Ischemic hepatitis, hepatic infarction, and ischemic cholangiopathy

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INTRODUCTION

The liver's complex vascular supply and high metabolic activity make it particularly vulnerable to circulatory disturbances. The severity and characteristics of hepatic injury depend upon the blood vessels that are involved and the degree to which injury is related to passive congestion or diminished perfusion [1,2].

There are several well-recognized forms of vascular injury to the liver, including Budd-Chiari syndrome, hepatic sinusoidal obstruction syndrome (veno-occlusive disease), passive congestion due to heart failure, hepatic infarction, and ischemic hepatitis. (See "Pathogenesis of liver injury in circulatory failure".)

This topic review will focus on ischemic hepatitis, hepatic infarction, and ischemic cholangiopathy, while discussions on Budd-Chiari syndrome, hepatic sinusoidal obstruction syndrome, and congestive hepatopathy are presented separately. (See "Budd-Chiari syndrome: Epidemiology, clinical manifestations, and diagnosis" and "Congestive hepatopathy" and "Hepatic sinusoidal obstruction syndrome (veno-occlusive disease) in adults".)

ISCHEMIC HEPATITIS (SHOCK LIVER, HYPOXIC HEPATITIS)

Ischemic hepatitis (also referred to as shock liver, hypoxic hepatitis, hypoxic liver injury, ischemic hepatopathy, and acute cardiogenic liver injury) refers to diffuse hepatic injury resulting from acute hypoperfusion [3-6]. Ischemic hepatitis accounts for 1 to 2.5 (and occasionally up to 10) percent of patients admitted to an intensive care unit [7-10].

The term hepatitis is somewhat of a misnomer since the injury is not mediated by an inflammatory process. Nevertheless, the profound elevation in aminotransferases is similar to that seen in toxic hepatitis (such as caused by acetaminophen) and acute viral hepatitis, two disorders that should be considered prominently as part of the differential diagnosis. (See "Approach to the patient with abnormal liver biochemical and function tests".)

The term ischemic hepatitis is preferable to "shock liver" since the syndrome can occur in the absence of shock. The diffuse nature of the injury distinguishes it from hepatic infarction, which represents focal injury.

The clinical, laboratory, and histologic features of ischemic hepatitis overlap considerably with those of congestive hepatopathy, since the underlying cause of both conditions is related to decreased cardiac output. Many cases of ischemic hepatitis occur in the setting of congestive heart failure, although there are many other potential causes [11-13]. (See "Congestive hepatopathy".)

Clinical manifestations — Any cause of shock or hemodynamic instability can cause ischemic injury to the liver, although in some reports only approximately one-half of patients with ischemic hepatitis had shock [10,14]. (See "Pathogenesis of liver injury in circulatory failure".)

Ischemic injury can also be caused by focal interruption of the hepatic blood supply, as occurs with hepatic sickle cell crisis and hepatic artery thrombosis in patients who have undergone liver transplantation or have preexisting portal vein thrombosis (loss of the hepatic artery alone generally does not cause ischemic hepatitis in otherwise healthy people). Ischemic hepatitis has also been described in the setting of severe respiratory failure, systemic hypoxemia, obstructive sleep apnea, and acute lower limb ischemia [14,15]. (See "Hepatic manifestations of sickle cell disease".)

The hemodynamic insult is usually apparent clinically before evidence of liver injury appears. Less commonly, ischemic injury may follow "subclinical" circulatory disturbances (due to transient reductions in hepatic perfusion), particularly in patients who are predisposed to ischemic injury such as those with preexisting passive congestion and those with portal hypertension [16,17].

Ischemic hepatitis is usually first detected because of elevations in liver biochemical tests following a hypotensive episode. Occasional patients have symptoms suggesting acute hepatitis, including nausea, vomiting, anorexia, malaise, and right upper quadrant pain [3,16]. Thus, ischemia should always be considered in the differential diagnosis of acute hepatitis, along with more common causes such as viral infection, drugs, toxins, autoimmunity, and metabolic disorders.

The characteristic pattern of liver biochemical tests consists of a rapid rise in serum aminotransferase levels associated with an early massive rise in lactate dehydrogenase (LDH) levels. Peak aminotransferase levels are typically 25 to 250 times the upper limit of normal and are reached within one to three days of the hemodynamic insult [18].

In the absence of ongoing hemodynamic instability, aminotransferase levels subsequently decline steadily, usually returning to normal within 7 to 10 days. The serum bilirubin level infrequently rises above four times the upper limit of normal, usually beginning its rise after aminotransferase levels have begun to decline. Serum alkaline phosphatase levels are rarely higher than twice the upper limit of normal.

Hepatic synthetic function usually remains normal or is only mildly impaired; the prothrombin time is infrequently prolonged by more than three seconds. Occasional patients develop changes in mental status, which generally reflect impaired cerebral perfusion rather than hepatic encephalopathy.

Hepatopulmonary syndrome develops in nearly one-half of patients but appears to be reversible following normalization of hepatic function [19]. The pathogenesis is believed to involve intrapulmonary vasodilation. (See "Hepatopulmonary syndrome in adults: Prevalence, causes, clinical manifestations, and diagnosis".)

Diagnosis — Ischemic hepatitis should be considered in the clinical settings described above. Few causes of liver injury result in the striking increases in aminotransferase levels (exceeding 1000 international unit/L or 50 times the upper limit of normal) seen in ischemic hepatitis. Besides ischemic hepatitis, the most common are acute drug- or toxin-induced liver injury (eg, acetaminophen toxicity, toxicity caused by certain herbal and dietary supplements) and acute viral hepatitis. On occasion, similar values can be seen in a number of other settings (see "Approach to the patient with abnormal liver biochemical and function tests"):

- During an acute exacerbation of autoimmune hepatitis.
- Spontaneous reactivation of chronic type B hepatitis.
- Superimposition of hepatitis D in a chronic carrier of hepatitis B virus.

- Miscellaneous disorders such as acute Budd-Chiari syndrome (especially those with concomitant portal vein thrombosis), hepatic sinusoidal obstruction syndrome, HELLP syndrome, acute fatty liver of pregnancy, hepatic infarction, and acute biliary obstruction.

These disorders cannot be distinguished based upon the pattern of liver biochemical tests alone. However, some features may suggest an ischemic rather than a viral cause of liver injury:

- An early rapid rise in the serum LDH level is unusual in viral hepatitis.
- A ratio of serum alanine aminotransferase to LDH of less than 1.5 early in the course of acute hepatitis suggests ischemic hepatitis rather than viral hepatitis [20].
- A rapid fall in serum aminotransferase levels after the initial rise is characteristic of ischemic liver injury and atypical for other causes of hepatitis.
- Ischemic hepatitis is often accompanied by additional evidence of end-organ hypoperfusion, especially acute tubular necrosis of the kidney. Thus, a concomitant, early rise in the serum creatinine level favors a diagnosis of ischemic hepatitis [11,18]. Other associations include rhabdomyolysis and, less often, intestinal ischemia and ischemic pancreatitis [10].

In addition to a careful medical history, reasonable evaluation might include serologic testing for acute viral hepatitis, a blood acetaminophen level, and right upper quadrant ultrasonography with Doppler studies of the portal and hepatic veins and hepatic artery in addition to evaluation for suspected underlying causes of ischemic injury such as cardiac or respiratory failure. There are no characteristic findings on physical examination, although some patients have right upper quadrant tenderness. However, physical examination may provide clues toward underlying liver disease, which may have increased the patient's susceptibility to the acute injury.

Pathology — The histologic hallmark of ischemic hepatitis is necrosis of hepatocytes in zone 3 of the hepatic acinus associated with a variable degree of architectural collapse around the central vein, depending upon the duration and extent of ischemia. With severe prolonged ischemia, necrosis may extend to the mid zonal hepatocytes. In rare patients, the necrosis may be predominantly mid zonal. There are characteristically few inflammatory cells.

There may be coexisting changes reflecting passive congestion, especially in patients with cardiogenic shock. These include sinusoidal engorgement, degeneration and variable degrees of hemorrhagic necrosis in zone 3, fatty change, and variable degrees of cholestasis with occasional bile thrombi in the canaliculi. In patients with chronic or recurrent heart failure,

reticulin and collagen accumulate in zone 3, eventually causing fibrous bands to extend outward from the central veins. (See "Pathogenesis of liver injury in circulatory failure".)

Despite extensive injury, hepatic architecture may return to normal after recovery from the ischemic event.

Management — Management of ischemic hepatitis should be aimed at restoring cardiac output and reversing the underlying cause of hemodynamic instability. Overly aggressive diuresis should be avoided since it may worsen hepatic perfusion. Patients should be monitored closely for evidence of end-organ hypoperfusion, particularly decreased renal function and altered mental status.

There is no specific therapy for ischemic hepatitis. Limited data suggest that intravenous administration of dopamine, at either "renal" or "cardiac" doses, leads to preservation, and perhaps augmentation, of hepatic blood flow, but the clinical benefit of such therapy has not been established [21]. Whether the effect on hepatic blood flow is due to selective dopaminergic vasodilation of the mesenteric bed or increased cardiac output, or both, is unclear.

Similarly, augmentation of cardiac output enhances hepatic perfusion, but the benefit on liver function is uncertain. Thus, the choice of pharmacologic therapy for cardiovascular support should be dictated by the overall hemodynamic condition of the patient, not its potential benefits on hepatic perfusion.

Improvement following treatment with intravenous N-acetylcysteine was described in a case report of ischemic hepatitis due to an antidepressant [22]. The mechanism of benefit may have been due to a cytoprotective effect. Limited data suggest that use of a statin prior to admission may protect against ischemic hepatitis [23].

Reperfusion injury may also influence hepatic recovery. Ongoing research is evaluating methods to reduce such injury in the setting of liver transplantation. However, no specific treatment has been proven to reduce reperfusion injury in patients with ischemic hepatitis.

Prognosis — Although ischemic hepatitis is nearly always self-limited, the patient's overall prognosis is poor, with mortality rates often above 50 percent [10,24]. Ischemic hepatitis is otherwise nearly always self-limited, although fewer than one-half of patients survive one year [10]. The severity of the liver injury correlates with the duration and extent of the hemodynamic compromise [25] and with the development of jaundice [26]. Prognosis is mostly related to the severity of the underlying systemic disease [13]. Among patients with ischemic hepatitis that

develops in the intensive care unit, the need for vasopressor therapy or the presence of septic shock, renal failure, or coagulopathy is associated with high mortality rates [27].

As noted above, serum aminotransferase elevations typically resolve spontaneously over 7 to 10 days in the absence of ongoing hypotension. Normalization of serum bilirubin may be more protracted. A continually rising bilirubin and progressive prolongation of the prothrombin time should raise the suspicion of acute liver failure.

Occasional patients develop acute liver failure, usually when ischemic hepatitis is superimposed upon chronic congestive heart failure or in patients with preexisting cirrhosis [17]. Mortality rates ranging from 60 to 100 percent have been described in patients with ischemic hepatitis complicating cirrhosis [28,29] and are highest in those with more severe encephalopathy and a higher serum phosphate level on hospital admission [30]. Hepatic decompensation has also been described in previously healthy patients, but the liver injury is usually overshadowed by the underlying condition that led to the liver injury.

HEPATIC INFARCTION

Hepatic infarction represents focal ischemic injury of the liver and thus should be distinguished from ischemic hepatitis, in which the injury is diffuse. Because the liver has a dual blood supply, hepatic infarction is less common than other forms of ischemic injury. However, the frequency may have increased since the advent of laparoscopic cholecystectomy, hepatic artery chemoembolization, and liver transplantation, all of which may result in a focal loss of blood supply to the liver.

Hepatic infarction typically results from occlusion of a single intrahepatic branch of the hepatic artery, in contrast to ischemic hepatitis, in which the liver injury is due to a systemic decrease in perfusion or oxygenation. Hepatic artery branches to the right hepatic lobe are affected most commonly. (See "Pathogenesis of liver injury in circulatory failure".)

Many causes of hepatic infarction have been reported:

- Iatrogenic ligation of the hepatic artery (usually the right hepatic artery) has been described most often after laparoscopic cholecystectomy [31].
- Thrombosis of the hepatic artery may be due to atherosclerosis, a hypercoagulable state, or liver transplantation [32,33]. Hepatic artery thrombosis following liver transplantation tends to occur at the anastomosis between the native and donor hepatic arteries.

- Hepatic artery embolization has been reported in patients with infective endocarditis [34], tumor embolism, or therapeutic embolization or chemoembolization [35].

- Hepatic infarction has been described following radiofrequency ablation of hepatocellular carcinoma [36,37], endoscopic ultrasound-guided celiac plexus neurolysis [38], and transjugular intrahepatic portosystemic shunt placement [39].

- Other causes include toxemia of pregnancy [40], sickle cell disease [41], antiphospholipid antibody syndrome [42] polyarteritis nodosa, hepatic artery aneurysms, cocaine toxicity, and aortic dissection. Hepatic infarction associated with toxemia of pregnancy is notable for its tendency to cause hepatic hemorrhage, which may lead to rupture of Glisson's capsule and catastrophic intraabdominal bleeding. (See "HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets)".)

Clinical manifestations — The cause of hepatic infarction is often known in many of the clinical settings described above. Hepatic infarction itself may not cause symptoms and may be detected only on an imaging study. Other patients can have moderate to severe clinical findings including fever, epigastric or right upper quadrant pain, back or right shoulder pain, jaundice, nausea, and vomiting.

A marked leukocytosis is common. The aminotransferases rise transiently, sometimes to massive levels.

Diagnosis — The diagnosis of hepatic infarction is suggested radiographically in patients with a compatible clinical history. On ultrasound, the detection of hypoechoic regions without Doppler flow and with multiple internal echogenic bands on different images and planes suggests areas of infarction [43]. Computed tomography (CT) is more sensitive compared with ultrasound for detecting a focal hepatic lesion, but CT appearance alone may not be sufficient for distinguishing a hepatic infarct from a liver abscess or tumor, which can have similar imaging features. Thus, ultrasound- or CT-guided needle aspiration of the lesion may be needed to establish a definitive diagnosis, particularly when an abscess or neoplasm cannot be excluded. The decision to perform a biopsy should be based upon the clinical setting, taking into consideration such factors as the risk of biopsy, patient comorbidities, probability of a specific diagnosis, and concerns related to risk of tumor seeding of the biopsy tract.

On an abdominal CT scan, a hepatic infarct appears most commonly as a focal, wedge-shaped lesion of low attenuation, which may extend to the capsular surface of the liver. It may also be round or oval-shaped and more centrally located, or irregular and parallel to the intrahepatic bile ducts [44,45]. The shape may change over time. A hepatic infarct is best seen with intravenous contrast imaging.

Some CT characteristics may be helpful in distinguishing a hepatic infarct from a pyogenic liver abscess or tumor. The presence of gas in the lesion is suggestive of infection (either a pyogenic liver abscess or a superinfected hepatic infarct), but the presence of gas does not exclude infarction. In addition, the absence of gas does not exclude an abscess. Splenic and renal infarcts may be identified radiographically, suggesting an embolic source of the liver findings. Mass lesions, including abscesses and tumors, tend to displace hepatic blood vessels. Thus, nondisplaced blood vessels running through a lesion are suggestive of an infarct rather than an abscess or tumor [45].

On magnetic resonance imaging, hepatic infarction typically appears as a wedge-shaped region of diminished T1 signal and increased T2 signal, a finding that is relatively nonspecific [46].

Doppler ultrasonography should be performed to assess the patency of the hepatic artery. Patients who are suspected of having an occluded hepatic artery may require magnetic resonance angiography or occasionally celiac arteriography for confirmation and more detailed localization depending upon the clinical setting.

Pathology — Characteristic histologic findings including a central zone of complete coagulative necrosis involving hepatocytes, portal tracts, and central veins, surrounded by a zone of inflammatory reaction, which is, in turn, surrounded by a zone of partial necrosis [31]. The involvement of all three zones of the hepatic acinus is markedly different from the histologic pattern seen in ischemic hepatitis, in which necrosis is confined predominantly to zone 3.

Management — As a general rule, no specific therapy for hepatic infarction is required once infection is ruled out. However, it is important to identify potential sources of emboli, such as infective endocarditis or tumor. In the absence of such a source, a hypercoagulable state, (eg, proteins C and S or antithrombin deficiency, factor V Leiden mutation, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, polycythemia vera, and possibly oral contraceptive use) should be considered. Occasional patients with hepatic infarction develop a pyogenic superinfection, which should be suspected if there is persistent worsening of fever, pain, and leukocytosis. Such patients may require aspiration of the lesion to confirm infection. (See "Pyogenic liver abscess".)

Further management depends upon the underlying cause of the infarction and its severity. Asymptomatic patients may be managed conservatively. Serial CT scans may show resolution of the infarct over weeks, residual scarring, calcification, or atrophy of the involved lobe of liver. The need for and frequency of follow-up imaging depends on the certainty of the diagnosis of infarction and the patient's clinical condition and comorbidities. In some patients, anticoagulation is indicated to prevent further systemic emboli or thrombosis. Patients who

develop hepatic infarction after liver transplantation often require urgent retransplantation. Hepatic infarction with rupture complicating toxemia of pregnancy requires emergent laparotomy, although in the absence of rupture, expectant management may suffice.

ISCHEMIC CHOLANGIOPATHY

The hepatic artery (via the peribiliary plexus) provides the exclusive blood supply to the major bile ducts. As a result, compromise of blood flow through the peribiliary plexus may lead to ischemic cholangiopathy, which involves principally the large perihilar extrahepatic bile ducts and less commonly, the intrahepatic bile ducts (figure 1) [47].

The most common setting for ischemic cholangiopathy is following liver transplantation [48,49]; the risk is particularly increased and the onset earlier with use of a non-heart beating donor graft [49,50]. (See "Liver transplantation in adults: Long-term management of transplant recipients".)

However, other causes have been described [47,51] including:

- Vascular injury during biliary tract surgery [52].
- Arterial infusion of the chemotherapeutic agent floxuridine for palliation of liver metastases from gastrointestinal adenocarcinomas [53].
- Chemoembolization and radiation therapy [54].
- Hypercoagulable states leading to occlusion of the peribiliary plexus [55].
- Biliary ischemia in patients with hereditary hemorrhagic telangiectasia [56].
- Secondary sclerosing cholangitis in critically ill patients, in whom cirrhosis can develop rapidly and the prognosis is poor [57-59]; sparing of the distal bile duct appears to be a distinguishing feature [60].
- Recovery from severe COVID-19 requiring mechanical ventilation and vasopressor support and often associated with biliary cast formation [61,62].

Clinical manifestations — Patients with ischemic cholangiopathy typically present with features suggesting biliary obstruction, such as pruritus, dark urine, clay-colored stools, and jaundice. Liver chemistries reveal a cholestatic pattern with elevations of serum bilirubin and alkaline phosphatase and variable elevations in serum aminotransferase levels. Occasional

patients develop acute bacterial cholangitis or cholangitic liver abscesses, with associated fever and right upper quadrant pain. (See "Pyogenic liver abscess".)

Diagnosis — Ischemic cholangiopathy should be suspected in the clinical settings described above. The main diagnostic challenge is to distinguish it from more common causes of biliary obstruction such as choledocholithiasis and malignancy. The biliary abnormalities may also closely resemble those seen in primary sclerosing cholangitis. (See "Primary sclerosing cholangitis in adults: Clinical manifestations and diagnosis".)

The diagnosis is generally by magnetic resonance cholangiopancreatography, which does not permit therapeutic intervention or biopsy. Most patients require cholangiography by an endoscopic or transhepatic route for further evaluation and possibly intervention.

Cholangiographic findings consist of multiple intra- and extrahepatic strictures with diffuse irregularity or beading of the ducts, a more limited number of discrete biliary strictures (usually affecting the large perihilar bile ducts), or disruption of ductal integrity with extravasation of bile and contrast.

Pathology — Liver biopsy is rarely useful and often misleading, because histology reveals only evidence of biliary obstruction, with no indication of the underlying ischemic process. Histologic features of ischemic cholangiopathy (when seen) include ischemic bile duct necrosis, cholangitis without necrosis, biliary casts, and biliary fibrosis [63].

Patients found to have a biliary stricture following liver transplantation should undergo Doppler ultrasonography of the hepatic vessels to rule out hepatic artery thrombosis. In questionable cases, arteriography should be performed.

Management — Limited data are available regarding the treatment of ischemic cholangiopathy, virtually all related to liver transplantation. Endoscopic therapy with dilation and stenting can be effective for treatment of a biliary stricture (see "Liver transplantation in adults: Long-term management of transplant recipients").

Ischemic cholangiopathy occurring within the first month after liver transplantation frequently requires urgent retransplantation [64]. Bevacizumab has been reported to reverse ischemic cholangiopathy in some patients with hereditary hemorrhagic telangiectasia [56], although thromboembolic complications have been reported [65].

SUMMARY AND RECOMMENDATIONS

- **Ischemic hepatitis** – Ischemic hepatitis (also referred to as shock liver, hypoxic hepatitis, hypoxic liver injury, ischemic hepatopathy, and acute cardiogenic liver injury) refers to diffuse hepatic injury resulting from acute hypoperfusion (see 'Ischemic hepatitis (shock liver, hypoxic hepatitis)' above):

  - **Clinical features** – Most patients have no symptoms referable to the liver but have marked elevation of serum aminotransferase levels after an episode of hypotension. Any cause of shock or hemodynamic instability can cause ischemic injury to the liver, although in some reports only approximately one-half of patients with ischemic hepatitis had shock. (See 'Clinical manifestations' above.)

  - **Diagnosis** – Ischemic hepatitis should be considered in the clinical settings described above. Few causes of liver injury result in the striking increases in aminotransferase levels (exceeding 1000 international unit/L or 50 times the upper limit of normal) seen in ischemic hepatitis. Besides ischemic hepatitis, common causes of striking aminotransferase elevations include acute drug- or toxin-induced liver injury (eg, acetaminophen toxicity, toxicity caused by certain herbal and dietary supplements) and acute viral hepatitis. (See 'Diagnosis' above.)

  - **Management** – Ischemic hepatitis is self-limited in most patients. Liver failure is uncommon but more likely in patients with pre-existing passive congestion or cirrhosis, or those with sustained hepatic ischemia. Thus, we suggest management be aimed at restoring cardiac output and reversing the underlying cause of hemodynamic instability (**Grade 2C**). (See 'Management' above.)

- **Hepatic infarction** – Compromise of hepatic arterial flow rarely may result in focal hepatic infarction, which must be distinguished from a liver abscess or tumor. Hepatic infarction has been described due to a variety of causes including hepatic arterial thrombosis (especially after liver transplantation), iatrogenic hepatic artery ligation, hepatic artery emboli, vasculitis, aortic dissection, and toxemia of pregnancy. (See 'Hepatic infarction' above.)

  - **Diagnosis** – The diagnosis of hepatic infarction is suggested radiographically in patients with a compatible clinical history. However, imaging appearance alone may not be sufficient to distinguish a hepatic infarct from a pyogenic liver abscess or tumor, which can have similar radiographic features. Thus, ultrasound- or computed tomography-guided needle aspiration of the lesion may be needed to establish a definitive diagnosis. (See 'Diagnosis' above.)

- **Management** – As a general rule, no specific therapy for hepatic infarction is required once infection is ruled out. Thus, we suggest supportive treatment only (**Grade 2C**). However, it is important to identify potential sources of emboli, such as infective endocarditis or tumor. In the absence of such a source, a hypercoagulable state, including proteins C and S or antithrombin deficiency, factor V Leiden mutation, antiphospholipid syndrome, paroxysmal nocturnal hemoglobinuria, polycythemia vera, and possibly oral contraceptive use, should be considered. (See 'Management' above.)

- **Ischemic cholangiopathy**

  - **Clinical features** – Ischemic cholangiopathy is observed most commonly after liver transplantation, although several other causes have been reported. Patients typically present with features suggesting biliary obstruction, such as pruritus, dark urine, clay-colored stools, and jaundice. The clinical and cholangiographic features may resemble primary sclerosing cholangitis. (See 'Ischemic cholangiopathy' above.)

  - **Diagnosis** – Ischemic cholangiopathy should be suspected in the clinical settings described above. The main diagnostic challenge is to distinguish it from more common causes of biliary obstruction such as choledocholithiasis and malignancy. The biliary abnormalities may also closely resemble those seen in primary sclerosing cholangitis. (See 'Diagnosis' above.)

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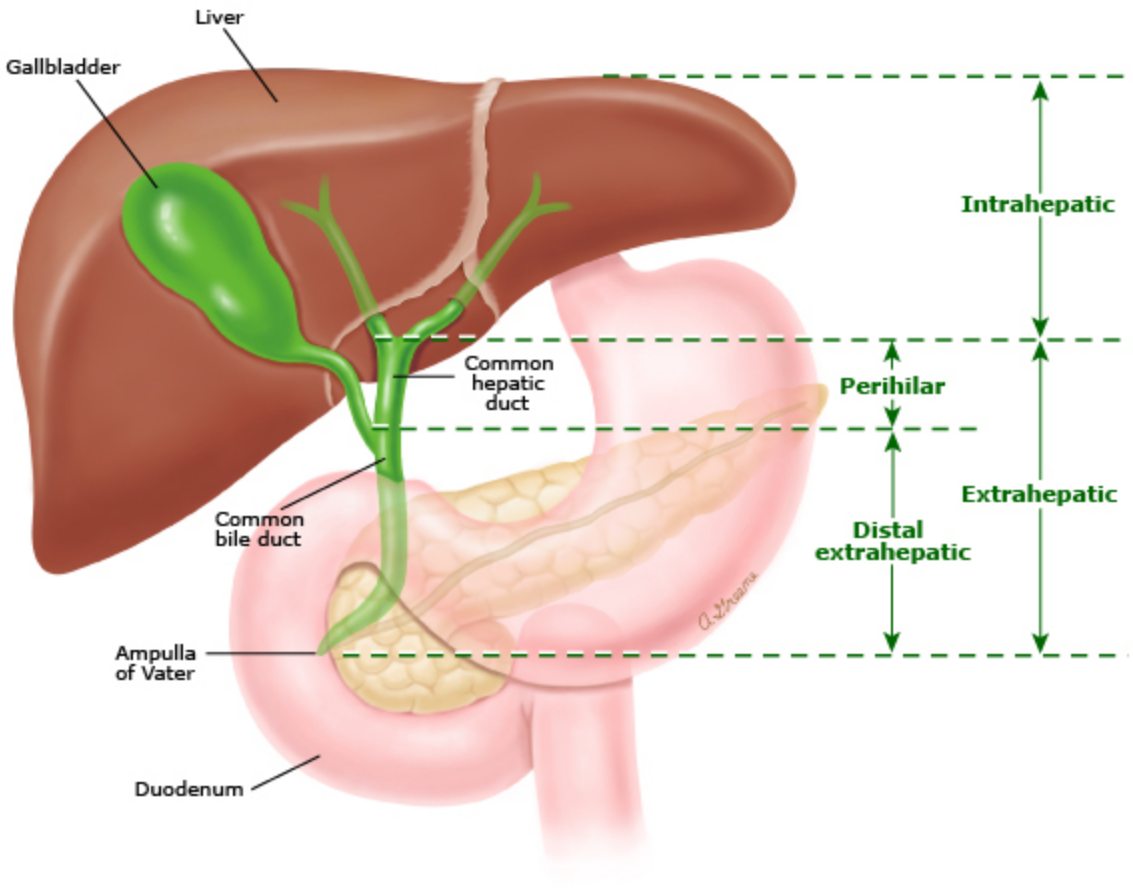
GRAPHICS

Anatomic classification of cancers of the human biliary tract



Classifications defined by: American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 8th Edition, Amin MB (Ed), Chicago: Springer Science+Business Media, LLC, 2017.

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