

DIAGNOSTIC APPROACH TO THE PATIENT WITH JAUNDICE FOLLOWING TRAUMA

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ABSTRACT

Background and Aims: Jaundice in trauma patients may reflect serious underlying pathology. The aim of this review was to determine the appropriate diagnostic approach to the patient with jaundice following trauma.

Methods: A MEDLINE search was performed to retrieve publications which outlined the causes of jaundice in trauma patients.

Results: The main causes of jaundice in trauma patients were found to be bilirubin overload caused by breakdown of transfused- and extravasated blood and hepatic dysfunction caused by sepsis, infections, initial shock and systemic hypotension. Bile duct injury or drug induced liver injury are rare. Liver function tests are often uninformative but commonly show a cholestatic pattern. Ultrasound, CT or ERCP are the diagnostic imaging methods most widely used. Abdominal ultrasound and CT may reveal specific organ injuries, bile duct dilatation, intraabdominal fluid collections, hematomas or acalculus cholecystitis. ERCP is often diagnostic and permits a therapeutic intervention when a bile duct injury is present.

Conclusions: The primary aim of the diagnostic approach should be to identify all cases of bile duct injury or obstruction. Sepsis and infections should be actively looked for. The number of blood transfusions must be calculated. Ultrasound, CT or ERCP are the diagnostic imaging methods most widely used.

Key words: Bilirubin; jaundice; postoperative; posttraumatic; trauma

INTRODUCTION

Jaundice is commonly observed in trauma patients, even in the absence of pre-existing hepatobiliary disease. Although posttraumatic jaundice may be severe it often runs a benign course (1, 2). In clinical practice, serum-bilirubin > 2 mg/dL (> 35 $\mu\text{mol} \cdot \text{l}^{-1}$) is the most commonly used criterion to establish the presence of hepatic dysfunction and serum-bilirubin is

used as the hepatic component of the multiple organ dysfunction score (3, 4). The occurrence of hepatic dysfunction in patients with multiple injuries is associated with greater consumption of hospital resources, more frequent development of complications, and increased mortality (4).

Jaundice in trauma patients is often the consequence of multiple factors working in concert. The contributing factors should be actively sought for and, whenever possible, treated. The causes contributing to the development of jaundice can broadly be divided into three main groups: prehepatic- (increased bilirubin load), intrahepatic- (impaired bilirubin conjugation and/or impaired bilirubin excretion) and posthepatic causes (extra-hepatic biliary obstruction).

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A key question to be addressed in jaundiced trauma patients is whether there is a correctable etiology of jaundice. Often, however, specific treatment of jaundice in trauma patients is not feasible because underlying bile duct injury or obstruction that can be corrected is not found. Considerable diagnostic and clinical acumen is required to discern which patients should be subjected to a surgical, radiological or endoscopical intervention and which patients should be followed expectantly.

The aim of this review of the available literature was to try to determine what would be the appropriate diagnostic approach to this complex diagnostic problem.

METHODS

An electronic search of the MEDLINE database was conducted for the period from January 1970 to June 2003 using the keywords 'jaundice' or 'hyperbilirubinemia' and 'trauma' or 'injury' to identify full texts of clinical studies and case reports which had pointed out the etiology of jaundice in trauma patients. The titles and abstracts of hits were assessed and the relevant articles were reviewed. The reference lists of included papers were cross referenced to identify additional relevant papers. *Journal of Trauma, Injury, Infection and Critical Care* was searched manually for the period of 1980–2003 to make a comparison with the computer search. As for reports on larger series of patients, articles in English as well as non-English language journals were included. As for case reports or small case series, only reports in English language journals were reviewed. A restriction of jaundice developing within 30 days following the trauma for inclusion in the review was made. Data extracted for review included leading author's name, year of publication, name of journal, the number of patients in each report, type of study and cause(s) of jaundice. For the patients found in the case reports or case series having a bile duct injury or obstruction the type of abdominal trauma, the presence of associated injuries, the time of onset of jaundice and the diagnostic methods used were recorded. Articles on patients with acute acalculus cholecystitis uncovered during the search were not reviewed in detail.

RESULTS

Sixty-three publications were found: 8 larger prospective or retrospective studies, 49 single case reports and 6 case series. The eight reports of large series of patients identified a total of 238 patients (Table 1) (1, 2, 5–10). Important causative factors of jaundice amongst patients in these series were increased bilirubin production due to hemolysis of transfused blood or breakdown of extravasated blood and hepatic dysfunction caused by bilirubin overload, sepsis, infections, initial shock, episodes of systemic hypotension during the postoperative course and jaundice as part of the multiple organ failure syndrome.

The case reports and case series included a total of 66 patients (Table 2). The 59 patients with a bile duct injury or obstruction were reviewed in detail. It should be noted that the number of reported cases of traumatic bile duct injuries in the literature is much higher than those found in this review. How-

ever, details about the occurrence of jaundice are not emphasized in such reports. In addition to bile duct injuries this review shows that injury to the gallbladder, pancreas, duodenum or diaphragm and hematomas from large vessel injury may cause obstruction of the bile duct leading to jaundice (11–17). The 59 patients included in the present study had all suffered abdominal trauma; 7 patients had suffered a penetrating trauma and 52 patients a blunt trauma. Bile duct injury or obstruction was diagnosed at a median of 7 days after the trauma incident and the onset of jaundice was noticed 1–2 days before the diagnosis was made. Associated extraabdominal injuries were reported in only 14 patients. Table 3 lists the diagnostic methods used to unravel bile duct injury or obstruction in these 59 patients.

Blood tests revealed a pattern typical of cholestatic injury, hepatocellular injury or hemolysis. In the reviewed larger serial reports presenting data on liver analytes, the jaundice was usually of the cholestatic type characterized by conjugated hyperbilirubinemia with modest increase in aminotransferase levels and marked elevation of alkaline phosphatase (1, 2, 7). This illustrates that jaundice in these cases arises from insufficient excretion for bilirubin rather than from insufficient hepatic uptake and/or conjugation of bilirubin. Cholestatic jaundice accompanies bile duct obstruction with high increase in bilirubin and alkaline phosphatase levels. Transient elevation of aminotransferase levels may be seen. Jaundice due to hepatocellular injury causes a moderate or high increase in aminotransferases and a mild to moderate increase in direct bilirubin, usually with modest increase in alkaline phosphatase. Bacterial sepsis is often associated with cholestatic hepatocellular injury and jaundice. Hemolytic jaundice is characterized by an increase in indirect bilirubin combined with a drop in haptoglobin. However, in trauma patients increased breakdown of transfused and extravasated blood is usually combined with an element of hepatic dysfunction, and often a larger fraction of direct bilirubin is seen. Transient enzymatic elevations follow all forms of traumatic hepatic injury, but persistent jaundice is encountered mainly in patients who develop post injury infection, often after a period of shock and transfusion requirement (18). Frequently, liver-associated analytes are uninformative in trauma patients and a mixed pattern may be found.

DISCUSSION

Review of all retrieved publications on jaundice in trauma patients demonstrated that a multiplicity of etiological factors is involved. The causes of hyperbilirubinemia in trauma patients could be divided into three primary pathophysiological mechanisms: (1) overproduction of bilirubin (prehepatic causes), (2) hepatocellular injury causing decreased conjugation or excretion of bilirubin (intrahepatic causes), and (3) extrahepatic biliary obstruction (posthepatic causes) (19).

TABLE 1
 Reports of larger series of patients ($n = 238$) with jaundice following trauma. (To convert bilirubin from $\mu\text{mol/l}$ to mg/dL , divide the value by 17.1).

Reference	Year	Journal	Number of patients	Type of study	Bilirubin level	Criteria	Etiological factors of jaundice
Labori ⁽²⁾	2003	Scand J Gastroenterol	53	Retrospective	> 100 $\mu\text{mol/l}$ (> 5.85 mg/dL)	Inclusion: Serum bilirubin > 100 $\mu\text{mol/l}$ within 30 days following trauma	Blood transfusion/Hematoma Sepsis/Infection Initial shock/Systemic hypotension Multiple organ failure Bile duct injury ($n = 1$), Major hepatic injury ($n = 3$) Alcohol liver cirrhosis ($n = 2$) Viral hepatitis ($n = 1$) Drug induced liver injury ($n = 2$) ($n = 44$)
Helftenbeim ⁽⁵⁾	1997	Chirurg	23	Prospective	> 2 mg/dL	Exclusion: Extrahepatic bile duct obstruction Notes: A study of postoperative jaundice in 97 patients/23 of the patients were trauma patients	Sepsis Shock Blood transfusions/Hematoma
Nakatani ⁽⁶⁾	1995	Surg Today	35	Retrospective	I: > 8 mg/dL ($n = 12$) II: > 2 mg/dL and < 8 mg/dL ($n = 23$) (bilirubin level at day 10)	Inclusion: Severe torso injury/Expected to require > 2000 ml blood within 48 h or expected to develop large hematomas or systolic pressure < 80 mmHg on admission Exclusion: Sepsis/Drug induced liver injury	Shock/Systemic hypotension Sepsis/Infection Blood transfusions/Hematoma
te Boekhorst ⁽⁷⁾	1988	J Hepatol	19	Retrospective	> 3 mg/dL		Blood transfusions/Hematoma Sepsis Initial shock/Systemic hypotension Multiple organ failure
Sarfeh ⁽¹⁾	1978	J Trauma	36	Retrospective	> 2 mg/dL	Inclusion: Vehicular accidents. Admission within 24 hr following trauma Exclusion: Major hepatic injury/Bile duct injury/Duodenal injury/Head of pancreas injury	Sepsis/Infection Shock/Systemic hypotension Blood transfusions/Hematoma
Janvier ⁽⁸⁾	1977	Anesth Analg	22	Retrospective	> 3 mg/dL	Exclusion: Extrahepatic bile duct obstruction	Blood transfusions/Hematoma Shock/Hepatic anoxia Sepsis/Infection
Champion ⁽⁹⁾	1976	J Trauma	38	Retrospective	> 3 mg/dL	Inclusion: Hypotensive on admission/One exchange transfusion of colloid within 12 h following the trauma Notes: Evaluating 55 bilirubin peaks in 38 patients	Hepatic dysfunction $n = 23$ Sepsis/Septicemia $n = 15$ Blood transfusions/Hematoma $n = 12$ Renal failure/Sepsis $n = 2$ Obstructive jaundice $n = 1$ Acute hemolytic transfusion reaction $n = 1$
Nunes ⁽¹⁰⁾	1970	Arch Surg	12	Retrospective	> 3 mg/dL	Exclusion: Patients requiring hepatic resections/Major hepatic injuries/Liver cirrhosis/Hepatic abscesses	Shock/Hepatic anoxia Blood transfusion/Hematoma Sepsis/Infection

The single case reports and case series mainly describe jaundice caused by bile duct injury or bile duct obstruction. These patients are important to identify because they usually need an additional surgical, radiological or endoscopic procedure. However, the majority of the larger series of patients encountered in this review report predominantly prehepatic or intrahepatic causes of jaundice in which continued medical management is necessary. It appears that neither bile duct injuries nor bile duct obstructions are the most frequent etiological factors causing jaundice in trauma patients.

The most common causative factor of jaundice in the serial reports was overproduction of bilirubin due to hemolysis of transfused blood and breakdown of extravasated blood. Hemorrhage into traumatized soft tissues, bone fracture sites and body cavities are often seen in major trauma patients. Such patients receive multiple blood transfusions at the time of primary treatment (2). The majority of bilirubin is derived from the breakdown of hemoglobin with a normal daily production rate in adults of 250–350 mg. After a trauma incident, this rate of production may be increased for a variety of causes: following breakdown of extravasated blood (5 g bilirubin per liter), accelerated hemolysis of transfused blood (500 mg bilirubin per liter in the first 24 hours from blood 2 weeks old) and hemolysis secondary to sepsis or drugs (20). Thus, substantial loads of bilirubin are delivered to the livers of trauma patients and may cause jaundice by overloading the liver's excretory capacity. Human studies show that bilirubin levels tend to peak at day 6–12 after the trauma incident and that the greater part of the blood transfusions are administered during the first 48 hours (1, 2). In patients who receive multiple blood transfusions after a trauma, serum bilirubin may rise strikingly, especially if the patient also suffers from hepatic dysfunction. Thus, animal studies have shown that large intravenous loads of unconjugated bilirubin can cause extensive hepatocyte canalicular membrane damage and intrahepatic cholestasis (21). By analogy, such hepatocyte damage and intrahepatic cholestasis would be detrimental to bilirubin excretory function if it occurs in patients.

Additional factors lead to perturbation in liver function in trauma patients. Thus, the reviewed publications show that jaundiced trauma patients have a high incidence of sepsis and infections. Jaundice may be associated with bacteremia caused by a wide variety of microbes (22). Jaundice occurring in patients with simple bacteremia is usually mild and of short duration, but when clinical sepsis is evident jaundice will be more pronounced and of longer duration. Infection of the liver, hemolysis and the effects of lipopolysaccharides and pro-inflammatory cytokines on bile acid transport are implicated (23–25).

In animal studies, bilirubin excretion is significantly decreased immediately after precipitation of hemorrhagic shock (26). Following sub lethal trauma in rats there is a significant reduction of bile flow and bile salt excretion which remains subnormal for at least 6 hours after trauma, but bile flow returns to

TABLE 2

Main causes of jaundice in 66 patients from case reports and case series.

Cause of jaundice	Number of patients
Bile duct injury	44
Bile duct stricture (intra- or suprapancreatic)	6
Gallbladder rupture	2
Duodenal hematoma	3
Pancreatic contusion	1
Hepatic herniation/ bile duct strangulation (diaphragmatic hernia)	1
External hematoma decompressing the common bile duct (hepatic artery pseudoaneurysm, lacerated portal vein)	2
Inherited disorder (Dubin Johnson/ glucose-6-phosphate dehydrogenase deficiency)	1
Sepsis/Breakdown of hematoma	6

TABLE 3

Diagnostic methods used in 59 patients with bile duct injury or obstruction.

Diagnostic method	No. of patients
Ultrasound	22
CT	38
Diagnostic peritoneal tap	13
ERCP	30
MRCP	1
HIDA scan	10
Intraoperative cholangiography	10
PTC	2
Arteriography	6
Venography	2
Upper gastrointestinal series	1

CT = computerized tomography
 ERCP = endoscopic retrograde cholangiopancreatography
 MRCP = magnetic resonance cholangiopancreatography
 HIDA scan = technetium-99m dimethyl iminodiacetic acid scan
 PTC = percutaneous transhepatic cholangiography

normal after 24 hours (27). Liver morphologic changes due to hemorrhagic shock are well recognized, and human studies have shown enzymatic and light and electron microscopic evidence of hepatocellular damage immediately after shock (28). This is followed by repair and regeneration of liver. Putatively, restoration of normal liver function after hemorrhagic shock may be delayed by intercurrent disease, e.g. systemic infection. Even modest enhancements of rate of endogenous bilirubin production could under such circumstances produce manifest jaundice.

Only in a few trauma patients have clear relationships between the occurrence of jaundice and types of anesthetic agents and drugs administered to the patients been demonstrated. Hepatotoxic drugs should nevertheless be considered and looked for in individual cases. Drug-induced liver injury can mim-

ic all forms of acute and chronic liver disease, but typically produces an acute hepatocellular injury or, less commonly, a cholestatic injury (29). Total parenteral nutrition induced cholestasis should be considered when jaundice develops in trauma patients on long term hyperalimentation (30).

Acute acalculus cholecystitis (ACC) may occur as a complication of trauma (31). Most trauma patients who develop ACC are hospitalized in intensive care units. They usually receive intravenous alimentation, mechanical ventilation, narcotics and antibiotics. Jaundice is common, but bilirubin levels show a wide variety and normal bilirubin values do not rule out ACC (32). The clinical and laboratory manifestations may be fever, jaundice, leukocytosis and right upper quadrant pain. However, the diagnosis of ACC rests on a high index of suspicion and the results of imaging studies (31).

Hereditary causes of jaundice in trauma patients are rare (33). Gilbert's syndrome, characterized by a mild unconjugated hyperbilirubinemia due to reduced bilirubin glucuronidation, is the most common congenital disorder in bilirubin metabolism (34). It is often asymptomatic and the serum bilirubin level is often less than 2 mg/dL. However, trauma patients with Gilbert's syndrome may experience striking increases in serum-bilirubin. Other liver analytes are normal and the jaundice generally resolves as oral feeding is resumed and an extensive diagnostic workup is not indicated.

An avulsion, transection or laceration of the extrahepatic bile ducts infrequently occur in surgical trauma patients. Bile duct injuries which have been reported have mostly been found in patients who have sustained blunt upper abdominal trauma (35). Diagnostic delays are common (36). When bile duct injuries have been overlooked, the patients typically return in 1 or 2 weeks presenting with jaundice, biliary ascites and inanition (37). The increased mortality and morbidity in this group of patients is attributed to delayed diagnosis of biliary peritonitis. Intrahepatic and extrahepatic bile duct injuries may lead to traumatic hemobilia or traumatic bilhemia. The jaundice of hemobilia is due to bile duct obstruction by a clot and occurs when there is a fistula between a vessel of the splanchnic circulation and the intrahepatic or extrahepatic biliary system (38). Traumatic bilhemia is caused by an intrahepatic biliovenous shunt caused by a central liver rupture of the liver veins and bile ducts (39). The flow direction of the stream of bile-blood mixture is determined by the low or negative pressure of the caval vein. A typical finding is excessive and rapid increase of total bilirubin level a few days after injury accompanied by no or moderate elevation of other liver enzymes.

Based on the findings in this review we propose a diagnostic workup of jaundiced trauma patients (Fig. 1).

CASE HISTORY

In the search for the etiology of jaundice in trauma patients, a thorough case history is necessary first of all. The presence of pre-existing chronic liver disease

is an important risk factor for the development of jaundice after a trauma incident. The case history should clarify whether pre-existing liver disease exists, as well as what drugs and anesthetic agents have been used, the time of onset of jaundice, the presence of initial shock and the number of blood transfusions the patient has received following the trauma incident. An assessment should be made regarding net retention of transfused red blood cells. The exact mechanism of injury will carry information about the most likely injury pattern and whether the patient has suffered an abdominal trauma. Often, such a history cannot be obtained directly from the patient. The patient's hospital record should be searched and the family consulted to obtain all information that is deemed necessary to get an understanding of the potential causes of the patient's jaundice.

PHYSICAL EXAMINATION

The physical examination should be conducted to determine whether the patient has been exposed to a blunt or penetrating abdominal trauma. The presence of abdominal trauma raises a suspicion of injury or obstruction to the bile duct. Light colored stools and dark colored urine suggest an obstruction of the common bile duct. Examination of the pelvis and extremities may reveal large hematomas surrounding fractures. The peripheral stigmata of chronic liver disease should be looked for.

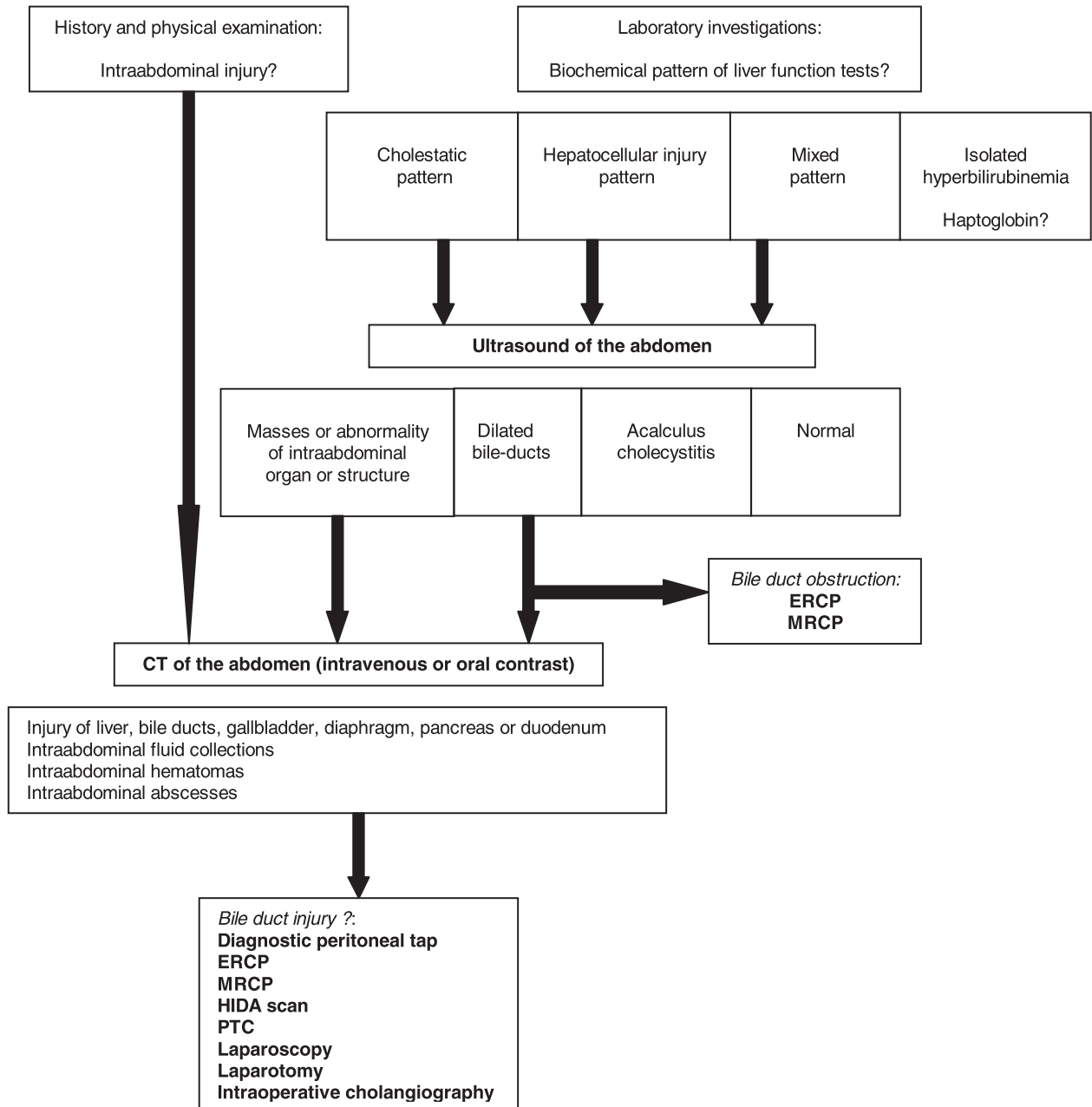
BLOOD TESTS

The following serological liver function test must be procured; bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyl transpeptidase and International Normalized Ratio (INR) (20, 40). Full blood count and samples for microbiological cultures must be collected routinely when the patients have fever ($> 38^{\circ}\text{C}$) and whenever there is clinical suspicion or evidence of infection.

IMAGING STUDIES

Diagnostic imaging can provide additional information and is deemed necessary whenever an intraabdominal injury or a bile duct obstruction is suspected. Ultrasound is often the first imaging modality chosen to evaluate jaundice in trauma patients. Ultrasound findings that will need further investigations or interventions are a dilated bile duct, a mass or abnormality of an intraabdominal organ or structure, ascites, intraabdominal fluid collections or findings suggestive of acalculus cholecystitis. The sensitivity and specificity of ultrasound varies with the examiner's skills in this technique. Computerized tomography (CT) may further delineate the pathological findings suggested by ultrasound. In patients who have been exposed to a blunt abdominal trauma, most modern trauma centers perform an abdominal CT at admission, but even CT with contrast does not necessarily reveal bile duct injury in the early post injury period (36). Therefore CT must be repeated if

<p>History:</p> <ul style="list-style-type: none"> - pre-existing hepatobiliary disease? - alcohol? - drugs/anesthetics? - family history of liver disease? - time of onset of jaundice? - bleeding/blood transfusions? - shock state? - mechanism of injury? - total parenteral nutrition? 	<p>Physical examination:</p> <ul style="list-style-type: none"> - peripheral stigmata of chronic liver disease? - signs of abdominal trauma? - lightened stool and dark urine color? - hematomas surrounding fractures? - pelvic-, abdominal- or thoracic hematomas? 	<p>Laboratory investigations:</p> <ul style="list-style-type: none"> - liver function tests (bilirubin, AST, ALT, ALP, γ-GT, INR) - full blood count - creatinine - microbiological samples
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CT= computerized tomography
 ERCP = endoscopic retrograde cholangiopancreatography
 MRCP = magnetic resonance cholangiopancreatography
 HIDA scan = technetium-99m dimethyl iminodiacetic acid scan
 PTC = percutaneous transhepatic cholangiography

Fig. 1. Diagnostic workup of jaundice in trauma patients.

an intraabdominal injury is suspected. If ultrasound or abdominal CT documents the presence of ascites or intraabdominal fluid collections, the next diagnostic maneuver is to perform a diagnostic peritoneal tap for bilirubin measurement. The presence of bile peritonitis or bilious ascites always suggests a bile duct injury.

Endoscopic retrograde cholangiopancreatography (ERCP) is used to demonstrate bile duct injuries. ERCP roentgenograms define the area of injury most precisely, but furnish little information about associated hepatic injuries. ERCP permits a therapeutic intervention either by stent or sphincterotomy and the role for ERCP in trauma patients is well documented in the literature (41, 42). Radionuclide scanning with technetium-99m dimethyl iminodiacetic acid (HIDA) permits definition of hepatic parenchymal abnormalities, whereas injury to the biliary tract is delineated during excretion of the tracer. HIDA scan has been used in children with a suspected bile duct injury and to evaluate suspected bile leaks following laparoscopic cholecystectomy (43, 44). The presence of dilated bile ducts makes an ERCP or magnetic resonance cholangiopancreatography (MRCP) mandatory. The role for MRCP in traumatic bile duct injuries is not well documented but studies show that iatrogenic bile duct injuries are well demonstrated at MRCP (45). Bile leaks result in the accumulation of fluid, usually in the subhepatic space, which is readily detected at MRCP. MRCP has a potential to depict strictures and excision injury and give an informative display of the anatomy of the bile ducts. However, MRCP cannot determine if a leak is active. The information derived from a combination of ERCP and MRCP may enable the radiologist to accurately classify the type of injury and helps to determine treatment, whether endoscopic, percutaneous or surgical.

In conclusion, even though jaundice in trauma patients can be managed by the same diagnostic tools as other jaundiced patients, this review shows that trauma patients differ in some important ways. By contrast to non-trauma patients, increased bilirubin load due to multiple blood transfusions and breakdown of extravasated blood is an important causative factor of jaundice. In addition to this, sepsis, infections, initial shock, systemic hypotension and multiple organ failure syndrome are other important factors in the development of jaundice in trauma patients. Extrahepatic bile duct injury or obstruction are rare but call for a high grade of suspicion because their diagnosis is difficult and often delayed with deleterious consequences for the patient. The main aim of the diagnostic approach in trauma patients should be to exclude bile duct injury or obstruction as causes of jaundice.

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