosis of acute-on-chronic liver failure).<sup>18</sup> The potential of bilirubin as a prognostic biomarker in this challenging subset of patients has been widely accepted and bilirubin values have been incorporated in the MELD and Child–Pugh scores that are used for liver transplantation allocation and prediction of survival, respectively.<sup>19,20</sup> New-onset jaundice in a patient who has cirrhosis should, therefore,

necessitate early investigation for the cause of decompensation and consideration for appropriate management and/or referral for transplantation, if applicable.

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#### Mistakes in...

- Mistakes in liver function test abnormalities and how to avoid them  
[<https://www.ueg.eu/education/latest-news/article/article/mistakes-in-liver-function-test-abnormalities-and-how-to-avoid-them/>].

#### UEG Week

- “Obstructive jaundice: From diagnosis to treatment” session at UEG Week 2015  
[<https://www.ueg.eu/education/session-files/?session=1419&conference=109>].
- “The jaundiced patient” presentation in the “Deranged liver and pancreatic biochemistry: What to do?” session at UEG Week 2014  
[<https://www.ueg.eu/education/document/the-jaundiced-patient/109159/>].
- “Common presentations in liver disease: jaundice” presentation in the “Common presentations in liver

disease and how to approach them” session at UEG Week 2013  
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#### Standards & Guidelines

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