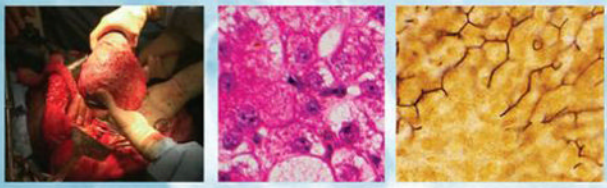
Practical Gastroenterology and Hepatology

Liver and Biliary Disease



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Practical Gastroenterology and Hepatology:
Liver and Biliary Disease

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Practical Gastroenterology and Hepatology

Liver and Biliary Disease

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Preface

Welcome to *Practical Gastroenterology and Hepatology*, a new comprehensive three volume resource for everyone training in gastroenterology and for those certifying (or re-certifying) in the subspecialty. We have aimed to create three modern, easy to read and digest stand-alone textbooks. The entire set covers the waterfront, from clinical evaluation to advanced endoscopy to common and rare diseases every gastroenterologist must know.

Volume three deals with disorders of the liver and biliary tree. Each chapter highlights, where appropriate, a clinical case which demonstrates a common clinical situation, its approach, and management. Simple, easy to follow clinical algorithms are demonstrated throughout the relevant chapters. Endoscopy and surgery chapters provide excellent video examples, all available electronically.

Each chapter has been written by the best of the best in the field, and carefully peer reviewed and edited for accuracy and relevance. We have guided the writing of this textbook to help ensure experienced gastroenterologists, fellows, residents, medical students, internists, primary care physicians, as well as surgeons all will find something of interest and relevance.

Each volume and every chapter has followed a standard template structure. All chapters focus on key knowledge, and the most important clinical facts are highlighted in an introductory abstract and as take-home points at the end; irrelevant or unimportant information is omitted. The chapters are deliberately brief and readable; we want our readers to retain the material, and immediately be able to apply what they learn in practice. The chapters are illustrated in color, enhanced by a very pleasant layout. A Web based version has been created to complement the textbook including endoscopy images and movies.

In this volume, part one addresses the anatomy and immunopathology of the liver and biliary tree. The emphasis here is, as in all volumes, on the practical and clinically relevant, as opposed to the esoteric. Part two deals with the approach the clinician should take in diagnosis of diseases in the liver and biliary tract. Basic history and physical techniques, laboratory, imaging and endoscopy modalities are discussed. Part three covers problem-based approach to important manifestations of liver injury and disease such as jaundice, liver tumors, right upper quadrant pain and acute liver failure. Part four follows with approaches to manifestations of chronic disease such as portal hypertension and hepatocellular carcinoma in addition to specific clinical scenarios such as pregnancy in the setting of chronic liver disease and adult problems in the survivor of pediatric liver disease. Part five covers the wide spectrum of viral, autoimmune and metabolic diseases that the gastroenterologist is likely to encounter, all designed to be succinct and clinically oriented. Part six covers the very relevant topic of liver transplantation. The reader will be left with important clinical pearls in the selection and management of patients with cirrhosis in need of liver replacement. Surgical details and medical/pharmacological principles are outlined. Section seven addresses a problem-based approach to the management of biliary tract disorders, ranging from stones and strictures to cancer and functional pain syndromes.

We have been thrilled to work with a terrific team in the creation of this work, and very much hope you will enjoy reading this volume as much as we have enjoyed developing it for you.

Nicholas J. Talley
Keith D. Lindor
Hugo E. Vargas

Foreword

The discipline of hepatology has blossomed into a comprehensive specialty that demands broad expertise. In that context, the textbook by Talley, Lindor and Vargas is timely and valuable. One need only peruse the topics within this section to realize how much has changed in the past few years—in particular, the emergence of liver transplantation as a life-saving intervention has rescued thousands of patients and buoyed clinicians by offering new hope and generating new principles of care for their patients. Viral hepatitis, acute liver failure, and non-alcoholic fatty liver are among the other important topics covered by this volume, reflecting the practical perspective of seasoned clinicians and thought leaders in the field. The work is infused with the excitement of hepatology and the practical wisdom of many of its practitioners. Therefore, it's a great personal privilege to introduce this thoughtful effort to the readers who will richly benefit from its unique clarity and breadth.

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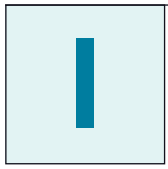

PART 1

Pathobiology of the Liver and Biliary Tract

1

CHAPTER 1
The Liver and Biliary Apparatus: Basic Structural Anatomy and Variations

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Summary
Understanding the anatomy of the liver may be complicated by the lack of anatomic consistency in its description. Although external observation of the liver presents a clear depiction of lobar division, appreciation of its functional anatomy is often made difficult by its complex intrahepatic architecture. In this chapter, the liver is approached through a clear delineation of the core features central to the clinical translation of its anatomy. The liver is described in terms of its location and surface anatomy, peritoneal relationships, surfaces and lobes, segmental anatomy, blood supply, and venous and lymphatic drainage. Descriptions combine gross anatomic features and histology with a commentary on the development and variations of the liver.

Introduction

The liver is one of the largest organs in the body, occupying at least 2–3% of the total adult body weight [1–3]. It weighs roughly 1200–1500 g in the average adult and, although not significant, reports have suggested that there may be population-specific variations in liver weight (1800–2600 g) [1].

Location and Surface Anatomy (Figure 1.1)

The liver appears wedge shaped, with its base to the right and its apex projecting to the left as it extends between the right and left upper quadrants. In its subdiaphragmatic position, the liver lies beneath the overlying ribs and cartilage. Its superior convex surface fills the concavity of the right dome of the diaphragm, reaching the fifth rib on the right and the fifth intercostal space, 7–8 cm from the midline, on the left. The upper margin may be traced at the level of the xiphisternal joint as it arches upward on each side. The right lateral margin therefore lies against the diaphragm and anterolateral thoracic wall, crossing the seventh to eleventh ribs along the midaxillary line. In comparison, the inferior border is sharp and may be followed just below the costal margin on the right extending to the left toward the fifth intercostal space. It is formed by a line joining the right lower, and upper left extremities [2–11].

Peritoneal Relationships

As the liver continues to grow and enlarges during its development, the ventral mesentery is modified to form membranous folds that not only enclose almost the entire liver but also provide diaphragmatic and visceral

Practical Gastroenterology and Hepatology: Liver and Biliary Disease, 1st edition. Edited by Nicholas J. Talley, Keith D. Lindor and Hugo E. Vargas.

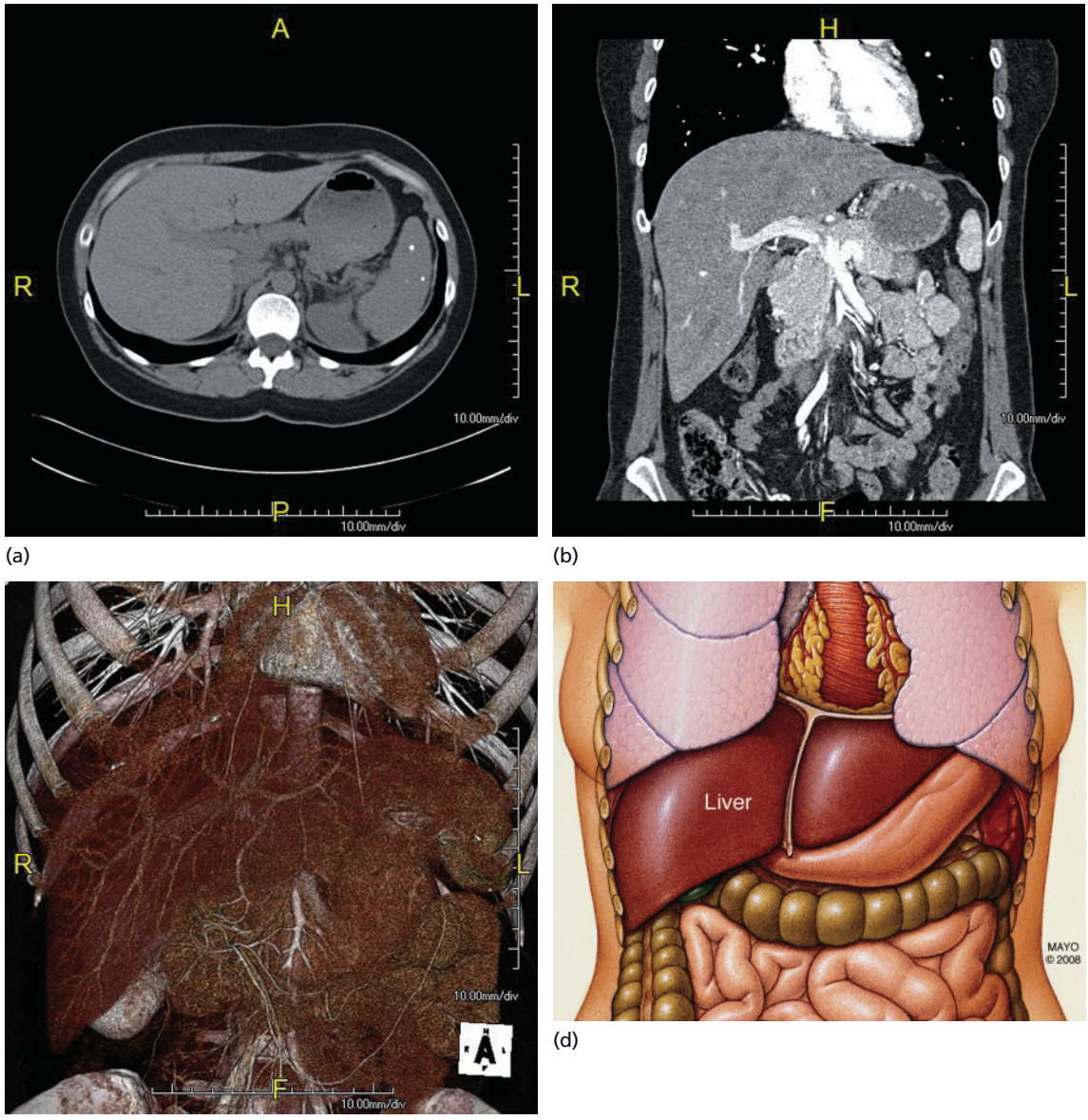


Figure 1.1 CT scans of liver *in situ*: (a) horizontal plane; (b) coronal plane. (c) Three-dimensional image of liver; (d) anterior view of liver in abdominal cavity. (Image (d) is courtesy of RF Morreale, 2008.)

attachments. At its upper pole, however, the liver makes direct contact with the developing diaphragm and, as a result, is devoid of peritoneum. This area is referred to as the "bare area" and persists as the only portion of the liver surface with no membranous covering.

Folds of peritoneum pass from the diaphragmatic and visceral surfaces, connecting the liver to two main structures (Figure 1.2): (1) the diaphragm and (2) the stomach. When entering the abdominal cavity during a dissection, a sickle-shaped anterior fold of peritoneum is visible.

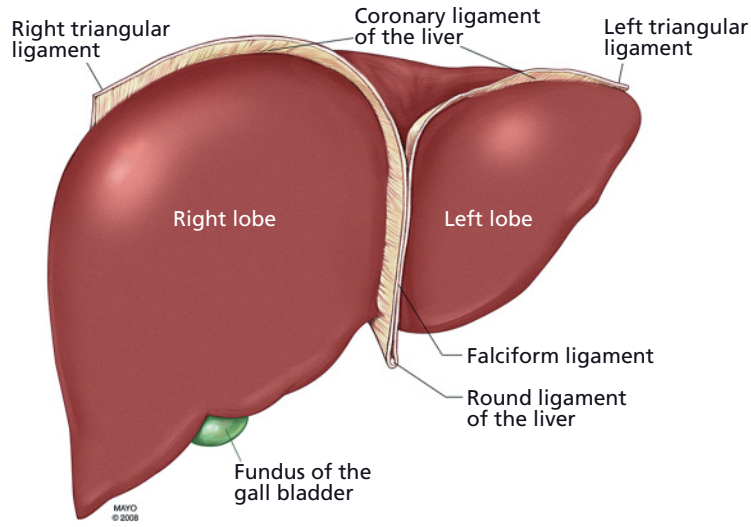


Figure 1.2 Peritoneal ligaments. (Courtesy of RF Morreale, 2008.)

This is known as the falciform ligament. It consists of two layers of adherent peritoneum and attaches the liver to the supraumbilical part of the anterior abdominal wall, as well as to the inferior surface of the thoracic diaphragm. Inferiorly, the falciform ligament is unattached and contains the ligamentum teres (obliterated left umbilical vein). As the falciform ligament ascends superiorly, it produces the left triangular ligament, which extends toward the left tip of the liver, but stops short, about two-thirds of the way along the superior margin, and is related to the lesser omentum along its posterior fold. As the falciform ligament passes superiorly and to the right, it gives rise to the upper layer of the coronary ligament, so named because it encircles the bare area of the liver. The inferior line of peritoneal attachment passes superiorly toward the summit of the liver, where it meets the leaf of the falciform ligament. These ligaments then attach to a groove, which lodges the ligamentum venosum (remnant of the ductus venosus). The coronary ligament fuses at its apex to form a small, rather insignificant right triangular ligament [2–11].

Visceral Surface

The visceral surface of the liver is best observed by superior rotation so that the inferior margin lies superiorly. Several key structures may be identified on this surface (Figure 1.3):

- Porta hepatis:
  - two layers of lesser omentum deviate to the right and enclose the portal triad (portal vein, hepatic artery, bile duct)
  - contains lymph nodes and nerves.
- Gall-bladder fossa:
  - located on the inferior slope of the visceral surface with cystic duct close to the right margin of porta hepatis
  - lies between the colic impression and the quadrate lobe.
- Quadrate lobe: between the gall-bladder fossa and fissure for ligamentum teres.
- Bare area: in contact with the diaphragm and right suprarenal gland.

In addition, the stomach, duodenum, hepatic flexure of the colon, and the right kidney form impressions on the visceral surface.

Lobes

Anatomically, the liver is divided into a larger right and a smaller left lobe using the line of attachment of the falciform ligament and fissures for ligamentum teres and ligamentum venosum. Functionally, the liver is divided along an oblique line that passes through the center of the bed of the gall bladder and the groove for the inferior vena cava (IVC) along the plane of the middle hepatic vein [12,13].

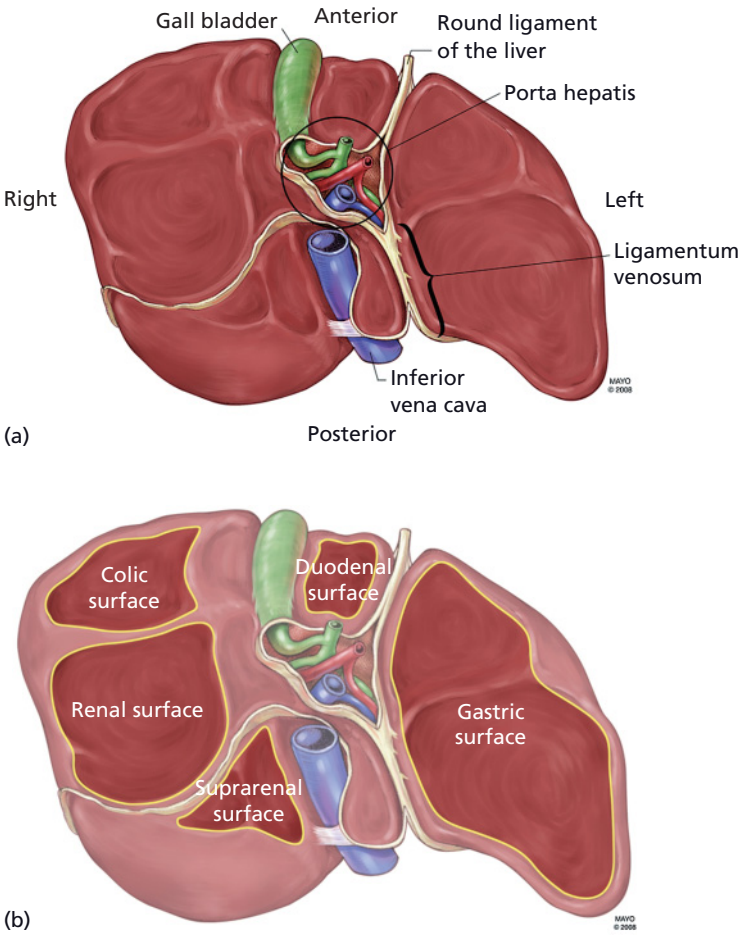


Figure 1.3 (a) Visceral surface of liver showing portal triad; (b) liver visceral surface impressions. (Courtesy of RF Morreale, 2008.)

The quadrate lobe is located on the superior part of the visceral surface, bound by the fissure for ligamentum teres on the left and the gall-bladder fossa on the right. Anatomically, it is considered part of the right lobe but remains, functionally, part of the left lobe.

The caudate lobe is located on the inferior part of the visceral surface of the liver, bound by the fissure for ligamentum venosum on the left and by the groove for the IVC on the right. The caudate lobe exhibits a complex anatomy and is said to be embryologically and anatomically independent of the right and left lobes of the liver [14,15]. It therefore remains a separate anatomic segment. The right portion of the caudate lobe extends as the caudate process which forms the superior boundary of the epiploic foramen. Description of the functional segments of the liver has been based on blood supply (systemic and portal) and venous and biliary drainage. Although there are several descriptions of segmental anatomy, the most commonly applied nomenclature is based on Bismuth's interpretation [16], where all hepatic segments, except for the caudate lobe, are defined by three vertical fissures and a single transverse fissure. Of these fissures, only one appears to be represented superficially (portoumbilical fissure) [12,13], while the others are related to three large hepatic veins. The right fissure, lying almost in the coronal plane, contains the right hepatic vein. The median fissure passes from the gall-bladder fossa to the left margin of the IVC. The left

fissure runs from the left side of the IVC toward the left margin of the liver (a point between the dorsal third and ventral two-thirds), passing inferiorly to the start of the ligamentum venosum. The portoumbilical fissure is marked by the attachment of the falciform ligament [12].

The simplest way to understand the segmental anatomy of the liver is to view it in four sectors (a left medial and left lateral sector and a right anterior and right posterior sector) which are then divided into eight segments [12,13]. The left lateral sector lies to the left of the falciform ligament attachment and the grooves for ligamentum teres and ligamentum venosum, with the left medial sector lying between these lines and the plane of the gall bladder and the IVC. There is no external marking between the right anterior and posterior sectors. The plane runs obliquely, posteriorly and medially from the middle of the front of the right lobe toward the groove for the IVC. The segments may be identified as follows (Figure 1.4):

- Segment I: caudate lobe
- Segments II and III: left hepatic vein passes between segments
- Segments IVa and IVb: quadrate lobe
- Segments V and VI: inferior segments of right anterior and right posterior sectors
- Segments VII and VIII: superior segments of right anterior and right posterior sectors.

The following are basic points on hepatic nomenclature [2,12,13,16]:

- All hepatic segments except for the caudate lobe are defined by three vertical divisions and a single transverse division.
- The middle hepatic vein divides the liver into right and left hemi-livers.
- The right hemi-liver is divided by the right hepatic vein into anterior and posterior segments.
- The left hemi-liver is divided by the left hepatic vein into medial and lateral segments.
- Four segments are divided by a transverse line that passes through the right and left portal branches.
- In a frontal view, eight segments are numbered clockwise.

Microscopic Organization

Structurally, the liver is composed of the following:

- Parenchyma:
  - organized plates of hepatocytes
  - normally one cell thick (in adults, two cell layers in children aged 6 years).
- Connective tissue stroma:
  - contains blood vessels, nerves, lymphatic vessels, and bile ducts
  - continuous with the fibrous capsule of Glisson, covering the surface of the liver.

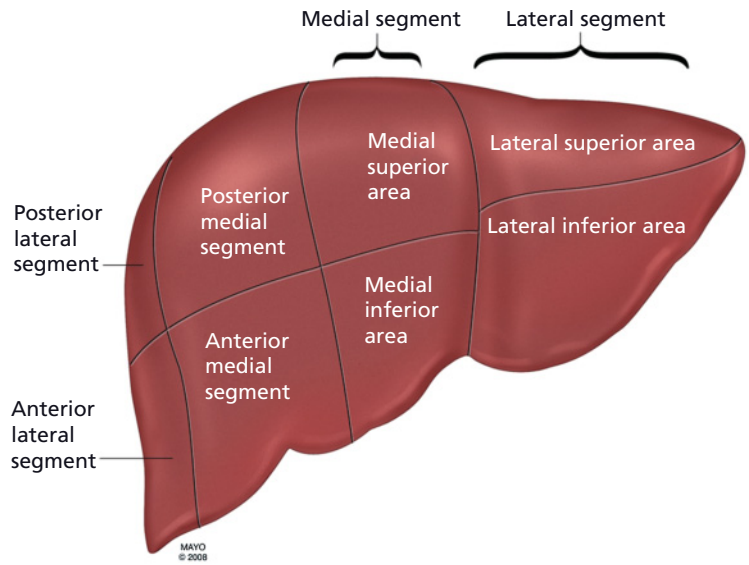


Figure 1.4 Liver segments. (Courtesy of RF Morreale, 2008.)

• Sinusoidal capillaries (sinusoids): vascular channels located between the plates of hepatocytes.
• Perisinusoidal spaces (spaces of Disse): located between the sinusoidal endothelium and hepatocytes.

The best approach to understanding the organization of the liver parenchyma is by visualizing a classic lobule. The architecture of this lobule is based on the distribution of the branches of the portal vein and hepatic artery within the liver and by the flow of blood when perfusing the liver [17–19].

Classic Liver Lobule

The liver lobule is roughly hexagonal, measures about 2.0 × 0.7 mm and consists of stacks of anastomosing plates of hepatocytes, one cell layer thick, separated by the anastomosing system of sinusoids that perfuse the cells with the mixed portal and arterial blood (Figure 1.5). At the center of the lobule is the terminal hepatic venule (central vein), into which the sinusoids drain. From the central vein, plates of cells radiate to the periphery of the lobule, as do sinusoids. Portal canals are located at the angles of the hexagon and bordered by the outermost hepatocytes of the lobule—loose stromal connective tissue (continuous with the fibrous capsule of the liver) characterized by the presence of the portal triads. Between the connective tissue stroma and the hepatocytes at the edges of the portal canal, a small space referred to as the space of Mall can be found. This space is thought to be one of the sites where lymph originates in the liver [17–19].

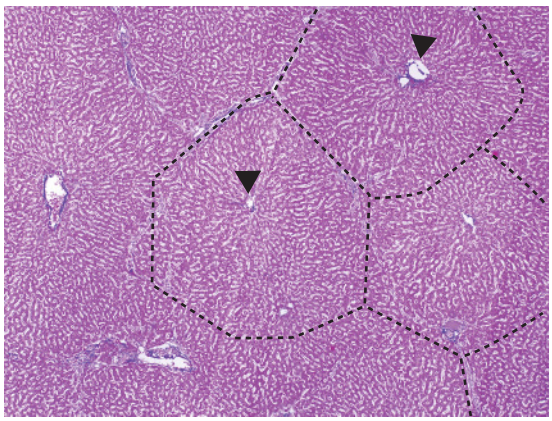


Figure 1.5 Organization of liver lobules (low magnification), ×85. Arrowheads indicate the central vein.

Hepatocytes

Hepatocytes are large, polygonal cells measuring between 20 and 30 μm and constitute about 80% of the cell population of the liver.

Polygonal Structure. Two of its surfaces face the perisinusoidal space. The plasma membrane of the two surfaces faces a neighboring hepatocyte and a bile canaliculus. Assuming that the cell is cuboidal, the remaining two surfaces would also face neighboring cells and bile canaliculi. The surfaces that face the perisinusoidal space correspond to the basal surface of other epithelial cells and those that face neighboring cells and bile canaliculi correspond to the lateral and apical surfaces, respectively, of other epithelial cells [17–19].

Hepatocyte Nuclei. Nuclei are large, spherical, and located in the center of the cell. In the adult liver, many cells are binucleate; two or more well-developed nucleoli are present in each nucleus. Cytoplasm is generally acidophilic [17–19].

Hepatocyte Organelles. The following organelles are visible through specific staining techniques [17–19]:
• Extensive smooth endoplasmic reticulum (sER) with varying metabolic activity. Under conditions of hepatocyte challenge by drugs, toxins, or metabolic stimulants, the sER may become the predominant organelle in the cell.
• Presence of mitochondria: as many as 800–1000 per cell.
• Large numbers of peroxisomes (200–300).
• Large Golgi apparatus consisting of as many as 50 Golgi units, each of which consists of three to five closely stacked cisternae, plus many large and small vesicles. Elements of the Golgi apparatus concentrated near the bile canaliculus are believed to be associated with the exocrine secretion of bile.
• Heterogeneous population of lysosomes concentrated near the bile canaliculus.
• Deposits of glycogen (in a well-preserved hematoxylin and eosin (H & E) preparation; glycogen is also visible as irregular spaces, usually giving a fine foamy appearance to the cytoplasm).
• Lipid droplets of varying sizes. The number of lipid droplets increases after injection or ingestion of certain hepatotoxins, including ethanol.
• Various amounts of lipofuscin pigment within lysosomes

Blood Supply

The liver receives about 70% of its blood via the portal vein and 30% from the hepatic artery [2–5]. The hepatic artery commonly arises from the celiac trunk but may sometimes come off the superior mesenteric artery or as a separate branch of the aorta. It divides into right and left branches. The right branch passes behind the common hepatic duct and divides into anterior and posterior branches within the liver. The left branch divides into medial and lateral branches within the liver. Occasionally, these branches may arise from the superior mesenteric artery (15%) or the left gastric artery (20%) and may be additional or replace the normal branches [2,3]. There is no communication between the right and left halves of the liver. The arteries are said to be "end-arteries" [2,12]. Figure 1.6 shows the arterial pattern and Figure 1.7 shows the liver vascular tree.

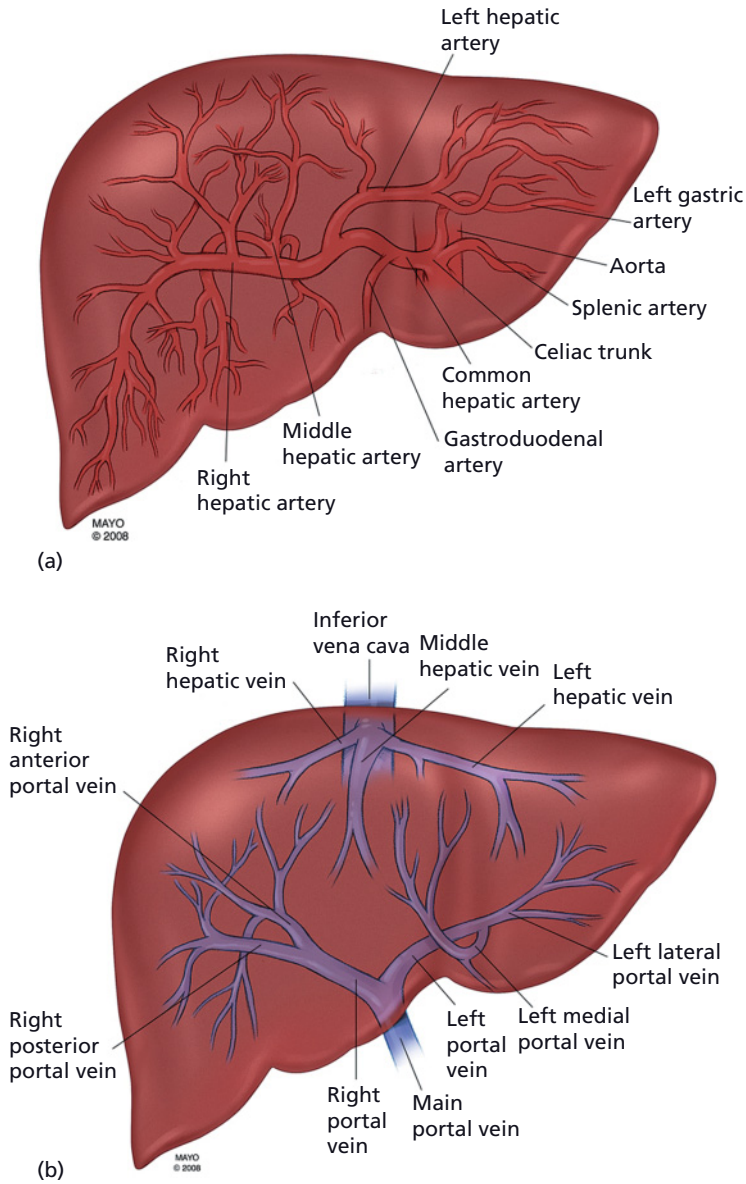
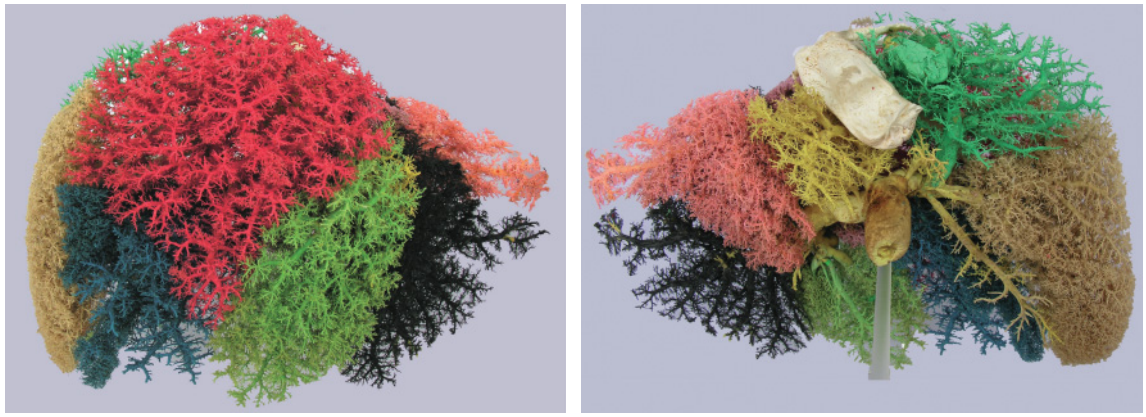


Figure 1.6 (a) Liver arterial pattern; (b) liver venous pattern. (Courtesy of RF Morreale, 2008.)



(a) (b)

Figure 1.7 Corrosion cast of liver vascular tree: (a) diaphragmatic surface; (b) visceral surface. (Courtesy of Hongjin Sui, 2008.)

The portal vein is formed by the union of the superior mesenteric and splenic veins behind the neck of the pancreas. It measures roughly 7–10 cm in length and has a diameter of 0.8–1.4 cm [2,3]. The portal vein has no valves. At the porta hepatis, the portal vein divides into right and left branches before it enters the liver. The right branch of portal vein is shorter than the left. It lies anterior to the caudate process, follows the distribution of the right hepatic artery and duct, and bifurcates into 17 anterior and posterior segmental branches, with further divisions into subsegmental parenchymal branches. The left branch of the portal vein is longer and has transverse and umbilical parts. It starts as the transverse part in the porta hepatis which, on its way to the left, gives off a caudate branch. After turning sharply at the level of the umbilical fissure, the umbilical part continues anteriorly in the direction of the round ligament to terminate in a blind end proximal to the inferior border of the liver, where it is joined by the round ligament [2–7,9,10].

Venous and Lymphatic Drainage

The venous drainage shows mixing of blood between the right and left halves of the liver. There are three main hepatic veins that drain into the IVC. A large *central vein* runs in between the right and left halves and receives blood from each. A right and left vein lie further laterally and, frequently, a middle hepatic vein joins the left vein close to the IVC. These veins have no extrahepatic course and drain into the IVC just below the central tendon of the diaphragm. In addition, there are several small hepatic veins that enter the IVC below the main veins, as well as a separate vein draining the caudate lobe. Anastomoses between the portal channels and the azygos system of veins have been observed in the bare area of the liver [2–5,11,12].

The lymphatic drainage may be summarized as follows [2]:

- Drainage into three to four nodes that lie in porta hepatis
- Drainage into pyloric nodes and celiac nodes
- Receives lymphatics from the gall bladder
- Communication with extraperitoneal lymphatics from bare area—perforate the diaphragm and drain into nodes of the posterior mediastinum; similar communications from the left triangular and falciform ligaments.

Interlobular Vessels

Interlobular vessels occupy the portal canals with only those that form the smallest portal triads sending blood into the sinusoids (Figure 1.8). Larger interlobular vessels branch into distributing vessels located at the periphery of the lobule. These distributing vessels send inlet vessels to the sinusoids. In the sinusoids, the blood flows centripetally toward the central vein. As the central vein courses through the central axis of the classic liver lobule, it becomes larger and eventually empties into a sublobular vein. Convergence of several sublobular veins forms larger hepatic veins which empty into the IVC [17–19].

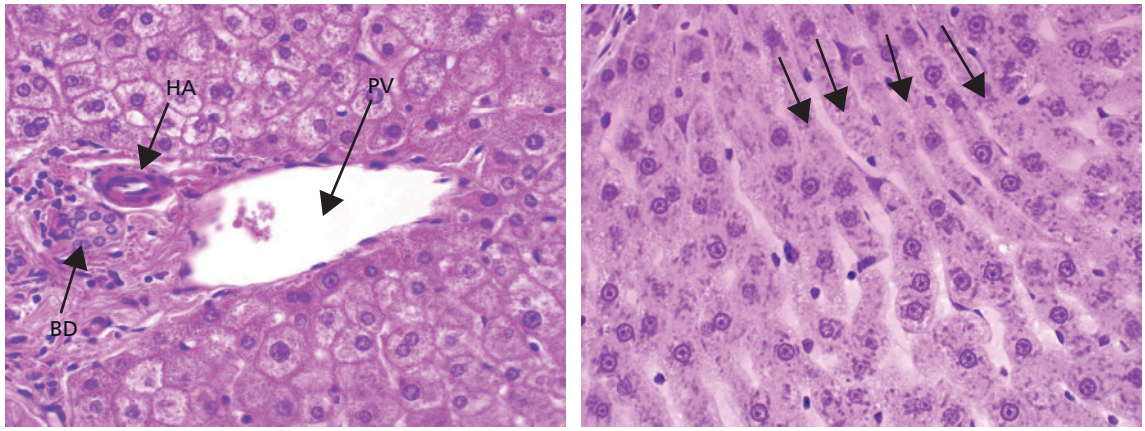


Figure 1.8 (a) Portal triad: H & E, ×650; (b) architecture of liver sinusoids and cords indicated by the arrows: H & E, ×320. BD, bile ductule; HA, hepatic artery; PV, portal vein.

Structurally, the portal vein and the hepatic artery, with their tributaries and branches, are typical of veins and arteries in general. In addition to providing arterial blood directly to the sinusoids, the hepatic artery provides arterial blood to the connective tissue and other structures in the larger portal canals. Capillaries in these larger portal canals return the blood to the interlobular veins before they empty into the sinusoid [17–19].

The thin-walled central vein receives blood from the hepatic sinusoids. Its endothelial lining is surrounded by small amounts of spirally arranged connective tissue fibers. The sublobular vein, the vessel that receives blood from the terminal hepatic venules, has a distinct layer of connective tissue fibers (both collagenous and elastic) just external to the endothelium. The sublobular veins and the hepatic veins, into which they drain, travel alone. As a result of their solitary nature, they can be readily distinguished in a histologic section from the portal veins that are members of a triad. Hepatic veins have no valves [17–19].

Hepatic sinusoids are lined by a thin discontinuous endothelium with underlying discontinuous basal lamina that is absent over large areas. As opposed to other sinusoids, hepatic sinusoids contain a phagocytic cell derived from monocytes referred to as a Kupffer cell in the vessel lining. Kupffer cells do not form junctions with neighboring endothelial cells but processes of Kupffer cells often seem to span the sinusoidal lumen and may even partially occlude it [17].

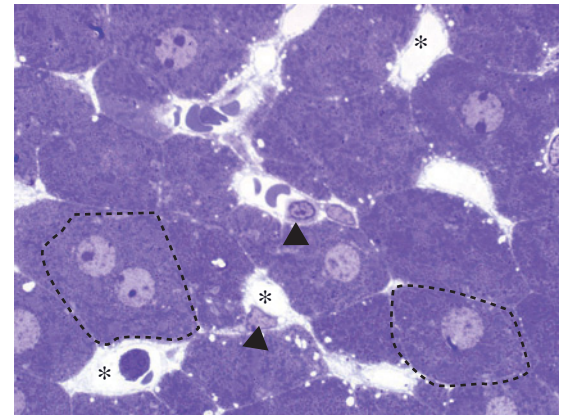


Figure 1.9 Photomicrograph of liver with highlighted hepatocytes: toluidine blue, osmium fixation, ×950. Asterisks indicate the hepatic sinusoids and arrowheads point to Kupffer cells.

The perisinusoidal space (space of Disse) is the site of exchange of materials between blood and liver cells (Figure 1.9). It lies between the basal surfaces of hepatocytes and the basal surfaces of endothelial cells and Kupffer cells that line the sinusoids. Small, irregular microvilli project into this space from the basal surface of the hepatocytes. As a result of the large gaps in the endothelial layer and the absence of a continuous basal lamina, there is no significant barrier between the blood plasma in the sinusoid and the hepatocyte plasma membrane. Proteins and lipoproteins synthesized by the hepatocyte are transferred into the blood in the perisinusoidal

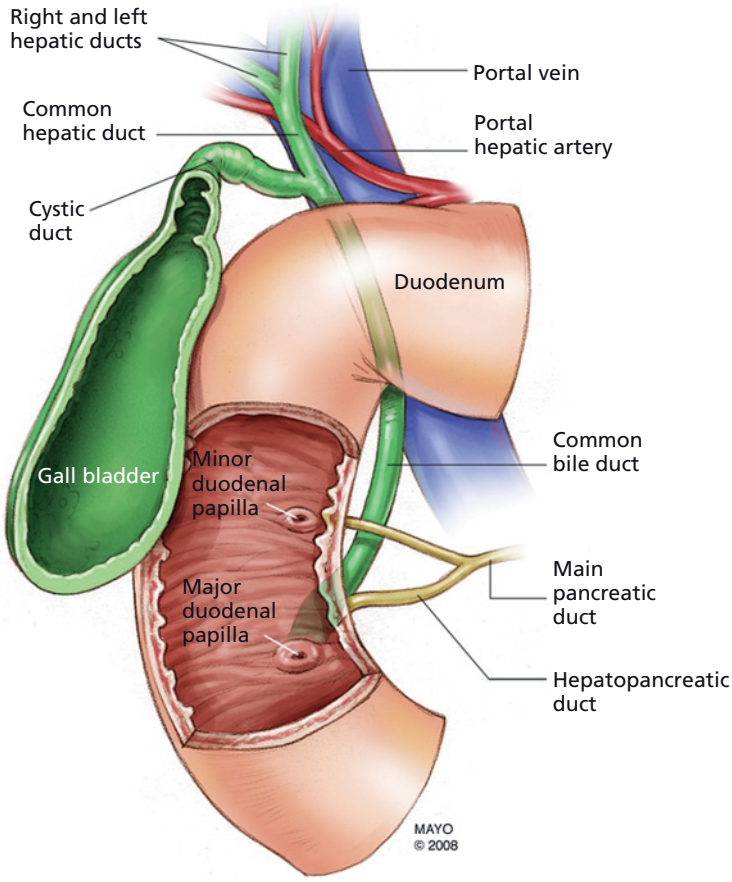


Figure 1.10 Gall bladder and biliary system.

space; this pathway is for liver secretions other than bile [17–19].

Lymphatic Pathway

Plasma that remains in the perisinusoidal space drains into the periportal connective tissue where a small space, the space of Mall, is described between the stroma of the portal canal and the outermost hepatocytes. Lymphatic fluid then enters lymphatic capillaries which travel with the other components of the portal triad [17].

Lymph in progressively larger vessels follows the same direction as the bile (i.e., from the level of the hepatocytes toward the portal canals and eventually to the hilum of the liver). About 80% of the hepatic lymph follows this pathway and drains into the thoracic duct [17] (Figure 1.10).

Innervation

Sympathetic fibers from the celiac ganglion give off nerves that run with vessels in the free edge of the lesser omentum and enter the porta hepatis. Parasympathetic fibers arise from the hepatic branch of the anterior vagal trunk and reach porta hepatis via lesser omentum [2,3].

The Biliary Apparatus

The biliary apparatus consists of three hepatic ducts (right, left, and common), gall bladder and cystic duct, and the bile duct. In terms of their relationship, the right and left hepatic ducts go on to form the common hepatic duct to the right side of the porta hepatis. The common hepatic duct is joined on the right side by the cystic duct, which enters at an acute angle to form the bile duct [2–6] (Figure 1.11).

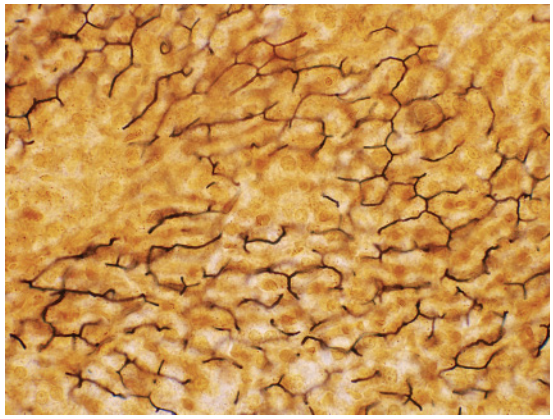


Figure 1.11 Photomicrograph of the liver showing bile canaliculi impregnated with gold. Gold stain ×420.

The common bile duct is about 6–8 cm long and its normal diameter does not exceed 8 mm. For descriptive purposes, the bile duct may be divided into three parts [2,3]:

1 Supraduodenal: lies in the free edge of the lesser omentum in front of the portal vein and to the right of the hepatic artery.

2 Retroduodenal:
- lies behind the first part of the duodenum, slopes down and to the right
- portal vein lies to the left of the duct with the gastroduodenal artery
- the IVC lies behind the duct.

3 Paraduodenal: slopes further to the right in a groove between the posterior surface of the head of the pancreas and the second part of the duodenum, and in front of the right renal vein.

Joins the pancreatic duct at a 60° angle at the hepatopancreatic ampulla.

Innervation

Parasympathetic fibers run from the anterior vagal trunk and sympathetic from the celiac ganglion [2,3].

Microscopic Anatomy

The biliary system is formed from channels of increasing diameter, through which bile flows from the hepatocytes to the gall bladder and then to the intestines. These structures are not only passive conduits, but also capable of modifying bile flow and changing its composition in response to hormonal and neural stimulation.

Cholangiocytes (epithelial cells), which monitor bile flow and regulate its content, line the biliary system. These cells are identified by their organelle-scant cytoplasm, presence of tight junctions, and complete basal lamina. An apical domain of cholangiocytes appears similar to hepatocytes, with microvilli projecting into the lumen. In addition, each cholangiocyte contains primary cilia that sense changes in luminal flow, resulting in alterations of cholangiocyte secretion [17–19].

Bile flows from the region of the terminal hepatic venule (central vein) toward the portal canal (a direction opposite to the blood flow) (centrifugal flow). The smallest branches of the biliary system are the bile canaliculi, into which the hepatocytes secrete bile. They form a complete loop around four sides of the idealized six-sided hepatocytes. They are approximately 0.5 µm in luminal diameter and are isolated from the rest of the intercellular compartment by tight junctions (part of junctional complexes). Microvilli of the two adjacent hepatocytes extend into the canalicular lumen. Near the portal canal, bile canaliculi join together to form a larger channel, known as the canal of Hering. Its lining is made of two types of cells, hepatocytes and cholangiocytes. The main distinction between the canal of Hering and the bile ductule is whether the structure is partially or completely lined by cholangiocytes. Bile ductules carry bile to the interlobular bile ducts. These ducts range from 15 µm to 40 µm in diameter and are lined by cholangiocytes, which are cuboidal near the lobules and gradually become columnar as the ducts near the porta hepatis. As the bile ducts get larger, they gradually acquire a dense connective tissue investment containing numerous elastic fibers. Smooth muscle cells appear in this connective tissue as the ducts approach the hilum. Interlobular ducts unite to form right and left hepatic ducts and, together, the common hepatic duct. The common hepatic duct is lined with tall columnar epithelial cells and possesses all the same layers of the alimentary canal, except the muscularis mucosae [17–19] (Figure 1.12).

The Gall Bladder

Gross Anatomy

The gall bladder is a pear-shaped organ that consists of a fundus, body, and neck. As already described, it lies in the fossa for the gall bladder on the visceral surface of the liver, adjacent to the quadrate lobe. The gall bladder is covered by the peritoneum over the liver, although some-

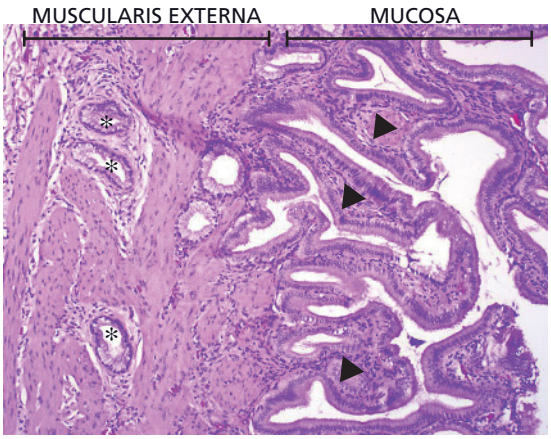


Figure 1.12 Photomicrograph of wall of gall bladder. Rokitansky–Aschoff sinuses are indicated by an asterisk, and the lamina propria of mucosal folds by arrowheads. H & E, ×100.

times it may hang free on a narrow mesentery and, only rarely, be embedded. It varies in size and shape, may be duplicated, with single or double cystic ducts, and very rarely absent. The *fundus* usually projects below the margin of the liver and may be located at the tip of the ninth costal cartilage where the transpyloric plane crosses the right costal margin. Internally, it is related to the left of the hepatic flexure of the transverse colon. The fundus is not normally palpable, except in disease. The body passes towards the right of the porta hepatis and is related to the first part of the duodenum. As the body narrows, it forms the *neck* which, with further narrowing, produces the cystic duct that passes backward and inferiorly to join the common hepatic duct in front of the right hepatic artery and its cystic branch [2,3,5–7].

The gall bladder receives its blood supply from the cystic artery (commonly a branch of the right hepatic artery, but may arise from gastroduodenal artery or main trunk of the hepatic artery) and its venous drainage is via numerous cystic veins. The cystic artery may be located in the Calot triangle which also contains the cystic lymph node.

Microscopic Anatomy

The empty or partially filled gallbladder has numerous deep mucosal folds. Deep diverticula of the mucosa, called Rokitansky–Aschoff sinuses, are sometimes present and extend through muscularis externa. The mucosal surface consists of simple columnar epithelium. Tall epithelial cells exhibit numerous, but not well-developed, apical microvilli, well-developed junctional complexes, numerous mitochondria in the apical and basal cytoplasm, and complex plications on the lateral basal membrane. The lamina propria is also very cellular, containing large numbers of lymphocytes and plasma cells. It is particularly rich in fenestrated capillaries and small venules, but there are no lymphatic vessels in this layer. Mucin-secreting glands are sometimes present in the lamina propria, especially near the neck of the organ. Cells that appear identical to enteroendocrine cells of the intestine are also found in these glands. External to the lamina propria is muscularis externa with numerous collagen and elastic fibers, among somewhat randomly oriented bundles of smooth muscle cells. Despite its origin from a foregut-derived tube, the gall bladder does not have muscularis mucosae or submucosa. External to muscularis externa is a thick layer of dense connective tissue containing large blood vessels, extensive lymphatic network, and autonomic nerves. The connective tissue is also rich in elastic fibers and adipose tissue. The layer of tissue where the gall bladder attaches to the liver surface is referred to as the adventitia. The unattached surface is covered by a serosa or visceral peritoneum consisting of a layer of mesothelium and a thin layer of loose connective tissue [17–19].

Developmental Anatomy and Variations of the Liver

At the start of the fourth week of intrauterine life, the liver is one of the first organs to develop, undergoing rapid growth to fill the abdominal cavity and amounting to 10% of the total fetal weight by the ninth week of development [20–23].

The liver, biliary system, and gall bladder are said to arise as a ventral outgrowth from the caudal part of the foregut. This ventral outgrowth is described as being "Y" shaped and known as the hepatic diverticulum. At the same time, a thick mass of splanchnic mesoderm, the septum transversum, develops on the cranial aspect of the coelomic cavity (between the developing heart and the midgut). The cranial part of the septum transversum gives rise to the pericardial cavity (and, eventually, pericardium) and the diaphragm. The caudal part is, however, soon invaded by the developing liver and, as the liver

grows, it is said to become surrounded by the septum transversum, which is then referred to as the ventral mesogastrium [20,21]. As the liver grows into the ventral mesogastrium, it divides into two parts. The larger, more cranial part is the primordium of the liver. The smaller, more caudal part gives rise to the gall bladder. The stalk of the hepatic diverticulum goes on to form the cystic duct and the stalk connecting the hepatic and cystic ducts to the duodenum forms the bile duct. It is important to note that, initially, the bile duct is attached to the ventral aspect of the duodenal loop. However, rotation of the duodenum carries the bile duct to its dorsal aspect, where it maintains its position throughout adult life [2,3,20–23].

As the endodermal cells now proliferate, they appear to give rise to intermingling *cords of hepatocytes* as well as the epithelial lining of the intrahepatic part of the biliary apparatus. These hepatic cords then anastomose around the early endothelial lined hepatic sinusoids [20–23].

The fibrous and hemopoietic tissue, as well as the Kupffer cells, are said to be derivatives of the mesenchyme of the septum transversum. Hemopoiesis usually begins at around week 6 and bile formation, around week 12 of development [3,20,21].

As liver development is not subject to frequent deviation, variations in liver anatomy are rare. However, cases have been recorded and are summarized below [24]:

- The liver may have no lobar division.
- Accessory lobes may be present or division of the liver into 12 lobes may be possible.
- A detached portion forming a short accessory appendage on the left lobe may be observed. In this case, the appendage is usually covered by a fold of peritoneum containing blood vessels.
- The presence of two additional lobes has been reported: (a) lobus posterior—projecting through the epiploic foramen (lying behind the stomach); and (b) lobus vena cava—projecting along the course of the IVC.
- The left triangular ligament may contain liver tissue.
- A bridge of liver segment of varying size may connect the quadrate and left lobes.
- A smaller accessory liver may be found adherent to the pancreas.
- Isolated masses of liver have been observed on the wall of the gall bladder, ligamentum teres, spleen, and greater omentum.

Reports highlighting variations of liver and biliary anatomy and its importance in clinical procedures continue to add to the banks of existing knowledge [25–27].

Take-home points

The liver:

- develops from a ventral outgrowth known as the hepatic diverticulum and grows into the ventral mesogastrium
- extends between right and left upper quadrants in a subdiaphragmatic position reaching as high as the fifth rib and as low as the eleventh rib on the right
- is related to the peritoneum by the falciform, coronary, and triangular ligaments, and connected to ligamentum teres and ligamentum venosum
- receives its blood supply from the hepatic artery (30%) and the portal vein (70%)
- consists of anatomic lobes and functional segments
- is connected to the biliary apparatus, which consists of the gall bladder, and hepatic, cystic, and bile ducts
- exhibits microscopic organization of hexagonally shaped lobules with a central vein
- may have developmental anomalies and variations present but these are rare.

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2

CHAPTER 2
Immunology of the Liver and Mechanisms of Inflammation

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Summary
A decade ago the liver was simply considered as the main organ for metabolism and detoxification of endogenous and exogenous substances. Over the past 10 years studies have indicated that the liver also plays a key role in several immunologic events, some of which contribute to the development of autoimmune hepatic disease (i.e., primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis), liver inflammation, and fibrosis. Innate immunity and adaptive immunity compromise a coordinated system that involves the liver parenchyma in both health and disease. To this extent, local immune and inflammatory events are key contributors to hepatic diseases and fibrosis. Improved understanding of these pathways provides the basis for better therapies of liver disease.

Introduction

Humans are protected from exogenous pathogens through the interplay of innate and adaptive immunity. Innate immunity represents a range of defense mechanisms that target pathogens in a non-specific manner and functions in the initial stages of an immune response. Adaptive immunity embodies a response of antigen-specific lymphocytes to antigen(s) of pathogens, including the development of memory lymphocytes against these antigens.

The liver is an organ with both immunological activity and reactivity. It not only represents an integral part of the immune system but its parenchyma could also be the grounds for several immune-mediated diseases. Hepatotropic virus-dependent diseases in which the host immune responses provoke inflammatory damage to virus-harboring hepatocytes, as well as autoimmune liver diseases that destroy the hepatic parenchyma, are examples of how malfunctional immunity could lead to organ-specific illness.

Practical Gastroenterology and Hepatology: Liver and Biliary Disease, 1st edition. Edited by Nicholas J. Talley, Keith D. Lindor and Hugo E. Vargas.

Innate Immunity of the Liver

The innate immune system has the capacity to recognize exogenous pathogens [1]. It comprises cells with killing capacities including monocytes, macrophages, neutrophils, and dendritic cells (DCs) as well as natural killer (NK) lymphocytes [2]. These cells possess pattern recognition receptors (PRRs) such as receptors for bacterial carbohydrates and toll-like receptors (TLRs) [3]. These molecules recognize components of microorganisms (e.g., lipopolysaccharides, glycolipids, flagellin) that lead to activation of immune cells (e.g., monocytes, macrophages, neutrophils, DCs, and NK cells), ultimately causing specific destruction of the activating organism or

infected cell in the case of virus-harboring hepatocytes. This damage is achieved by either release of cytotoxic agents or phagocytosis. Another way in which the innate immune system detects pathogens is by activating receptors on NK cells [4]. These receptors recognize alterations of host cells secondary to damage from infection or tumor transformation, e.g., the molecule of NK group 2 member D (NKG2D) represents such a receptor, which recognizes the stress-inducible ligand molecule, the major histocompatibility class (MHC) I chain-related molecule (MICA) [5]. Interaction of these receptors with a ligand results in immediate killing of the infected or tumor cell by an NK cell.

In general, the innate immune response is activated in a very short period of time after liver injury from an invader (e.g., bacteria, virus). Those innate defense functions occur constantly and are more frequent in tissues with high exposure to foreign antigens (e.g., digestive system, hepatic parenchyma). A basic element of the innate immune system is its ability to recruit extra inflammatory cells from other sites of the body to the area of invasion or damage by exogenous agents. This function is achieved via chemical messengers that are released from activated cells of the innate immune system. including cytokines and chemokines [6]. These molecules not only act locally at the site of liver damage but also operate in a universal manner because of their release from the tissue of origin (e.g., hepatic parenchyma) into the systemic circulation, thus having an effect on other tissues and organs.

Adaptive Immunity of the Liver

When an invading bacterium or virus circumvents the innate immunity, adaptive immunity is initiated, the first step of which relates to activation of T lymphocytes. These cells remain in an inactive state until they encounter an infectious agent in the lymphoid tissues of the body. Detection of an antigen from a microorganism causes proliferation and differentiation of T lymphocytes into an effector stage. Naïve T lymphocytes are activated by antigen-presenting cells (APCs), which are able to capture, process, and display antigens of bacteria or viruses on the surfaces [7]. APCs present fragments of microorganism(s) on their plasma membrane together with MHC molecules. Subsequently, the T cells recognize the peptide/MHC complexes via specific T-cell receptors (TCRs). T cells demonstrate great diversity in antigen recognition, thus offering the immune system an enormous repertoire of effector cells with antigen specificity.

Activation of naïve T cells requires the simultaneous engagement of a series of accessory molecules on the T-cell surface, with corresponding co-stimulatory molecules on the surface of the APCs, which are induced by bacteria or other signals of the innate immune system, e.g., the B7 family of molecules (CD80, CD86, and B7 homolog) which are present on the APCs contribute co-stimulatory messages to T cells via CD28 and inducible co-stimulatory receptors (ICOS). In the end, if the interaction between the TCR and the peptide/MHC is maintained over a threshold amount of time, the naïve T cell is activated, leading to clonal proliferation and differentiation into effector cells. This process lasts for days and results in changes in the cell surface of these molecules. As a result, the effect of T cells migrates from the lymphoid tissue to the site of infection. Effector T cells can then respond in a variety of ways to the same peptide/MHC complexes without the need for co-stimulation.

The differentiation of naïve T cells into functional effector cells is governed by signals from the innate immune system, e.g., macrophages and DCs release interleukins IL-12 and IL-18, and NK cells produce interferon γ (IFN-γ), causing development of CD8 cytotoxic T cells and CD4 T-helper 1 (Th1) cells. On the other hand, IL-4 and IL-6 promote the development of CD4 T-helper 2 (Th2) cells. Another population of CD4 T cells (i.e. regulatory T cells) produces IL-10 and transforming growth factor β (TGF-β) and suppress Th1 responses; therefore they are implicated in the maintenance of immunologic tolerance [8].

Overall, it appears that innate and adaptive immune systems are not independent but an interactive system controlling and regulating each other, e.g., many cells of the adaptive immune system have evolved antigen recognition effector mechanisms that are characteristic of innate immunity. Indeed, subsets of T and B lymphocytes can recognize known protein antigens, which are not subject to antigenic drift and are therefore relatively conserved between classes of pathogens. Moreover, natural killer T (NKT) cells have TCRs and are able to

recognize antigens presented by the non-classic antigen-presenting molecule, CD1 [9].

Antigen-presenting Cells and the Liver

As a result of its unique location in the human body, the liver is a site of interaction with external microorganisms and other pathogens. To this end, it contains several types of APCs including Kupffer cells, liver sinusoidal endothelial cells (LSECs), and DCs (Figure 2.1). Kupffer cells are located in the sinusoidal lumen and represent approximately 80% of the body's macrophages. They are effective in eliminating endotoxins and invading microorganisms. Both lipopolysaccharides (LPSs), an element of the bacterial wall, and the TLR4 ligand stimulate Kupffer cells. Activated Kupffer cells can present antigen and activate effector CD+ T cells in vitro [10]. LSECs line the hepatic sinusoidal space and participate in sinusoidal blood flow regulation, filtration, and antigen uptake and processing. LSECs express adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1), as well as apoptosis-related molecules such as the Fas ligand and TNF receptor apoptosis-inducing ligand (TRAIL) [11]. Finally, the DCs of the liver represent "immature" APCs. They express MHC and other plasma membrane molecules, which makes them able to activate T cells, as well as capture, process, and present antigens. Moreover,

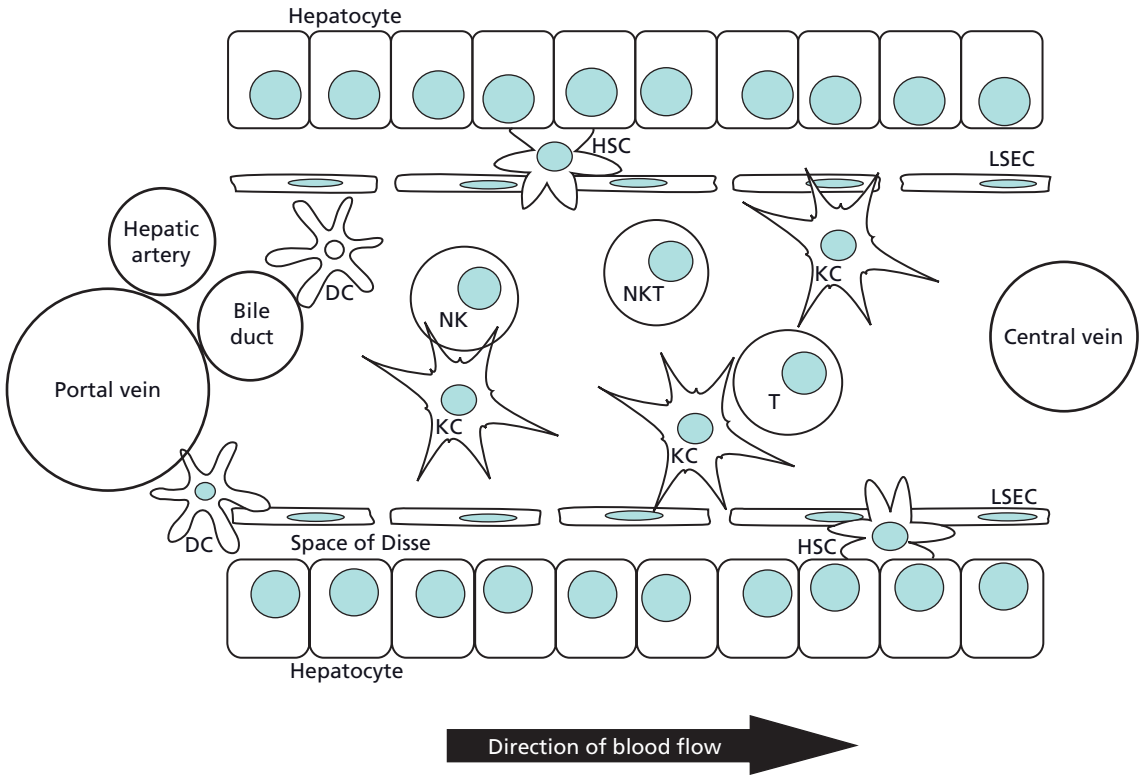

Figure 2.1 As the blood percolates through the hepatic sinusoids it interacts with the immune cells of the liver. DC, dendritic cells; HSC, hepatic stellate cell; KC, Kupffer cells; LSEC, liver sinusoidal endothelial cells; NK, natural killer cells; NKT, natural killer T cells. (Modified from Gershwin ME, Vierling JM, Manns MP *Liver Immunology: Principles and Practice*. New York: Springer: 2007. With kind permission of Springer Science and Business Media.)

DCs can prime both naïve and antigen-specific T cells, perform phagocytosis, and be involved in chemotaxis.

Immunity, Inflammation, and Liver Fibrosis

Hepatic fibrosis is a ubiquitous response of the liver to chronic injury. The concept of interaction between the immune system and inflammation of the liver resulting in a fibrogenic response has been the most exciting recent development in the field of hepatic fibrosis. Central to this concept is the activation of HSC after hepatic damage/injury (Figure 2.2). However, from the initial event to development of liver fibrosis there are several phases. The first "initiation stage" is characterized by alteration of the phenotype and function of hepatic stellate cells (HSCs). The second "perpetuation stage" is defined by the chronic/persistent nature of these changes (Figure 2.2). The third step refers to potential "resolution" of fibrosis and is due to apoptosis or reversion of the phenotypic characteristics of activated HSCs.

The initiation stage of activation of HSCs is driven by paracrine effects of surrounding cells such as LSECs, hepatocytes, Kupffer cells, and platelets, e.g., hepatocyte apoptosis after liver injury promotes HSC activation via Fas and TRAIL [12]. In addition, activation of Kupffer cells contributes to HSC activation. Subsequently, during the perpetuation stage. an increase in extracellular matter occurs within the liver. Platelet-derived growth factor (PDGF) is the most important mitogen of HSCs. Moreover, HSCs could migrate toward chemical signals produced by cytokines (Table 2.1). Figure 2.2 provides an overall schema of the pathways involved in HSC activation. Consequently, extracellular matrix is produced, deposited, and degraded or persists. A lack of balance between production and degradation of matrix leads to liver fibrosis. To this end, matrix metalloproteases, key biological enzymes, are involved in remodeling of the matrix [13]. Resolution of hepatic fibrosis does occur and is associated with either inactivation or apoptosis of HSCs. Indeed, HSCs in culture were reported to be sensitive to CD95- and TRAIL-mediated apoptosis [14].

In response to various liver injuries regardless of etiology (e.g., viral agents, hepatotoxins, autoimmunity, or ischemia), hepatocyte damage causes the recruitment of neutrophils and macrophages. These cells, in addition to tissue macrophages of the liver (i.e., Kupffer cells), produce cytokines and chemokines leading to local as well as systemic effects. Cytokines are soluble peptides that function as messenger molecules mediating immune

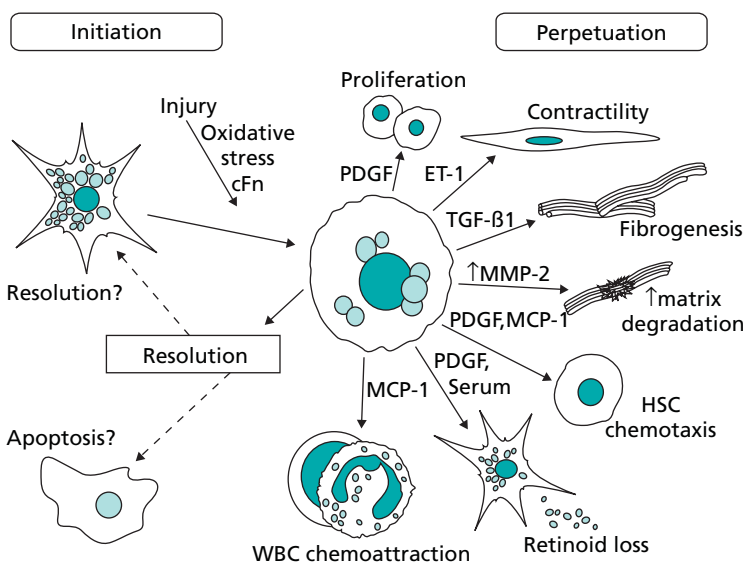

Figure 2.2 After liver damage/injury, hepatic stellate cells are activated and transformed into proliferative, fibrogenic, and contractile myofibroblasts. This step (i.e., initiation) may be reversed, leading to resolution, or continues indefinitely (i.e., perpetuation step), causing permanent liver disease. ET-1, endothelin; HSC, hepatic stellate cell; MCP-1, monocyte chemoattractant protein-1; MMP-2, matrix metalloprotease-2; PDGF, platelet-derived growth factor; TGF-β_1, transforming growth factor β_1; WBC, white blood cell; (Modified from Gershwin ME, Vierling JM, Manns MP *Liver Immunology: Principles and Practice*. New York: Springer: 2007. With kind permission of Springer Science and Business Media.)

Table 2.1 Cytokines involved in liver disease.

Cytokine	Origin	Outcome	Associated condition
IL-1	Macrophages Antigen-presenting cells	Proinflammatory Fever	Alcoholic liver disease Liver regeneration
IL-6	Antigen-presenting cells Th2 cells	Proinflammatory Fever Activates T lymphocytes Differentiates B lymphocytes Acute phase response	Alcoholic liver disease Liver regeneration
TNF-α	Macrophages	Proinflammatory Fever	Alcoholic liver disease NASH Liver regeneration Ischemia–reperfusion
IL-12	Activated hepatocytes	Stimulates NK and T cells Stimulate IFN-γ production	Ischemia reperfusion Viral hepatitis
TGF-β	Macrophages Th3 cells	Anti-inflammatory Inhibits B, T, and NK cells Stimulates fibrogenesis	Liver regeneration Liver fibrosis
IL-10	B and Th2 cells Macrophages	Anti-inflammatory Inhibits IFN production Stimulates B lymphocytes	Control of inflammation
IFN-α	Macrophages	Inhibits viral replication Stimulates NK cells	Viral hepatitis
IFN-γ	Th1 cells NK cells	Modulates IL-1 and TNF-α Increases MHC expression Inhibits viral replication	Viral hepatitis

IFN, interferon; IL, interleukin; MHC, major histocompatibility complex; NASH, non-alcoholic steatohepatitis; NK, natural killer; TGF-β: transforming growth factor β; Th, T helper; TNF, tumor necrosis factor.

and inflammatory reactions, e.g., cytokines mediate the inflammatory response which results in regeneration of liver tissue and ultimately the deposition of fibrous tissue by activation of HSCs. In case the inflammation continues for a long period of time, persistent production of cytokines may lead to scar tissue formation and liver cirrhosis (Table 2.1), e.g., Kupffer cells produce TNF-α, IL-1, IL-6, interferon, and TGF-β as well as chemokines. These cells, in addition to autoimmune cells, generate an anti-inflammatory reaction, which is the first line of defense to invaders. Another major source of cytokines is CD4 T lymphocytes (e.g., Th1 and Th2). These cells can be distinguished by their pattern of cytokine production, e.g., Th1 cells produce IL-2 and INF-γ, whereas Th2 cells produce IL-4, IL-5, IL-6, IL-10, and IL-13.

In addition, cells other than the CD4 lymphocytes can produce chemokines. The cytokine network activates a response in damaged tissues and acts through the local recruitment of a distinct combination of effector cells. Chemokines are a distinct cytokine subfamily which recruits specific leukocyte subsets to the area of injury or invasion. This system includes more than 50 members, divided into 4 families on the basis of their structure. The largest family includes 28 members mainly active on mononuclear cells (i.e. lymphocytes and monocytes) and is characterized by the presence of two cysteine residues adjacent to each other in the N-terminal portion of the molecule. The biologic effect of the chemokines is mediated by a subfamily of G-protein-coupled receptors with seven-transmembrane domains. An important interaction between the liver and cytokines can be seen in the

acute phase response as a result of tissue injury, infection, or inflammation. This is a non-specific first line of defense against a range of invaders.

Other immune cellular components of the liver that are rare in other organs of the body include NKTs. These cells arise in the thymus and express TCR and NK cell receptors. After activation, NKTs produce cytokines (e.g., IFN-γ, TNF-α, IL-4, IL-10, and IL-13), thus affecting the local and adaptive immune system with both pro- and anti-inflammatory molecules. NKTs also cause cytotoxicity via CD1d. This is one of the five polymorphic MHC class I glycoproteins which are expressed on APCs and hepatocytes.

Take-home points

- The liver is an immunologic organ with both innate immune capacity and the ability to adapt immune responses.
- As a result of its unique anatomic position (i.e., receiving blood from the intestine via the portal vein) and structural organization (i.e., sinusoids with APCs), the liver is an immunologic site that orchestrates local and systemic immune functions.
- The hepatic APCs include (1) Kupffer cells, (2) LSECs, and (3) DCs that modulate both immune responses and immune tolerance.
- The hepatic parenchyma can induce peripheral immune tolerance as demonstrated by lack of liver allograft rejection in the presence of MHC mismatch.
- Liver injury causes recruitment of neutrophils and macrophages which leads to local production of cytokines, resulting in an inflammatory response and regeneration of the liver tissue including activation of HSCs.
- As HSCs undergo activation they proliferate and develop new phenotypic features such as fibrogenesis, contractility, matrix degradation, chemotaxis, and chemoattraction of white blood cells. These changes of HSCs as well as the interaction with the immune system contribute to fibrosis of the liver.

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II

PART 2

Diagnostic Approaches in Liver Disease

3

CHAPTER 3

Approach to History Taking and Physical Examination in Liver and Biliary Disease

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Summary
Basic history taking and physical examination skills help the clinician to direct the very complex diagnostic array of technology available to diagnose liver disease. The clinician needs to be attentive to changes in areas other than the abdomen that may be affected by liver disease in order to better evaluate the ongoing disease process.

Case

A 57-year-old woman with a known history of well-compensated hepatitis C virus and hypertension presents to the emergency department complaining of abdominal pain, fever to 101 F, and chills. She has been experiencing the above symptoms for several days and has had decreased oral intake due to the acute illness.

She does not usually take any medications, but has been taking acetaminophen (paracetamol) 500 mg every 6–8 h for the past few days. She has not consumed any alcoholic beverages in the past week but generally drinks a glass of wine with dinner. She denies smoking and has no history of intravenous drug use.

Introduction

Today's physician has a myriad of assessment and diagnostic tools available; laboratory tests range from the standard to the obscure and body imaging techniques to almost the microscopic level. Indeed, information gleaned from the visual, auditory, tactile, and olfactory examination of the patient and the interpretation of the data can be considered less than definitive, given the exacting nature of the numbers and interpretive reports produced by the laboratory and radiology. There is greater security in laboratory values and images than in the art of history taking and interpretation of findings. Furthermore, clinicians frequently disagree with each other about the physical findings of examination, whereas it is more difficult (although not impossible) to argue the validity of an objective laboratory value.

Patients rarely present with a single symptom or complaint. The examiner will more likely be sorting through multiple complaints and symptoms while gathering corresponding or conflicting signs found during the physical examination. Even when presented with empirical data, the art is in the inspection, percussion, auscultation, and palpation and the ability to process all available data into a meaningful diagnosis.

In 1958, the late Dr Franz Ingelfinger stated that the cause of jaundice can be identified in approximately 85% of patients after careful history and physical examination and review of standard laboratory data [1]. This is still quite true today.

Practical Gastroenterology and Hepatology: Liver and Biliary Disease, 1st edition. Edited by Nicholas J. Talley, Keith D. Lindor and Hugo E. Vargas.

History Taking in Liver and Biliary Disease

Jaundice or icterus, the yellow coloring most noticeable on the eyes, face, hands, and trunk, results from the retention and deposition of biliary pigments. The onset of jaundice is indicative of parenchymal liver diseases such as hepatitis or cirrhosis, or of obstruction of the extrahepatic biliary tree, as in choledocholithiasis or carcinoma of the pancreas, and less often by disorders of brisk hemolysis. Scleral icterus occurs when the serum bilirubin rises above 3.0 mg/dL in adults [1].

Careful questioning of the patient can reveal much about the onset of jaundice and lead the clinician to a diagnosis. Table 3.1 lists the important historical points to review in a patient with liver disease. Question the patient about the onset and duration of the jaundice, and whether or not it was accompanied by symptoms of anorexia, nausea, vomiting, chills, fever, itching, or weight loss. Knowing whether or not the patient associates with other people who have also developed jaundice leads the examiner to suspect a communicable disease. Jaundice accompanied by fever and chills is considered obstructive cholangitis until proven otherwise. Painless jaundice in an older patient may be the first symptom of cancer of the head of the pancreas. Prior history of inflammatory bowel disease would suggest an association with primary sclerosing cholangitis.

During the interview portion of the history and physical, patients should be questioned about recent changes in weight. Anorexia and nausea are among the first signs of liver disease and may be extreme with muscle wasting in cirrhosis. An unexplained weight loss of 10 lb (4.5 kg) is worrisome for a neoplasm.

Case

Patient appears to be in no acute distress; her physical exam reveals a thin white woman, alert and oriented, icteric, with dry mucous membranes. Her abdomen is soft but mildly tender on palpation diffusely with no hepatomegaly or splenomegaly. In the emergency department abdominal ultrasonography reveals no abnormality, lab results show normal complete blood count (CBC), metabolic panel shows mild hypokalemia at 3.4 mmol/L, serum creatinine is 168 µmol/L, and liver injury tests reveal aspartate transaminase (AST 4200 IU/L), alanine transaminase (ALT 5500 IU/L), alkaline phosphatase 440 IU/L, and total bilirubin 7.5 mg/dL with direct bilirubin 4.8 mg/dL.

Viral Hepatitis

The onset of viral hepatitis may be abrupt or insidious due to the variation in incubation periods. The incubation period for hepatitis A averages 30 days, for hepatitis B 6 weeks to 6 months, averaging 12–14 weeks, and for hepatitis C 6–12 weeks. Questions related to viral hepatitis include history of blood transfusion, especially if before 1990 when serologic testing for hepatitis C became available, intravenous drug use, tattoos, or body piercing [2]. High-risk sexual practices include anal

Table 3.1 Important historical points to review in a patient with liver disease.

General questions
Family history of liver disease
Exposure to potential hepatotoxins
Presence and onset of jaundice, pruritus, anorexia, or nausea
Symptoms of biliary colic or cholangitis (fever, chills, right upper quadrant pain)
History of "colitis" or inflammatory bowel disease (association with primary sclerosing cholangitis)
History of unintentional weight loss
Hepatitis exposure questions
Blood product transfusions (especially before 1990)
Intravenous drug abuse
Occupational needle stick exposures: – non-sterile tattoos or body piercing – high-risk sexual behaviors – recent travel to endemic areas – exposure to patients with known viral hepatitis – ingestion of raw shellfish
Medication-related questions
Review all prescription and over-the-counter medications
Review all vitamins and supplements (patient may not consider medications)
Alcohol-related questions
Type of alcohol consumed, amount, pattern, frequency
Age of onset of drinking
Date of last drink
Consequences of drinking (social or legal)
CAGE questions

intercourse, sex with a prostitute, history of sexually transmitted infections, multiple sexual partners of more than five a year, or intercourse with a person infected with chronic viral hepatitis [1]. Taking an occupational history alerts the examiner to high-risk professions, e.g., health professionals, especially workers in renal dialysis units, operating rooms, or trauma units with exposure to intravenous drug users, or those with a history of a needle-stick injury. Risk factors for hepatitis A include travel to the endemic areas of Mexico, Latin America, and the African subcontinent, ingestion of raw contaminated shellfish, or exposure to groups of people where clusters of hepatitis are known to occur such as outbreaks in restaurants, mental health institutions, or day care centers [1].

Drug-induced Liver Disease

Drug-induced liver disease can mimic viral hepatitis, biliary tract obstruction, or other types of liver disease. The most common offenders are non-steroidal anti-inflammatory drugs, analgesics, and antibiotics because of their widespread use. Acetaminophen toxicity is now the most common cause of acute hepatic failure in the USA, accounting for 40% of cases [3]. Review all medications including prescription and over-the-counter (OTC) drugs. Ask about the use of vitamins, especially vitamin A, as well as OTC supplements purchased in a health food store. Careful questioning about potentially hepatotoxic drugs or exposure to hepatotoxins may uncover a second agent that increases the toxicity of the first, e.g., acetaminophen and alcohol. Other exposure to hepatotoxins may be discovered by questioning the patient about work history and hobby interests. Exposure to certain industrial chemicals such as carbon tetrachloride or vinyl chloride is well known to cause liver disease.

Case

On questioning the patient and the family, she has recently been using, in addition to acetaminophen, several OTC cold medicines, and the family cannot verify the quantities consumed. The husband is worried because he heard that there was a hepatitis A epidemic in the neighboring state.

Non-alcoholic Fatty Liver Disease

Metabolic causes for non-alcoholic fatty liver disease (NAFLD) include obesity, diabetes mellitus, hyperlipidemia, hypothyroidism, abetalipoproteinemia, rapid weight loss, and total parenteral nutrition. Other causes include medications such as corticosteroids, amiodarone, diltiazem, tamoxifen, irinotecan, oxaliplatin, highly active antiretroviral therapy, and toxins (carbon tetrachloride and yellow phosphorus). Steatosis is a hallmark of insulin resistance syndrome characterized by obesity, diabetes, hypertriglyceridemia, and hypertension. In NAFLD, patients with obesity, diabetes, and advanced age have additional risk for advanced hepatic fibrosis and cirrhosis. Many patients with fatty liver disease present with mild right upper quadrant discomfort but are usually otherwise asymptomatic unless they have complications of end-stage liver disease.

Alcoholic Liver Disease

Clinical findings in alcoholic liver disease can vary widely from asymptomatic fatty liver to severe alcoholic hepatitis or cirrhosis presenting with coagulopathy, encephalopathy, and jaundice. Although chronic alcohol abuse may be denied or downplayed by many patients with alcoholic liver disease, confirming this is critical to making the diagnosis. Important questions not only to ask the patient but also to corroborate with family and friends include type and amount of alcohol consumed, pattern and frequency of drinking, age of onset of alcohol use, and date of last drink. In addition note any psychosocial consequences of alcohol abuse such as arrests for public intoxication or driving under the influence. Four questions that can be useful in identifying patients with excessive alcohol use form the acronym CAGE [4]:

1 Has the patient tried to **C**ut back on alcohol use?

2 Does the patient become **A**ngry when asked about his or her alcohol intake?

3 Does the patient feel **G**uilty about his or her alcohol use?

4 Does the patient need an **E**ye opener in the morning?

Two or more affirmative responses are seen in most patients with alcoholism. In contrast, over 80% of non-alcoholic patients have a negative response to all four questions and virtually none has an affirmative response to more than two questions. The CAGE criteria have been considered to be an efficient and effective screening

tool for detecting alcoholism with a sensitivity and specificity of 0.71 and 0.90, respectively, with a cutoff of two or more affirmative responses [5].

Physical Examination

When assessing the patient with jaundice or abnormal liver tests, much is gleaned from the initial inspection of the patient, proceeding in a head-to-toe fashion. As pieces of data are gathered in what appears to be haphazard fashion, affecting different organ systems along the way, by completion there will be enough information to develop a reasonable diagnosis.

Note the color of the patient's skin. Jaundice is most easily seen on the face, the sclera of the eyes, and the palms of the hands. Scleral icterus can be detected by examining the patient in natural daylight if possible because incandescent light may mask the presence of icterus. Cyanosis of the mucous membranes indicates hypoxemia, which may be due to hepatopulmonary syndrome. This syndrome is caused by pulmonary microvascular vasodilation in patients with portal hypertension, resulting in dyspnea and hypoxemia that worsen in the upright position and improve when the patient is recumbent. Pallor is suggestive of anemia. When inspecting the general characteristics of the face, the presence of temporal wasting is a sign of advanced chronic liver disease or a neoplasm whereas bulging cheeks can be the result of parotid enlargement of alcoholic liver disease. Note the presence of spider angiomas most commonly found on the face, neck, upper anterior chest, and thorax, in the distribution of the superior vena cava. Multiple spider angiomas can signify the presence of portal hypertension. While giving attention to the face, pause to note the patient's mental status for signs of confusion, and be alert for the odor of fetor hepaticus. Inside the mouth, look for a reddened tongue due to vitamin B deficiencies resulting from alcoholism or the white plaque of lichen planus which can be associated with hepatitis C and other liver disorders.

Patients presenting with jaundice require a thorough assessment of the heart and lungs. Cases of congestive heart failure can cause chronic passive congestion of the liver. In the neck, look for bulging neck veins due to portopulmonary hypertension. The venous distension can be enhanced by applying gentle manual pressure to the abdomen over the liver (hepatojugular reflux). As the examiner progresses down to the arms and hands, additional signs of muscle wasting in the shoulders may be noted as well as the presence of tattoos or needle tracks which indicate a high-risk lifestyle. Skin redness and excoriation over the chest and back indicate pruritus, especially with a "butterfly distribution" at the interscapular region that is spared from redness, indicating the limits of the patient's reach when scratching. Generalized itching may be a sign of renal or hepatic disease and can be severe in patients with primary biliary cirrhosis and primary sclerosing cholangitis. Gynecomastia in men, along with sparse facial, axillary, and pubic hair, is often found in patients with advanced liver disease.

The hands may exhibit clubbing of fingers. Clubbing, although not exclusive to liver disease, combined with palmar erythema and spider nevi, indicate liver disease and cirrhosis. When digital clubbing is due to liver or lung disease, the fingers return to normal after a transplantation. Nails may be thickened, brittle, ridged, or flat in cases of liver disease. Examine the nails for changes in the nailbed, especially an increase in the size of the lunula, giving the cirrhotic patient's nails a "half-and-half" appearance. The upper extremity tremor of asterixis indicates liver disease, although it can also be elicited in other non-hepatic causes of metabolic encephalopathy [6].

The presence of Dupuytren contracture is more a characteristic of alcoholism than liver disease. Caused by a shortening of the palmar fascia, it causes a flexion deformity of some of the digits, giving the hand a claw-like appearance in extreme cases. Dupuytren contracture can also be seen in diabetes mellitus, reflex sympathetic dystrophy, Peyronie disease, or malignancy, although, when seen in combination with parotid enlargement and gynecomastia, it invariably indicates chronic alcoholism.

The legs and feet mirror what is seen in the arms and hands with toe clubbing, plantar erythema, and plantar fibrosis. Signs of muscle wasting that were seen in the face and shoulders will also be present in the legs, as well as sparse hair growth patterns and xanthomas on the knees. Spider nevi are not seen on the lower extremities. Petechiae on the legs are due to thrombocytopenia and high venous pressures in the legs. Patients with hepatitis C may have lower extremity findings of palpable purpura

due to cryoglobulinemic vasculitis [2]. The feet and legs are also the site of dependent edema, the degree of which is assessed by various methods accorded to the examiner, including the amount of pitting within a range of +1 to +4, the depth of the pit, how far it extends upward from the feet toward the abdomen, or simply grading it as trace, mild, moderate, or severe.

Examination of the Abdomen

The examination of the abdomen begins with inspection followed by auscultation, percussion, and palpation. The patient should lay flat with the abdomen fully exposed, the arms at the sides, and the legs flat. Any areas of tenderness should be assessed last to avoid tightening of the abdominal muscles. The abdominal examination is important in determining the presence of intraperitoneal fluid (ascites); the size of solid organs such as liver and spleen can be determined on percussion. Palpation reveals the size and quality of the liver, whether it is soft, firm, hard, or irregular, and whether the left lobe is palpable across the midline, usually a sign of chronic liver disease.

Inspection

Inspect the abdomen, looking for any asymmetry, distension, or masses. An everted umbilicus is a sign of increased abdominal pressure and may be a sign of ascites, a large abdominal mass, or an umbilical hernia. The abdominal venous system is rarely observable in the normal individual and, if it is visible, the drainage of blood flow in the lower two-thirds of the abdomen is caudal, down toward the feet. The drainage of the blood in a cephalad direction, toward the head, is indicative of vena caval obstruction. In patients with the portal hypertension of cirrhosis, the increased pressure is transmitted to collateral venous channels which become dilated over time. The appearance of these dilated vessels, which appear to radiate out from the umbilicus, is known as caput medusae.

The presence of ascites is detected by observing the movement of the intra-abdominal fluid. When a patient with ascites is in the supine position the fluid moves to the sides and results in bulging at the flanks. When the patient turns to the side, the fluid flows to the lower side and, when the patient stands, the fluid sinks into the lower abdomen. At this point in the examination, if ascites is suspected, a more thorough assessment can be done to detect its presence. A test for shifting dullness is one such measure. When a patient lies supine, free fluid in the abdomen gravitates to the flanks and the intestines float upward. Percussion in this position reveals an area of tympany above an area of dullness. If the patient then turns on to one side, the area of dullness "shifts" to the dependent side as the gas-filled intestine floats to the top and the uppermost area then becomes tympanic.

An additional test for ascites is the presence of a fluid wave. The examiner taps the left flank sharply with one hand, while the other hand is placed against the opposite flank. In addition, a third hand belonging to either the patient or another clinician is placed with the ulnar surface along the midline of the abdomen to stop transmission of an impulse by subcutaneous adipose tissue. If ascites is present, a fluid wave will be felt in the opposite flank. The test may give a false-positive result in patients who are obese. Both the test for shifting dullness and the fluid wave test are unreliable in detecting ascitic fluid of less than 1000 mL [1].

Auscultation

Examiners may perform auscultation before percussion or palpation to avoid altering bowel sounds, although there is no evidence that this matters! Auscultation is used to identify the presence of bruits or peritoneal friction rubs to aid in the diagnosis of liver disease.

Bruits are systolic sounds created by turbulent blood flow through diseased or compressed blood vessels. Abdominal bruits are useful in the diagnosis of renal artery stenosis and aortic aneurysm. Epigastric bruits are common in thin individuals, especially after a meal. Bruits located over the liver are associated with alcoholic hepatitis, hepatoma, hepatic artery aneurysm, hepatic arteriovenous fistula, or pancreatic cancer. A venous hum at the umbilicus is indicative of Cruveilhier–Baumgarten syndrome which presents with splenomegaly, portal hypertension, and a patent umbilical vein [7].

Peritoneal friction rubs, similar to pericardial or pleural rubs, are a sign of inflammation or infection. Heard over the liver, they suggest a diagnosis of primary and metastatic malignancies, or may occur during the first 4–6 hours after liver biopsy. Rubs may occur with or without concomitant hepatomegaly. In general, rubs are

non-specific. In patients with known liver tumors, less than 10% have a rub [7].

Percussion

Percussion of the abdomen is useful in determining the size of the liver and spleen, and can determine if ascites is present. The focus on assessing liver size is in identifying hepatomegaly rather than in attempting to detect a small liver seen in patients with chronic cirrhosis. At the right midclavicular line, begin midchest at the third rib and percuss downward. The resonant tones of the chest will gradually change to dullness as the volume of the air-filled tissue of the lung overlying the liver decreases. Continue percussing downward until the dullness becomes tympanic over the colon. The lower border of liver dullness indicates to the examiner where the liver edge should be palpable.

Vertical liver span is judged by liver dullness and measures approximately 10–12 cm in men and 8–11 cm in women. Generally, a span of less than 12–13 cm makes hepatomegaly unlikely [7]. The difficulty in measuring liver span is in the organ's irregular shape and the fact that an accurate measurement depends on properly identifying the midclavicular line. Multiple clinicians will vary in their assessments of liver span in spite of each achieving accurate measurements due to the variability in determining the location of the midclavicular line.

Percussion over the spleen is used to detect splenic dullness. The spleen is normally located in the left upper quadrant within the rib cage against the posterolateral wall of the abdominal cavity. As the spleen enlarges, it remains close to the abdominal wall and the tip moves down toward the midline. As splenic enlargement is difficult to palpate, percussing an area of dullness is a useful sign. With the patient supine and breathing normally, percuss in the lowest intercostal space in the left anterior axillary line. Normal percussion gives either the resonant or the tympanic tone of the air-filled colon and stomach. A dull tone is a positive test for splenomegaly.

Certain conditions present challenges when assessing liver or spleen size by percussion. Chronic obstructive pulmonary disease makes assessment of the upper border of the liver difficult and results in a false-positive measurement of the size of the liver. Distension of the colon obscures the lower border liver dullness and may result in underestimation of the size of the liver, a false-negative assessment.

Palpation

Once percussion has given the examiner the approximate size and location of the liver, palpation is the next and final portion of the examination. The abdomen is palpated to further assess the size, shape, and quality of the liver. First, light palpation is used progressing to deep palpation as abdominal muscles relax. To palpate the liver, the right hand is placed above the right iliac fossa and below the area of liver dullness. The examiner presses inward and upward, gradually working higher until the edge of the liver is appreciated. The patient may be asked to take a deep breath. As the diaphragm descends, the liver is brought down which facilitates palpation of the lower edge. The normal liver edge has a firm, smooth shape, not hard, and the left lobe should not be palpable across the midline. Normally, the liver edge is sharp; a rounded edge indicates liver disease. Enlargement of the liver can be seen in acute hepatitis, or chronic liver disease. A markedly enlarged liver (>10 cm below the costal margin) occurs in primary and metastatic tumors of the liver, alcoholic liver disease, severe congestive heart failure, infiltrative diseases of the liver such as amyloidosis and myelofibrosis, and chronic myelogenic leukemia.

A non-palpable liver does not rule out hepatomegaly but it does reduce the likelihood that an enlarged liver is present. Conversely, a palpable liver is not necessarily enlarged or diseased, but it does increase the possibility of hepatomegaly [8].

If the earlier percussion gave signs of an enlarged spleen, the examiner may palpate the spleen, although this is more difficult than palpating the liver. Normally, the spleen is not palpable. To palpate the spleen, the examiner starts with the right hand above the left iliac fossa and, with gentle pressure through curled fingers, works toward the left costal margin. If the spleen is not felt, the patient is turned onto the right side, allowing the examiner to palpate the left upper quadrant as the patient takes a deep breath. The spleen may be felt as it descends during inspiration. Causes of splenomegaly include portal hypertension due to cirrhosis of the liver, hyperplasia, congestion, infection, or infiltration by tumor or myeloid elements [8].

Take-home points

- Despite our technological advances, history taking is pivotal to accurate diagnostic tests.
- The physical examination should be focused on the abdomen but, because the impact of liver disease is systemic, attention should be addressed to other regions such as the skin, fingers, muscle mass, and head and neck.
- The use of basic examination skills such as observation, palpation, and percussion will generally narrow the differential diagnosis before more detailed evaluation is completed.

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4

CHAPTER 4

Assessment of Abnormal Liver Injury Tests

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Summary

Evidence of hepatic injury on routine biochemical evaluation should prompt a rapid decision-making process in the clinician. Elevations of hepatocellular injury tests (aspartate transaminase or AST, alanine transaminase or ALT) should be evaluated with an eye to the relative magnitude, pace of elevation, and relative increase over other markers. In this way, appropriate resources can be devoted to rapid evaluation. Increases in cholestatic injury tests (alkaline phosphatase liver fraction, γ-glutamyl transpeptidase, and bilirubin) should prompt assessment of biliary tree anatomy and consideration of autoimmune, metabolic, or toxic injury of the liver. Finally, the liver's ability to synthesize factors such as albumin and factor V is a very quick gauge of the extent of the liver injury.

Case

A 57-year-old woman with a known history of well-compensated hepatitis C virus infection and hypertension presents to the emergency department complaining of abdominal pain, fever to 101 F, and chills. She has been experiencing the above symptoms for several days and has had decreased oral intake due to the acute illness.

She does not usually take any medications, but has been taking acetaminophen (paracetamol) 500 mg every 6–8 h for the past few days. She has not consumed any alcoholic beverages in the past week but generally drinks a glass of wine with dinner. She denies smoking and has no history of intravenous drug use.

The patient appears to be in no acute distress; her physical exam reveals a thin white woman, alert and oriented, no scleral icterus, dry mucous membranes, her abdomen is soft but mildly tender on palpation diffusely, and no hepatomegaly or splenomegaly. In the emergency department abdominal ultrasonography reveals no abnormality, lab results show normal complete blood count (CBC), metabolic panel shows mild hypokalemia at 3.4 mmol/L, and liver injury tests reveal aspartate transaminase (AST) 12 IU/dL, alanine transaminase (ALT) 150 IU/dL, alkaline phosphatase 140 IU/dL, and total bilirubin 1.5 mg/dL, with direct bilirubin 0.8 mg/dL.

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Approach to Patient with Abnormal Liver Injury Tests

Enzymes Suggesting Hepatocellular Necrosis

Aminotransferases

Aspartate aminotransferase or transaminase (AST; formerly SGOT—serum glutamic–oxaloacetic transaminase) and alanine aminotransferase or transaminase (ALT; formerly SGPT—serum glutamic–pyruvate transaminase) are indicators of hepatocyte membrane injury. AST and ALT play a role in gluconeogenesis, catalyzing

the transfer of the α-amino groups of aspartic acid and alanine, respectively, to the 2-oxo (α-keto) group of ketoglutaric acid, resulting in the formation of oxaloacetic acid and pyruvic acid [1,2]. ALT is primarily located in the cytoplasm of hepatocytes and is a more specific test for hepatic injury, whereas AST is located in both the cytoplasm and the mitochondria, and found in a variety of extrahepatic sites: cardiac muscle, skeletal muscle, kidneys, brain, pancreas, lungs, leukocytes, and erythrocytes [3]. As a result of this lack of specificity, isolated elevations in AST can occur due to injury to skeletal muscle (marathon running, weight lifting, rhabdomyolysis) or cardiac muscle (acute coronary syndrome), and its hepatic origin needs to be confirmed with measurement of serum ALT [4,5]. Liver cell membrane damage, with or without necrosis, can lead to elevation of the transaminases and the level of elevation correlates poorly with extent of liver injury [2].

The ratio serum AST:ALT can be helpful in formulating a differential diagnosis. Most forms of acute liver injury present with AST:ALT <1; however, alcoholic hepatitis characteristically presents with AST:ALT >2 [6]. Moreover, cirrhosis from any cause can lead to AST:ALT >1 [7]. The level of elevation in the transaminases should be a major consideration in the development of a differential diagnosis. Generally chronic hepatitis (viral, autoimmune, steatosis-related hepatitis) presents with modest elevations (two to four times the upper limit of the normal range), alcoholic liver disease may present in a wide range but rarely exceeding an absolute level of 500 IU/dL, and extreme elevations, >1000–2000 IU, generally represent acute and severe toxic, viral, autoimmune, or ischemic injury to the liver. The causes of elevation in transaminases are varied and often reflect the population studied; this is illustrated by the following examples.

Among 19 877 Air Force recruits who volunteered to donate blood, 99 (0.5%) had elevated ALT [8]. Etiology for the abnormality was found in only 12 of the 99: 4 hepatitis B, 4 hepatitis C, 2 autoimmune hepatitis, 1 cholelithiasis, and 1 appendicitis.

In a cohort of 100 blood donors with elevated ALT, the etiology was related to alcohol in 48%, fatty liver in 22%, hepatitis C in 17%, 4% other, and 9% no diagnosis [9]. Another study of 149 asymptomatic patients with high ALT undergoing liver biopsy found 56% with fatty liver, 20% non-A, non-B hepatitis, 11% alcohol use, 3% hepatitis B, 8% other cause, and 2% no identifiable risk factor [10]. Yet another study showed that 81 of 1124 patients referred for chronic abnormal serum transaminases, in whom a cause could not be identified noninvasively, underwent liver biopsy and the majority (84%) had steatosis or steatohepatitis [11].

The prevalence of elevated ALT (ALT >43 IU/dL) or AST (AST >40 IU/dL) among 6823 participants in the National Health and Nutrition Examination Survey (NHANES) was evaluated between 1999 and 2002. This revealed elevated ALT in 8.9%, more than double the previously available estimate. This prevalence was high, 7.3%, even among people with no history of hepatitis C or excessive alcohol use, and strongly associated with risk factors for non-alcoholic fatty liver disease [12].

Case

In our case we have to consider a broad differential diagnosis because the absolute elevations in the hepatocellular injury enzymes are modest but may be in a continuum, which requires the clinician to further investigate and probably follow the progress of the liver injury in this woman. The AST and ALT levels are moderately elevated. She was consuming acetaminophen for her symptoms but the level of elevation is not as high as can be seen in patients who present with this toxicity, and the amount of acetaminophen reported (≤2 g/day) would rarely cause liver toxicity, even in a patient with underlying hepatitis C virus infection. Similarly, acute ischemic or viral etiologies of elevated transaminases generally present with *extreme* increases of AST and ALT. Although autoimmune hepatitis can present with extreme values as mentioned earlier, it can also present with modestly elevated transaminases as seen in this patient. Alcoholic hepatitis can present with modest AST and ALT elevations but this patient's history makes this less likely. The classic presentation of AST:ALT >2 seen with this entity is not present in this case. Given the clinical context of this situation and the degree and ratio of AST and ALT, the patient's known history of chronic hepatitis C viral infection is most likely the cause of her modest transaminase elevation.

Lactate Dehydrogenase

The utility of lactate dehydrogenase (LDH) in the differential diagnosis of liver disease is limited by its lack of specificity. This enzyme is present in the cytoplasm of a wide variety of tissues. Elevated levels can be secondary to skeletal or cardiac muscle injury, hemolysis, stroke,

renal ischemia, and acute and chronic liver disease [1]. Ischemic hepatitis and malignant infiltration of the liver are scenarios in which LDH is characteristically elevated.

Enzyme Elevations Suggestive of Cholestasis

Alkaline Phosphatase

Alkaline phosphatase (AP) comprises a group of enzymes that catalyze the hydrolysis of organic phosphate esters, optimally at an alkaline pH [2]. AP isoenzymes are found in the liver, bone, intestines, kidney, placenta, leukocytes, and various neoplasms. The liver and bone are the major sources of AP [13]. The precise function of this family of enzymes is unclear but its production is increased in tissues undergoing increased metabolic activity. Women in their third trimester of pregnancy have increased levels due to a high concentration in the placenta and rapidly growing adolescents can have levels twice those of adults because of high bone turnover. People with blood type O or B can have elevated AP levels after the ingestion of a fatty meal due to an influx of intestinal AP [3]. This provides the rationale for obtaining fasting levels of AP. There have also been reports of elevation of intestinal AP as a result of a benign familial condition that increases the levels of this enzyme. AP is also known to increase with age, particularly in women. Normal AP levels in a healthy 65-year-old woman are more than 50% higher than the levels in a healthy 30-year-old woman [14].

The first step in evaluating elevated AP is identifying the source. The most sensitive and specific methods are electrophoretic separation on polyacrylamide gel or Sepharose; however, these are not commonly available tests [3]. A more practical alternative is to check the serum γ-glutamyl transpeptidase (GGT) or 5′-nucleotidase because these enzymes usually rise in parallel with AP in hepatic disease and are not elevated in bone disorders. Isolated elevation in AP without corresponding abnormality in GGT or 5′-nucleotidase suggests a bone rather than a hepatic disorder.

Causes of Elevated AP. Elevation of AP in liver disease results from increased synthesis and not from impaired biliary secretion. Although levels of AP two to three times the upper limit of normal are non-specific and can be seen with a wide variety of liver diseases, striking elevations should raise concerns for cholestatic disorders and hepatic infiltration [1]. Cholestatic conditions include partial obstruction of bile ducts, primary biliary cirrhosis, primary or secondary sclerosing cholangitis, adult biliary ductopenia (the so-called vanishing bile duct syndrome), and drug toxicity(e.g., anabolic steroids, phenytoin). Examples of infiltrative conditions include granulomatous disease such as sarcoidosis, tuberculosis, and primary or metastatic neoplastic disorders [1,3]. Serum AP elevation in infiltrative diseases is probably due to compression of small, intrahepatic bile ducts and subsequent leakage of the enzyme into the circulation. In rare situations, other cancers (e.g., a lung neoplasm) can present with elevation of an AP isoenzyme without liver or bone involvement. The "Regan isoenzyme" is biochemically distinct from the hepatic AP [15] and is a true paraneoplastic enzyme. With the increased number of applications for bone marrow transplantation (BMT) two entities that are increasingly seen include venoocclusive disease or sinusoidal obstruction syndrome (SOS) and hepatic graft-versus-host disease, both of which have a cholestatic presentation that has AP elevation as a hallmark.

©-Glutamyl Transpeptidase

GGT catalyzes the transfer of the γ-glutamyl group from γ-glutamyl peptides such as glutathione to other peptides and amino acids. It is found in hepatocytes and biliary epithelium, but, similar to AP, it also has a wide extrahepatic distribution including pancreas, kidney, spleen, heart, lung, and seminal vesicles [16]. GGT can be elevated in patients with chronic obstructive pulmonary disease (COPD), diabetes, and alcoholism [17], and patients taking anticonvulsants (e.g., phenytoin, barbiturates) and warfarin [18]. As a result of its low specificity, GGT is not a reliable indicator of liver disease in isolation. Its major clinical utility lies in helping to confirm the origin of an abnormal AP level: GGT does not rise in bone disorders but does rise in parallel with AP in hepatic diseases. Another debatable use of the enzyme has been to diagnose unreported alcohol use. GGT, a microsomal enzyme, is inducible by alcohol and its sensitivity for detecting alcohol ingestion has ranged from 52% to 94% [19,20]. Its lack of specificity makes isolated measurement of GGT for detection of surreptitious alcohol use questionable, and its best use is in combination with other liver injury tests for detecting diseases of hepatic

origin or supporting use of alcohol with ratios of transaminases (AST:ALT) >2.

Bilirubin

Bilirubin, a tetrapyrrole pigment, is a breakdown product of heme-containing proteins [21], most of which is produced from hemoglobin catabolism. The bilirubin normally present in serum (≤1 mg/dL) is a balance between production and hepatic removal [2]. Hyperbilirubinemia can result not only from overproduction of bilirubin, but also from impaired uptake, conjugation, and excretion. The first step in evaluation of elevated total bilirubin is fractionation to determine the levels of direct and indirect bilirubin. Direct bilirubin is the water-soluble, conjugated form that can be filtered through the glomerulus and excreted in urine. Liver parenchymal disease and bile duct obstruction can lead to elevations in conjugated bilirubin and subsequent urobilirubinemia. Indirect bilirubin, the unconjugated form, is bound to albumin, creating a moiety that is too large to be filtered through the glomerulus and is not present in urine. Elevations of unconjugated bilirubin can result from overproduction, impairment of uptake, or conjugation. Most of the serum bilirubin in a healthy adult is unconjugated.

Unconjugated Hyperbilirubinemia. Indirect hyperbilirubinemia can result from disorders causing bilirubin overproduction, including hemolysis and ineffective erythropoiesis. Hemolysis can be due to conditions such as spherocytosis, sickle cell anemia, pyruvate kinase deficiency, glucose-6-phophate dehydrogenase deficiency, microangiopathic hemolytic anemia, and paroxysmal nocturnal hemoglobinuria. Diagnosis of hemolytic conditions is supported by examination of the peripheral smear, in addition to laboratory tests such as low haptoglobin and elevated reticulocyte and LDH levels. Ineffective erythropoiesis can be seen with vitamin B_{12}, folate, and iron deficiencies.

Impaired hepatic uptake or bilirubin conjugation can lead to indirect hyperbilirubinemia. Medications such as rifampin can lower hepatic uptake of bilirubin. The most common genetic entity associated with elevated levels of indirect bilirubin is Gilbert syndrome, a variant that affects up to 7% of the population. Impaired conjugation results from reduced levels of uridine diphosphate (UDP) glucuronosyl transferase and this leads to mildly elevated bilirubin levels, generally <6 mg/dL. Two other inherited conditions are Crigler–Najjar syndrome types I and II, the former with complete absence of bilirubin-UDP glucuronosyl transferase activity and the latter with reduced levels of enzyme activity. Type I is extremely rare and affects neonates who present with severe jaundice (bilirubin >20 mg/dL) and neurologic impairment due to kernicterus. In Crigler–Najjar syndrome type II, patients may live to adulthood with bilirubin ranging from 6 mg/dL to 25 mg/dL.

Conjugated Hyperbilirubinemia. Direct hyperbilirubinemia (conjugated bilirubin >50%) results from acquired or inherited impaired hepatic excretion and subsequent excretion into the serum [1]. It can be secondary to acquired conditions such as biliary obstruction and parenchymal liver disease, or inherited disorders such as benign recurrent intrahepatic cholestasis (BRIC), and Dubin–Johnson and Rotor syndromes. Dubin-Johnson syndrome and Rotor syndrome typically present as aymptomatic jaundice in the second decade of life. The defect in Dubin–Johnson syndrome is altered excretion of bilirubin into bile ducts and in Rotor syndrome it is thought to be due to defective hepatic storage of bilirubin [22,23]. Both are benign conditions with no intervention or treatment required. BRIC generally presents in adolescence or early adulthood with jaundice, nausea, malaise, weight loss, and pruritus. Episodes can last from weeks to month with subsequent clinical and biochemical recovery. BRIC is thought to be associated with intrahepatic cholestasis of pregnancy or use of oral contraceptives. Again, no specific treatment is required of this benign and non-progressive condition [24].

Hepatic Synthetic Function

Prothrombin Time

Most clotting factors are synthesized in the liver, so, when prolonged, the prothrombin time, which measures the rate of conversion from prothrombin to thrombin, can be an indicator of decreased hepatic synthetic capacity. However, the prothrombin time (PT) can be prolonged secondary to other conditions such as vitamin K deficiency, consumption of clotting factors (e.g., disseminated intravascular coagulopathy or DIC), and congenital deficiency of clotting factors. Vitamin K is necessary for the γ-carboxylation and normal function of several hepatic clotting factors (V, VII, IX, and X), and its deficiency can result in an abnormal PT despite good liver

function. Hypovitaminosis K can be secondary to malabsorption, antibiotic use, and dietary deficiency. If the PT is prolonged, a trial of vitamin K may be given and the PT should improve if the problem is vitamin K deficiency but not if there is hepatic synthetic dysfunction. If invasive procedures are needed in the setting of liver disease, fresh frozen plasma can be given to temporarily improve the PT. Factor VIII is synthesized extrahepatically in the vascular endothelium and reticuloendothelium, and its levels are normal or increased in liver disease. A consumptive coagulopathy such as DIC should be suspected when factor VIII levels are decreased in the setting of a prolonged PT.

Albumin

Albumin, one of the most important plasma proteins, is made in the liver with normal range 3.5–4.5 g/dL. The serum level is a balance of the rate of synthesis and degradation and volume of distribution [2]. In addition to parenchymal liver disease, albumin synthesis is affected by nutritional status, osmotic pressure, systemic inflammation, and hormones [25,26], and hence hypoalbuminemia is not specific for liver disease. Protein-losing enteropathies, chronic infections/inflammation, and nephrotic syndrome can all lead to lower serum albumin levels. Albumin levels are decreased in chronic liver disease and indicate significant liver damage and decreased synthetic capacity. As a result of albumin's long half-life (20 days), acute conditions such as medication-related hepatotoxicity, acute viral hepatitis, and obstructive jaundice tend to be associated with normal levels of albumin [2]. One notable exception is patients presenting with ascites, who, despite an acute illness with normal or increased albumin synthesis, can have low levels of albumin due to increased volume of distribution. Prealbumin, which is also synthesized in the liver but has a shorter half-life, can be useful to assess severity of liver dysfunction in acute conditions.

Ultimately the assessment of hepatic function requires not only biochemical change assessment but also inclusion in the evaluation of factors that may be gleaned from the physical examination and may be more difficult to quantify. For example, a patient presenting with fulminant liver failure may initially not exhibit the very high elevation transaminases that have been described above. However, the physical examination will reveal a patient who may be slowly developing hepatic encephalopathy and will ultimately have significant increases in the liver enzymes that will lead to the eventual diagnosis.

Take-home points

- If a patient presents with AST- and ALT-predominant injury, evaluate duration and magnitude of elevations. These are key to making clinical decisions.
- The patient with cholestatic-predominant injury deserves imaging to evaluate the biliary anatomy. In these cases metabolic, autoimmune, and toxic injuries should also be considered.
- Elevations in bilirubin deserve careful attention and should include consideration of the patient's age and medical history if not easily diagnosed with imaging techniques.

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5

CHAPTER 5
Imaging of the Liver and Biliary Tree

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Summary
Recent major technological advances in computed tomography (CT) and magnetic resonance imaging (MRI) have enabled the accurate, non-invasive detection and characterization of hepatic lesions. Due to its relative lower cost, availability, and widespread distribution, CT is often the primary imaging modality in the initial evaluation of the liver. However, with the comparatively superior lesion-to-liver contrast, the ability to utilize hepatocyte-specific contrast agents, and the lack of ionizing radiation, MRI is realizing an increasingly greater role in this regard. For assessment of the gall bladder and biliary system, ultrasound (US) remains a basic modality for the prompt diagnosis of stones and acute inflammatory or obstructing processes. Advanced CT and MR techniques are utilized for evaluating equivocal US findings, oncologic staging, preoperative planning, and postoperative complications. This chapter reviews the discriminating imaging features of commonly encountered hepatobiliary pathology at cross-sectional imaging.

Liver Pathology

As the liver can be primarily or secondarily involved by numerous vascular, metabolic, infectious, and neoplastic processes, the clinical history can have a significant impact on the imaging differential diagnoses. For example, primary hepatic malignancies are more common in the presence of chronic, diffuse liver diseases such as cirrhosis, hemochromatosis, and steatohepatitis; whereas metastatic disease, particularly from gastrointestinal tumors, is more common in a normal liver. Thus, an orderly approach to the diagnosis of focal hepatic lesions includes a familiarity with the distinguishing imaging characteristics in conjunction with knowledge of any underlying pre-existing clinical condition. This section will highlight the most relevant and common CT and MR imaging features of select focal and diffuse hepatic pathologic processes.

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Hepatic Cyst

Cystic lesions of the liver have been described as developmental or the sequelae of trauma, infection, or neoplastic disease. Developmental hepatic cysts are common, reported to occur in 5–14% of the population, with a strong female predilection [1]. These are generally asymptomatic and found incidentally. True hepatic cysts are lined by cuboidal epithelium, but do not communicate with the biliary tree [2].

Simple cysts are well-defined, homogenous lesions on non-enhanced CT, exhibiting low attenuation values similar to water, without perceptible enhancement following intravenous contrast administration (Figure 5.1). At MR (Figure 5.2), cysts demonstrate low T1 signal, and very high T2 signal relative to the background liver. With prolonged T2 weighting, cysts will remain hyperintense

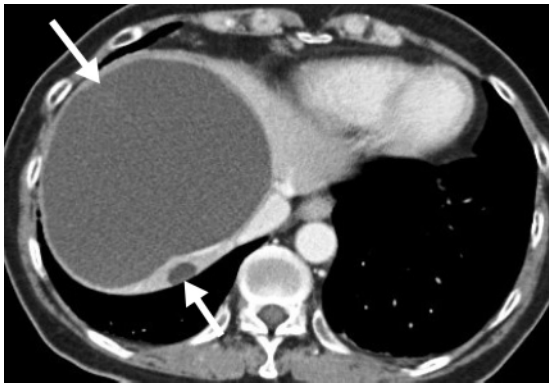
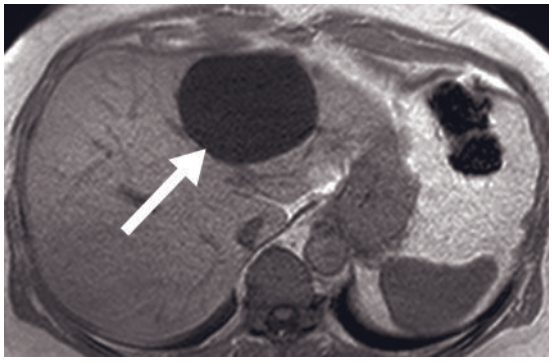
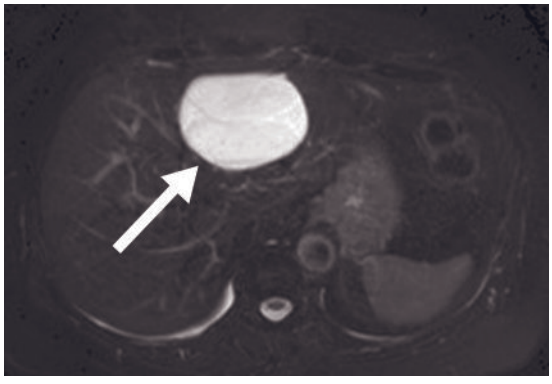


Figure 5.1 Hepatic cyst. Contrast-enhanced CT image shows two water-attenuation cysts near the dome of the liver (arrows). Both show a thin, well-defined wall, without mural nodule, septation, or enhancement.



(a)



(b)

Figure 5.2 Hepatic cyst. A simple hepatic cyst will show (a) homogeneous hypointensity on T1-weighted (arrow) and (b) homogeneous hyperintensity on T2-weighted (arrow) images.

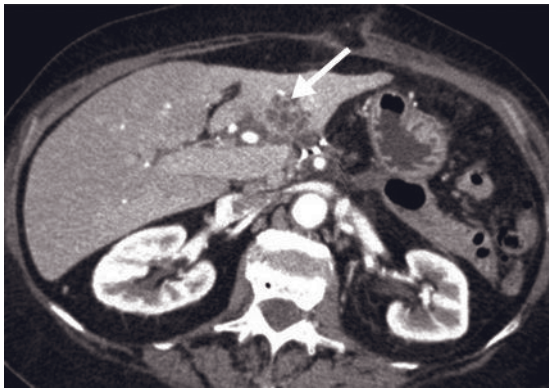
as compared to hypovascular hepatic metastases, a specific discriminating feature [3]. No perceptible enhancement should be present following administration of intravenous gadolinium contrast agents.

The differential diagnoses include:

- Polycystic liver disease: consider if more than 20 varying-sized hepatic cysts and no or minimal renal cysts.
- Bile duct hamartoma (also know as Meyenburg complexes) [4]: this is an incidental finding, thought to represent a failure of involution of embryonic bile ducts. This entity can be mistaken for metastases, but should be considered if numerous, small (< 1.5 cm) cystic hepatic lesions are present without a history or findings of adult polycystic kidney disease.
- Necrotic/cystic metastases [5–7]:
  - Necrotic: generally related to an aggressive solid metastasis that has outgrown its blood supply or has undergone therapy. It can be differentiated from a simple cyst due to the presence of thickened, irregular wall enhancement.
  - Cystic: more often represent metastasis from a mucinous primary (e.g., colorectal, ovary). With careful evaluation, these lesions can be identified involving the serosal surface of the liver and not within hepatic parenchyma.
- Abscess: etiology can be pyogenic, amebic, or fungal. Clinical symptoms of abscesses are related to the coexistence of sepsis. The imaging findings include: gas/air–fluid level; thick, progressively enhancing wall; perilesional edema and hyperenhancement; and satellite clustered microabscesses [8,9] (Figure 5.3):
  - Pyogenic: typically *Clostridium* species and Gram-negative bacteria, which enter the liver via the portal venous system or biliary tree, i.e. portal phlebitis or ascending cholangitis.
  - Amebic: due to the protozoan *Entamoeba histolytica*; it represents the most commonly encountered hepatic abscess on a worldwide basis.
  - Fungal: *Candida albicans* is most common.

Hemangioma

Hemangiomas are the most common benign hepatic neoplasm, with a reported incidence of up to 20% in autopsy series [10]. These are more frequent in women, are generally asymptomatic, and are discovered incidentally. However, giant hemangiomas (> 4–6 cm diameter) can present with non-specific abdominal symptoms,



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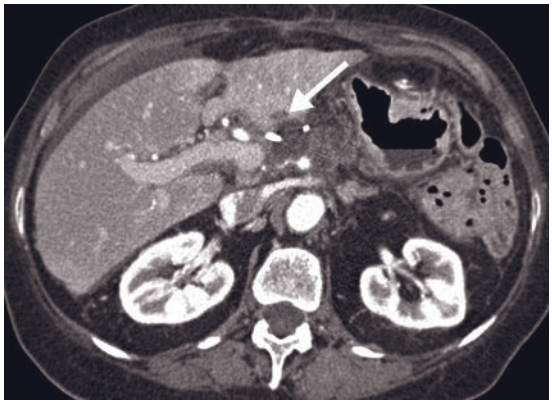


(b)

Figure 5.3 Hepatic abscess. (a) Initial contrast-enhanced CT shows a multiseptated lesion involving the left lobe of the liver (arrow) in a patient with fever and elevated white count. Fine needle aspiration consistent with a hepatic abscess. (b) After antibiotic therapy, a follow-up CT 7 weeks later shows minimal residual inflammatory changes in the liver (arrow).

related to the mass-effect on the hepatic capsule or adjacent abdominal structures.

The characteristic CT appearance (Figure 5.4) is of a well-circumscribed hepatic mass with peripheral, nodular, interrupted enhancement following contrast administration [11]. On precontrast images, hemangiomas should be of similar attenuation to the blood vessels, and likewise should have persistent, similar blood pool enhancement on delayed post-contrast images [12]. With MRI (Figure 5.4), hemangiomas show bright T2 signal, similar-to-slightly decreased as compared to hepatic cysts, and an enhancement pattern identical to CT [13,14]. MRI is arguably the most sensitive and specific diagnostic modality, with one series demonstrating a specificity of 100% in differentiating hemangiomas from metastases [15].

Pitfalls to diagnosis include "hypervascular" small hemangiomas and chemotherapy-treated metastases. The former can be differentiated from other hypervascular hepatic lesions as small hemangiomas maintain persistent enhancement on delayed scans, while other hypervascular lesions will lose enhancement on delayed images. Although treated metastases may appear to have slowly progressive centripetal enhancement, these lesions can be differentiated by an intact, rather than interrupted, ring of early enhancement [16].

Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) is the second most common benign hepatic neoplasm. Like hemangiomas, these are most often found in women, and are detected incidentally. Although there is no definitive association, FNH in women on oral contraceptives can increase in size with a resultant increase in the rate of complications [17]. FNH is thought to represent a congenital hamartomatous malformation or a hyperplastic hepatic response to an underlying vascular malformation [18]. Pathologically, these lesions typically contain a central scar with abnormally arranged surrounding hepatocytes and bile ductules, and the presence of Kupffer cells. Although mostly solitary, up to 23% are multiple, and they can be associated with hemangiomas [19].

On CT, FNH is generally homogenous and isoattenuating to adjacent liver parenchyma prior to contrast administration. Except for a hypodense central scar, FNH exhibits prompt homogenous arterial phase enhancement which rapidly fades on portal-phase images, nearly indistinguishable from the adjacent liver. Delayed enhancement of the central scar can be a specific feature. (Figure 5.5) [20].

Although the contrast enhancement dynamics are identical to CT, the advantage of MRI in the diagnosis FNH is that it can confirm its hepatocyte composition by exhibiting isointense signal to the adjacent liver parenchyma in T1- and T2-weighted sequences. In addition, the ability to use liver-specific MR contrast agents (not available for CT) aids in determining the correct diagnosis. Due to the presence of Kupffer cells, FNH will show marked T2 signal loss with superparamagnetic iron oxide

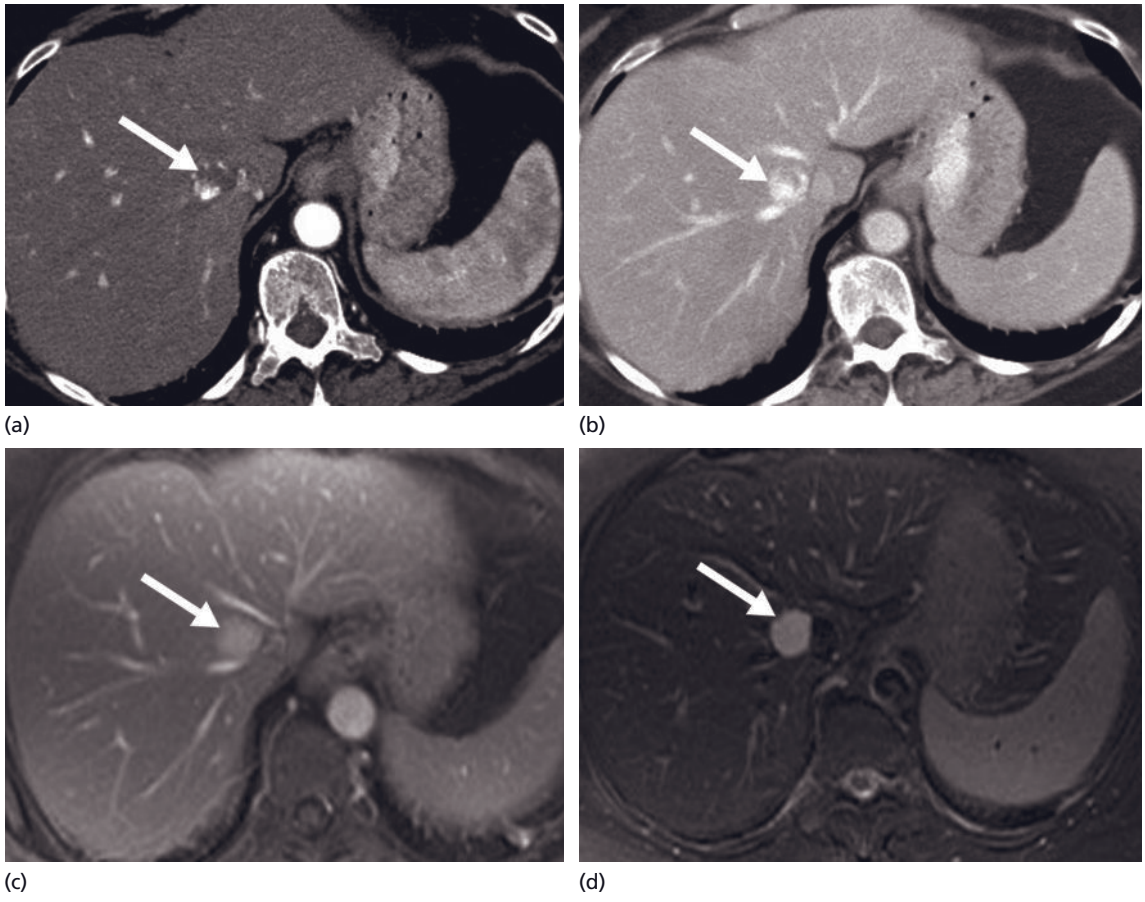


Figure 5.4 Hemangioma. (a) Arterial phase and (b) portal venous phase CT images show a hemangioma (arrows) adjacent to the confluence of the right and middle hepatic veins with the inferior vena cava. Note early peripheral, nodular, interrupted enhancement, similar to enhancing hepatic vessels (a), that progressively fills in on the later phase (b). (c) On further delayed phases, hemangiomas will classically demonstrate persistent hyperenhancement relative to the liver, as seen on this 2-min delayed MR acquisition (arrow). (d) With MR, hemangiomas are nearly as hyperintense as cysts on T2-weighted sequences (arrow).

(SPIO) and ultrasmall superparamagnetic iron oxide (USPIO) contrast agents [21], and can demonstrate T1 hyperintensity with hepatobiliary contrast agents [22]. When present, the central scar will often be bright on T2-weighted sequences (Figure 5.5).

Differential diagnoses include hepatic adenoma, hepatocellular carcinoma (HCC) (including the fibrolamellar variant), and hypervascular metastases. In contrast to FNH, hepatic adenomas typically exhibit more signal heterogeneity, due to fat, blood, or calcifications; show a more heterogeneous enhancement pattern; and do not contain a central scar. HCC usually develops in the setting of chronic liver disease and has a surrounding capsule/pseudocapsule. Fibrolamellar HCC is often large at presentation (> 10 cm), and can be differentiated on the basis of marked signal/enhancement heterogeneity; a larger, irregular T2 hypointense scar; or the presence of calcifications. As hypervascular metastases by definition are not of hepatocyte origin, these are often T2 hyperintense, as opposed to FNH.

Hepatic Adenoma

Hepatic adenomas occur less frequently than hemangiomas and FNH, are related to oral contraceptive use, and

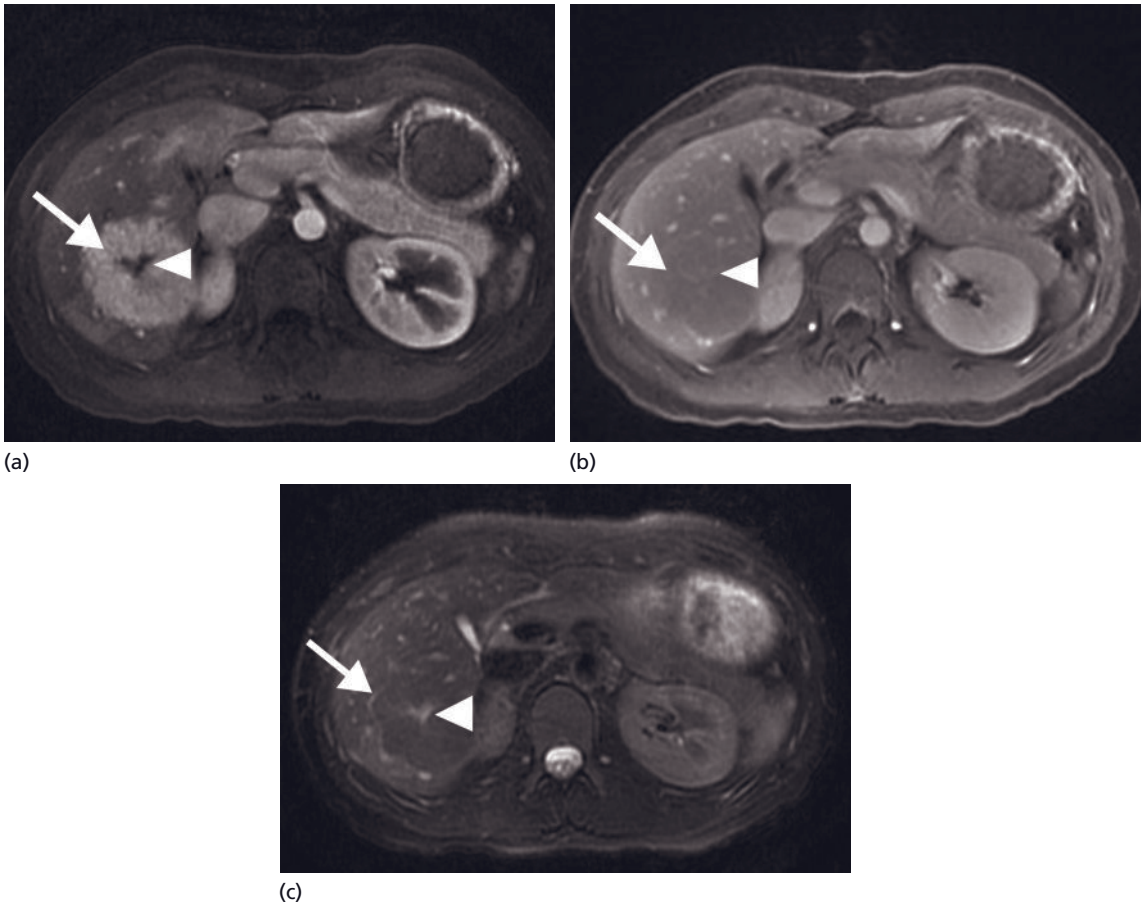


Figure 5.5 Focal nodular hyperplasia (FNH). (a) Axial, arterial phase MR image demonstrates a hypervascular right hepatic lobe mass (arrow) with hypoenhancing central scar (arrowhead). (b) Portal-venous phase MR image shows that the FNH becomes isointense to liver (arrow), but there is delayed enhancement of the central scar (arrowhead). (c) Axial T2-weighted sequence shows that the FNH (arrow) is similar in intensity to the adjacent liver, except for a hyperintense scar (arrowhead).

again have a female predilection. These can occur spontaneously, but have also been associated with anabolic steroid use and type I glycogen storage diseases. Histologically, adenomas are composed of hepatocytes, but lack the functioning bile ductules present in FNH. Kupffer cells are also variably present, and thus the spectrum of appearances with liver-specific contrast agents. Clinically, most patients are asymptomatic; however, due to a tendency for spontaneous rupture/hemorrhage and potential for malignant transformation, accurate diagnosis is required for management [23,24]. In general, a hemorrhagic liver mass in a young woman taking oral contraceptives is highly suggestive of an adenoma.

On CT, adenomas can have a variable appearance, complicated by their fat content, necrosis, hemorrhage, and/or calcifications [25]. Although fat is always hypodense, the appearance of blood varies with its acuity; acute blood is hyperdense, which becomes isodense and finally hypodense over time. Due to their rich hepatic arterial supply, adenomas show early hypervascularity, but this is typically more heterogeneous and to a lesser degree than with FNH (Figure 5.6). On portal venous and delayed scans, most adenomas will show "washout",

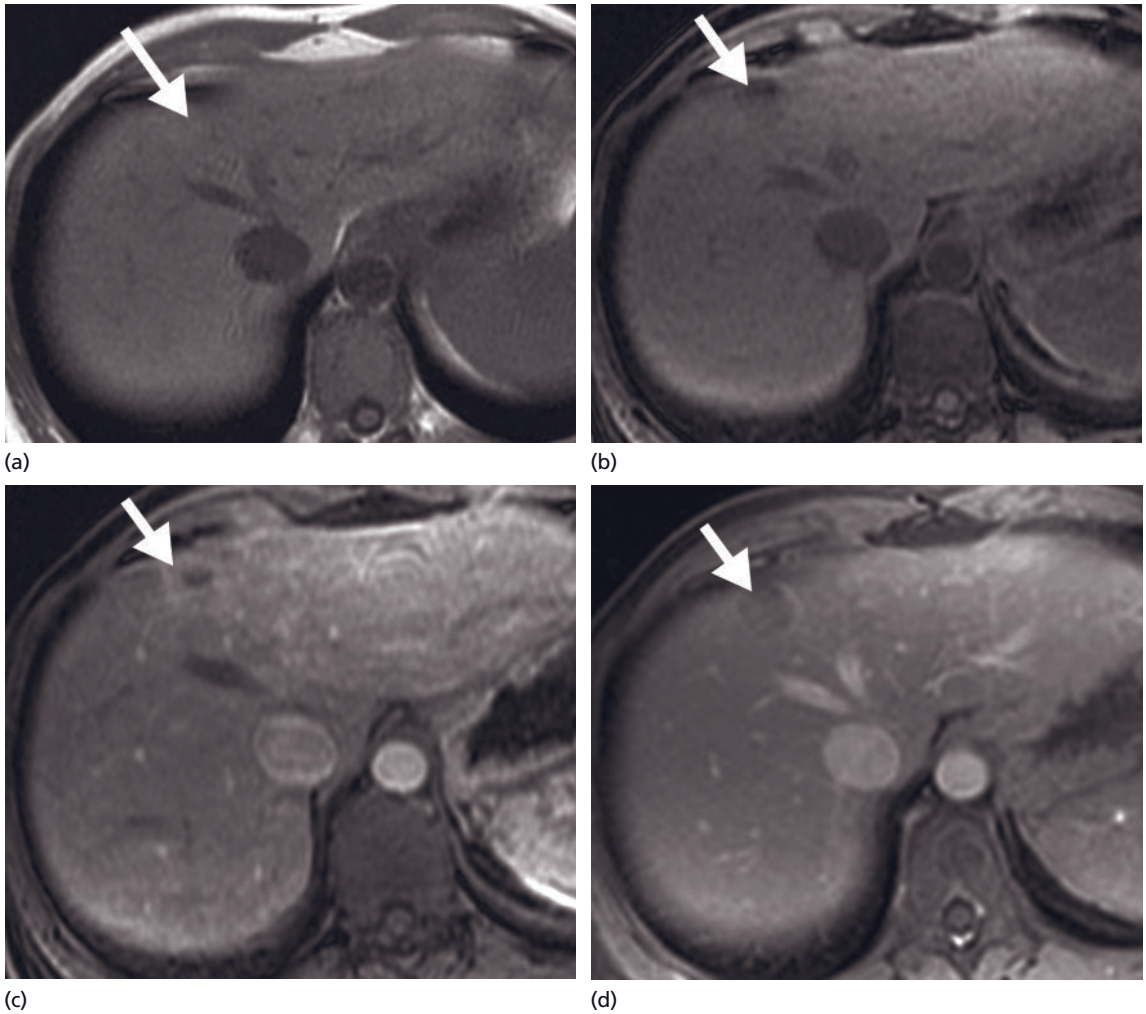


Figure 5.6 Hepatic adenoma. (a,b) Axial, T1-weighted images show a medial segment left lobe lesion that is subtly hyperintense on the in-phase sequence (a, arrow), then becomes heterogeneously hypointense on the fat-saturated sequence (b, arrow), consistent with a fat-containing mass. (c) Following contrast administration, this hepatic adenoma is heterogeneously hypervascular on the arterial phase sequence (arrow), but then (d) shows "washout" (becomes hypointense to liver) on a delayed-phase acquisition with a visible enhancing capsule/pseudocapsule (arrow).

i.e. relative hypoenhancement compared to adjacent liver. A delayed, enhancing capsule/pseudocapsule also helps in differentiation from FNH; however, this finding can mimic HCC (Figure 5.6). MR signal characteristics are likewise variable, dependent on intratumoral composition, but generally show iso- to moderate T2 hyperintensity, and a spectrum of mild hypo- to mild hyper-intensity on T1-weighted sequences [26]. The contrast enhancement features on MR are similar to those on CT.

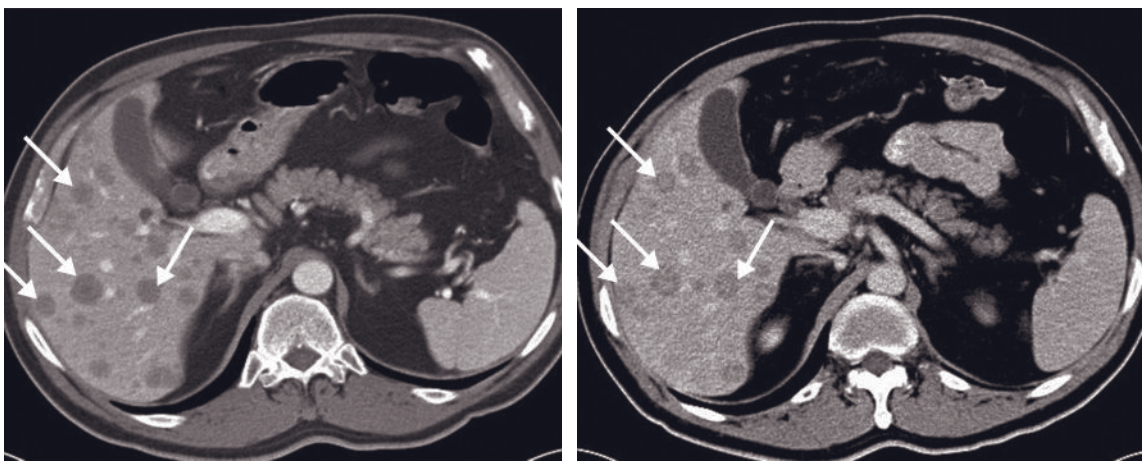
Differential diagnoses include FNH, HCC, and hypervascular metastases. In contradistinction to adenomas, FNH typically shows isoattenuation/isointensity to adjacent liver; homogenous, rather than heterogeneous hypervascularity; no capsule/pseudocapsule on delayed scans; a central scar; and hyperintensity with hepatobili-

ary-specific contrast agent [22]. HCC can have similar CT and MR imaging characteristics, but generally occurs in association with chronic liver disease. Differentiating multiple adenomas from hypervascular metastases can be difficult, requiring correlation with patient history and histologic evaluation.

Hepatic Metastases

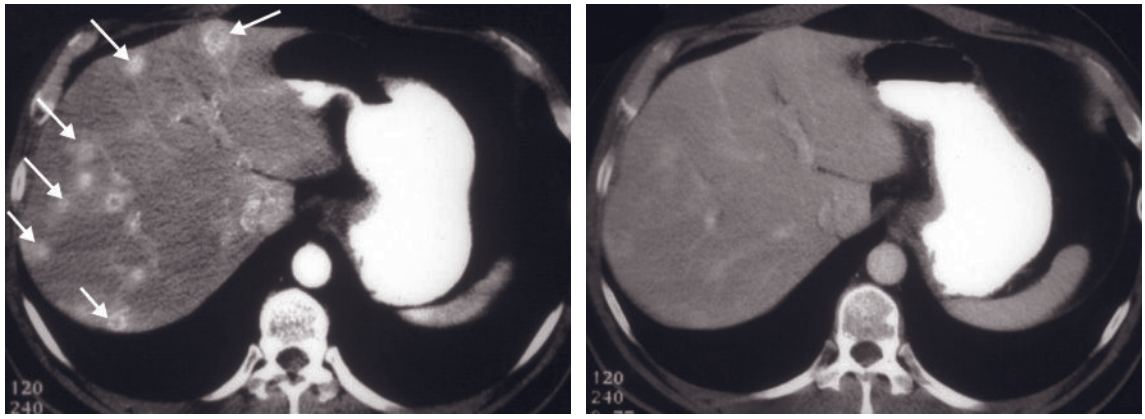
Metastases are the most common malignant hepatic tumor, occurring as much as 18 times more frequently than primary neoplasms [27]. These will generally appear as multiple, discrete lesions, but can present as solitary or even confluent masses. The imaging appearance is dependent on the underlying vascularity. Hypovascular metastases show decreased attenuation/signal compared to normal liver on portal venous phase images. An uncommon but relatively specific sign is "peripheral washout" (Figure 5.7). The most common primary tumor showing hypovascular hepatic metastases is colon adenocarcinoma, but other sources include breast, lung, and pancreas. In contrast, hypervascular metastases exhibit transient, intense enhancement on arterial phase CT or MR, and are poorly visualized on portal phase images (Figure 5.8). The most common hypervascular hepatic metastases are neuroendocrine tumors (including pancreatic islet cell, carcinoid, and pheochromocytoma), renal cell carcinoma, thyroid carcinoma, melanoma, and sarcomas.

CT has an advantage over MR in the detection of calcifications in hepatic metastases. Primary malignancies that can result in calcified metastases include mucinous gastrointestinal carcinomas, pancreatic islet cell, sarcomas, and ovarian cystadenocarcinomas [27]. On the other hand, MR provides greater contrast difference between the liver and metastases as opposed to CT [28]. In general, metastases show low signal on T1-weighted sequences. Exceptions include hemorrhagic or mucinous metastases and melanoma, which can be T1 hyperintense. Hypovascular metastases are moderately bright on T2-weighted sequences, and can be distinguished from hemangiomas which are much brighter, particularly with more heavily T2-weighted sequences. Although the T2 signal intensity can mimic hemangiomas, hypervascular metastases are generally more heterogeneous and ill-defined on T2-weighted sequences, and will exhibit contrast washout, rather than the persistent enhancement of hemangiomas, on delayed scans [11,14,29]. Also, MR with liver-specific contrast agents may be more sensitive than CT in detecting liver metastases [30,31].



(a) (b)

Figure 5.7 Hypovascular metastases. (a) Portal-venous and (b) delayed-phase contrast-enhanced CT images demonstrate multiple hypoenhancing colon carcinoma metastases (arrows). On the delayed image (b), several metastases show the "peripheral washout sign", i.e., central hyperdensity with peripheral hypodensity (arrows).



(a) (b)

Figure 5.8 Hypervascular metastases. (a) Arterial phase CT image demonstrate numerous hypervascular metastases from a primary gastrointestinal neuroendocrine tumor (arrows). (b) Portal-venous phase image shows that the metastases have decreased enhancement and are nearly imperceptible. This is in contrast to hypovascular metastases which are best seen on the portal-venous phase images.

Cirrhosis and Hepatocellular Carcinoma

Cirrhosis is a premalignant condition that is the irreversible sequelae of various hepatic insults, including inflammatory–infectious (hepatitis), toxic (alcohol), and metabolic (hemochromatosis, Wilson disease, alpha-1 antitrypsin deficiency syndrome, etc) processes. Pathologically, cirrhosis is characterized by diffuse fibrosis with architectural distortion, nodular formation, and altered vascularity. The nodules range from "benign" regenerative, to premalignant dysplastic, and frankly malignant HCC. The discrimination of these different cirrhotic nodules is often challenging as there can be considerable overlap in both imaging and histologic features. Nevertheless, as the overall long term survival rate for HCC is poor (5-year survival approximately 5%), early liver transplantation provides the only opportunity for cure [32]. Thus, radiological imaging plays a pivotal role in early diagnosis and resultant patient management and prognosis.

Classic hepatic imaging features of cirrhosis include peripheral nodular contour, with central organ atrophy (right anterior segment/left medial segment) and peripheral organ hypertrophy (left lateral segment and caudate) [33] (Figure 5.9). Quantitative volume analysis of these morphologic changes have also been proposed in the diagnosis of cirrhosis [33–36]; however, these techniques have not gained widespread use in clinical practice. An expanded gall-bladder fossa [37] and the presence of a right posterior hepatic notch [38] have been identified as simple, qualitative visual findings that are highly indicative of cirrhosis; with enlargement of the hilar periportal space [39] an indicator of early cirrhosis.

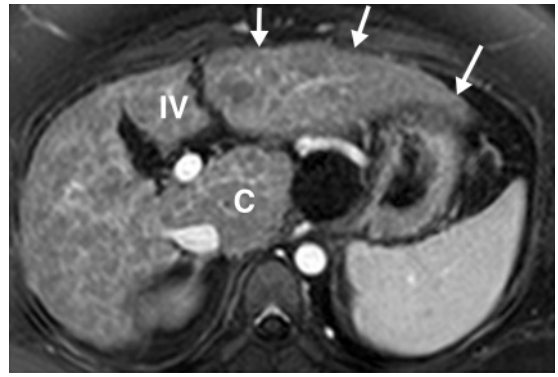


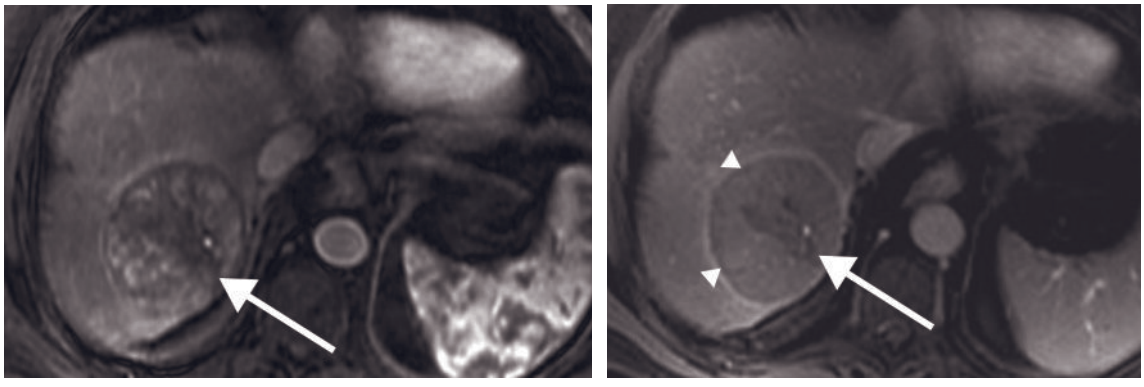
Figure 5.9 Axial, contrast-enhanced MR image demonstrates typical caudate (C) and left lateral segment (large arrows) hypertrophy, with left medial segment atrophy (IV) and peripheral contour nodularity.

Regenerative nodules (RNs) are difficult to visualize on CT due to its limited contrast resolution, appearing isodense to liver on multiphasic images. On MR, RNs are

typically isointense on the precontrast sequences, and then demonstrates a similar enhancement pattern as the background cirrhotic liver [40]. Delayed, progressive enhancement of surrounding fibrous septa can increase conspicuity of RNs on MR. These usually are less than 1–1.5 cm in size, but can uncommonly be larger. Infrequently RNs can demonstrate decreased T1 and T2 signal due to iron deposition, the characteristic MR appearance of siderotic-type nodules. Because of their increased T2-weighted signal characteristics, early changes of HCC can be seen as foci of increased T2 signal within a low-signal siderotic RN [41].

Dysplastic nodules (DNs) are thought to represent an intermediate step in the stepwise transition from RNs to HCC. Low-grade DNs are composed of mildly abnormal hepatocytes with dysplasia, but without histologic features of malignancy. These are of low malignant potential and can slowly progress into HCC. Conversely, high-grade DNs have architectural and cytologic atypia, and may even contain microscopic foci of HCC. These nodules can rapidly progress to frank HCC [42]. On MRI, DNs can have a variable T1-weighted appearance, but are most conspicuous when T1 hyperintense. The increased T1 signal may relate to intranodular copper, manganese, or fat, but this is not well understood. With T2-weighted sequences, DNs are hypo- or iso-intense. Neither RNs nor DNs should have increased T2 signal, aiding in their differentiation from HCC. In general, DNs should not be hypervascular following contrast administration, particularly the low-grade variety. However, high-grade DNs may be hypervascular [43].

As a cirrhotic nodule progresses from RN → DN → HCC, the dominant vascular supply changes from portal vein → hepatic artery → abnormal neoarteries due to tumor angiogenesis [44]. Therefore, the distinguishing imaging feature for HCC is increased hypervascularity on hepatic arterial phase enhanced images. It is thus critically important to employ multiphasic dynamic-enhanced sequences in any examination for HCC surveillance [45]. It has been proposed that in the setting of cirrhosis, a hypervascular mass greater than or equal to 2 cm with delayed-phase washout and capsular enhancement (Figure 5.10) is presumptive evidence for HCC, often not requiring tissue sampling for confirmation, particularly if the alpha-fetoprotein (AFP) level is significantly elevated, or there has been progressive increase in size on serial exams [46]. Other findings that are highly suggestive or supportive of HCC include T2-weighted hyperintensity or demonstration of fat on T1-weighted out-of-phase sequences [47–55]. As a minority of HCCs are relatively hypovascular, i.e. not seen on arterial phase imaging, careful evaluation of delayed/equilibrium phase images and/or the addition of an SPIO contrast agent may improve detection [56].



(a) (b)

Figure 5.10 Hepatocelluar carcinoma (HCC). (a) Axial, arterial phase contrast-enhanced MR image shows a heterogeneously, hypervascular mass (arrow) in this cirrhotic patient. (b) Portal-venous phase MR image demonstrates washout of this HCC (arrow), with a visible surrounding capsule (arrowheads).

Take-home points

- Although once primarily the purview of clinical and invasive means, the diagnosis of hepatic disease is now regularly assessed with cross-sectional imaging (CT and MR).
- Benign hepatic lesions (cysts, hemangiomas) are frequently encountered lesions that can be diagnosed at imaging without the need for biopsy.
- Focal nodular hyperplasia can be reliably differentiated from other hypervascular liver lesions (including adenoma) with the use of hepatocyte-specific MR contrast agents.
- As hepatic metastases can present as hypervascular or hypovascular masses, knowledge of the underlying primary malignancy helps in determining the appropriate imaging protocol.
- In the setting of hepatic cirrhosis, hypervascularity with washout is a key feature for differentiating HCC from regenerative/dysplastic nodules.

Gall-bladder/Biliary Pathology

Cholelithiasis/Choledocholithiasis

CT is less sensitive in the detection of gall stones (75%) as compared to ultrasound (98%) [57] (Figure 5.11). This is due to the fact that the CT appearance of gall stones is dependent on the composition and pattern of calcifications, i.e. stones with high calcium content are visible, while those with high cholesterol content are difficult to detect. With MR cholangiopancreatography (MRCP), biliary stones are visible as well-defined, low signal foci outlined by surrounding high signal bile, independent of calcium content [58] (Figure 5.11). Although the spatial resolution is less than with endoscopic retrograde cholangiopancreatography (ERCP), the higher contrast resolution with MRCP allows for detection of stones as small as 2–3 mm; with reported diagnostic accuracy of 89–97% [59–62].

Adenomyomatosis

Adenomyomatosis, a form of hyperplastic cholecytoses, is a common gall-bladder condition, found in up to 5% of cholecystectomy specimens [63]. It is characterized by hyperplastic changes of the gall-bladder wall, including thickening of the muscular layer and mucosal outpouching and overgrowth (Rokitansky–Aschoff sinus). As adenomyomatosis can present in a diffuse, segmental, or localized morphologic pattern, differentiation from gall-bladder carcinoma is important [64]. MR has been shown to be superior to US and CT in the diagnosis of adenomyomatosis, with an accuracy of 93% [65]. Demonstration of the Rokitansky–Aschoff sinuses is the key finding for accurate diagnosis; represented as small, cystic structures in the area of gall-bladder wall thickening, the so-called MR "pearl necklace sign" [63] (Figure 5.12). Mucin-producing well-differentiated gall-bladder adenocarcinomas can rarely mimic this sign [66]; thus, critical evaluation of the cystic changes as well as surveillance may be required.

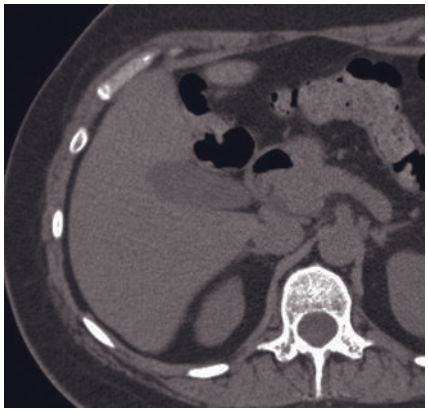
Gall-bladder Carcinoma

Primary carcinoma of the gall bladder has a low overall incidence (up to 1% of autopsy specimens), but is the fifth most common malignancy of the gastrointestinal tract, and is the most common malignant tumor of the biliary tract [67,68]. The most frequent presentation is that of an infiltrating, irregularly-enhancing mass with regions of internal necrosis replacing the gall bladder within the gall-bladder fossa (Figure 5.13). On MR, gall-bladder cancers are T1 hypointense and heterogeneously T2 hyperintense. Associated findings include gall stones and regional spread, including hepatic invasion and/or involvement of vascular, biliary, nodal, and peritoneal structures [69]. An associated finding that is better depicted on CT is the circumferential wall calcifications of a porcelain gall bladder (Figure 5.14).

The diagnosis of gall-bladder cancer can be difficult when confined to the gall-bladder wall (diffuse or segmental), or when obscured by layering gall stones. Normal gall-bladder wall thickness is 3 mm or less, but abnormal thickening can be due to various causes including cholecystitis, adenomyomatosis, suboptimal distension, hepatitis, hypoproteinemia, as well as others. In general, gall-bladder cancer has a tendency for more marked and asymmetric thickening, but accurate diagnosis requires careful inspection for local invasion, metastases, or lymphadenopathy. Intraluminal, polypoid gall-bladder carcinomas are more likely to be well-differentiated, confined by the muscularis propria, and thus have a better prognosis [70].

Cholangiocarcinoma

Cholangiocarcinoma is an epithelial adenocarcinoma that can involve any bile duct segment, but is usually



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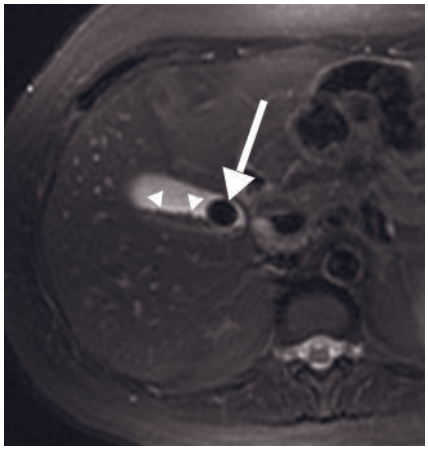

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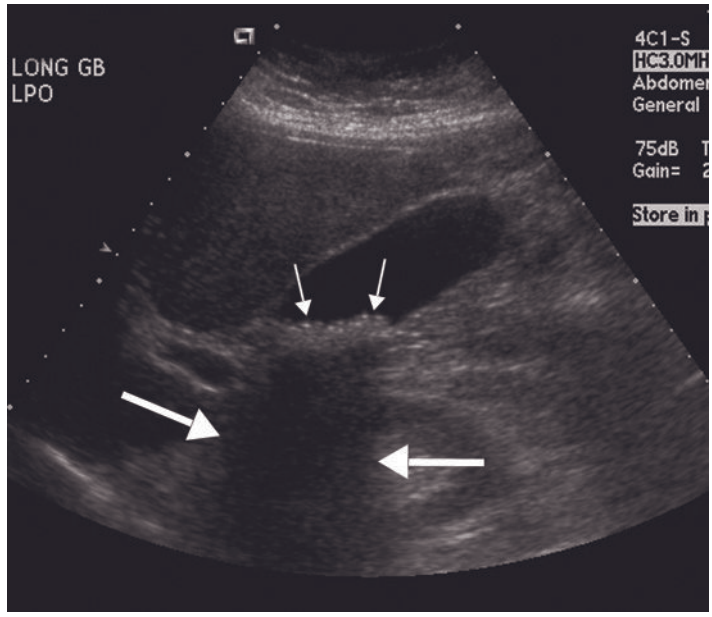


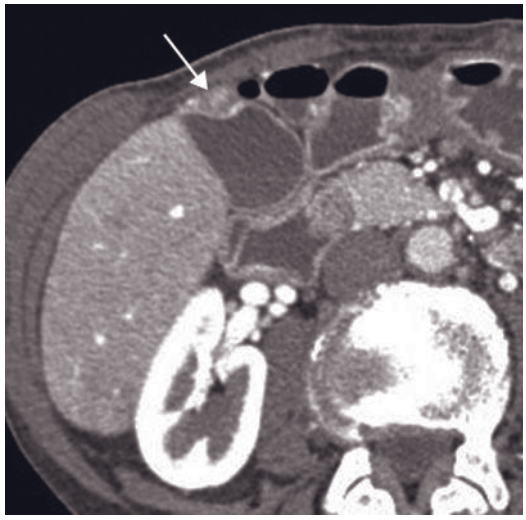
(c)

Figure 5.11 Cholelithiasis. (a) Non-enhanced CT without evidence for gall stones, as most are not radiopaque. (b) However, the corresponding axial, T2-weighted MR image readily shows numerous small gall stones (arrowheads) and a single, larger stone (arrow). (c) Ultrasound image in the same patient also demonstrates numerous, layering echogenic stones (arrows) with characteristic hypoechoic distal shadowing (arrows).

classified as peripheral intrahepatic, hilar, or extrahepatic [71]. Location is an important factor in the growth pattern of this tumor, with peripheral intrahepatic carcinomas often manifesting as a discrete hepatic mass; while hilar and extrahepatic carcinomas more commonly demonstrate an infiltrative pattern.

With both CT and MR, peripheral intrahepatic cholangiocarcinomas typically present as large, well-defined masses with lobulated margins, with an initial peripheral rim, and subsequent progressive, delayed hyperenhancement [72] (Figure 5.15). On T2-weighted sequences, this subtype displays heterogeneous increased signal, with variable amounts of central low signal related to fibrosis. As the imaging and histologic differentiation of this subtype from hepatic metastatic adenocarcinoma remains problematic, reasonable exclusion of an extrahepatic primary is often required [73].

Infiltrating hilar (Klatskin) and extrahepatic carcinomas present with abnormal duct wall thickening (generally > 5 mm) on cross-sectional imaging; with abrupt, irregular, and asymmetric luminal narrowing and upstream duct dilatation. Similar to the peripheral intrahepatic subtype, these forms usually exhibit persistent hyperenhancement on delayed post-contrast sequences.



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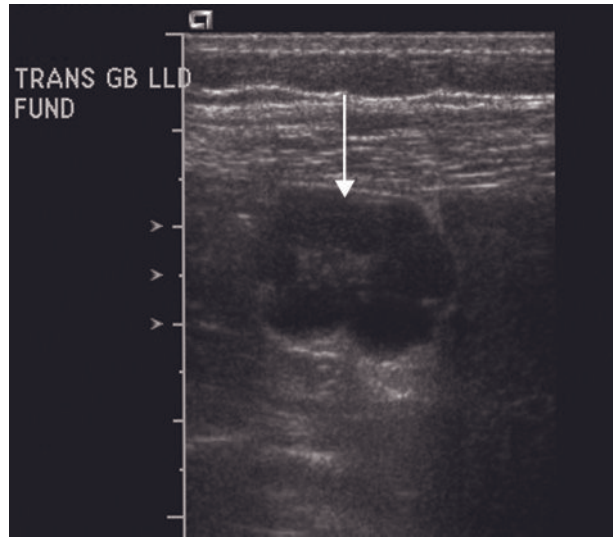

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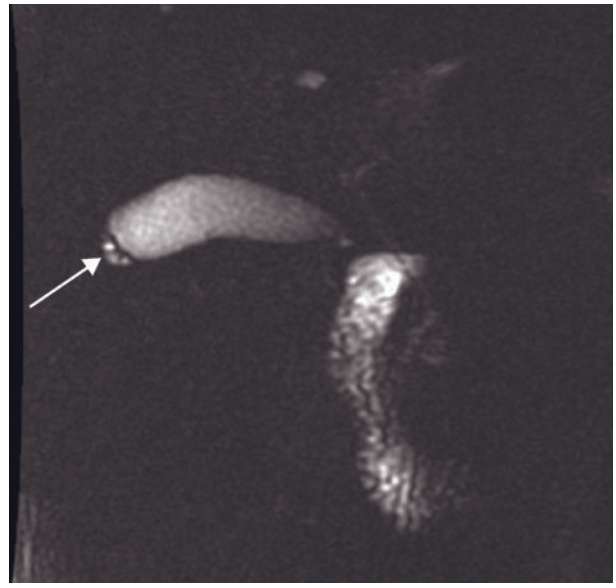


(c)

Figure 5.12 Focal adenomyomatosis. (a) Contrast-enhanced CT shows focal thickening of the gall-bladder fundus (arrow). (b) Corresponding ultrasound and (c) MRCP images demonstrate that the apparent focal thickening on CT is related to a cluster of cystic changes (arrows); incidental focal adenomyomatosis.

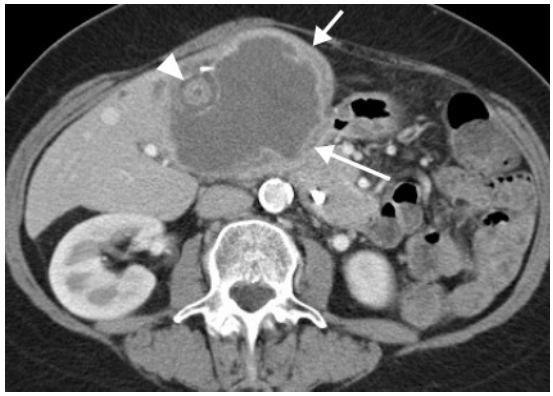


Figure 5.13 Gall-bladder carcinoma. Contrast-enhanced CT image demonstrates a necrotic mass centered at the gall-bladder fossa (arrows). The clue to the correct diagnosis is the lamellated gall stone (arrowhead) associated with the mass.

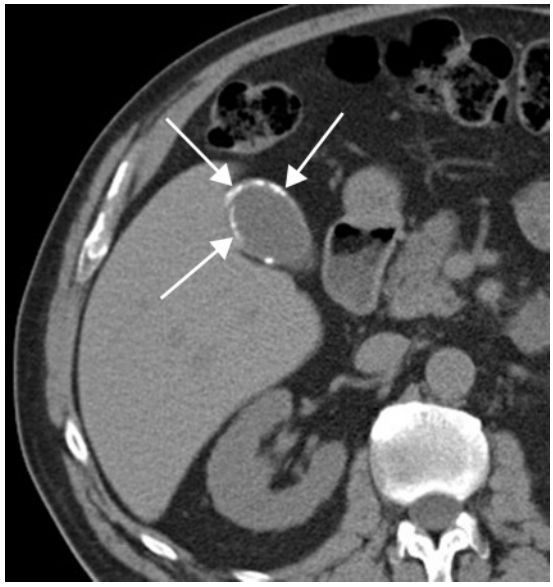
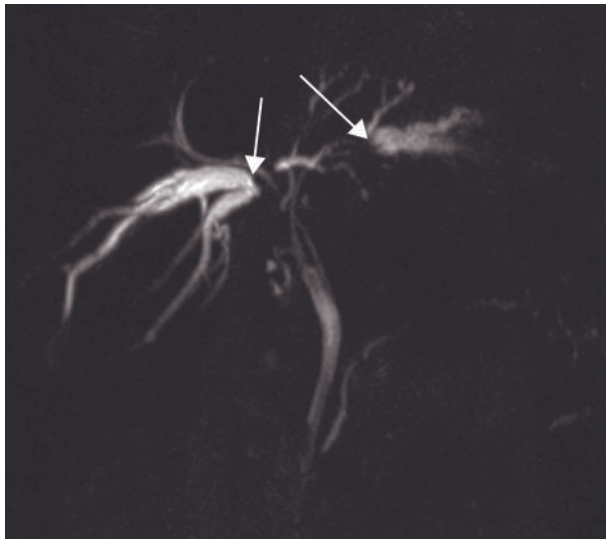


Figure 5.14 Porcelain gall bladder. Non-enhanced CT image demonstrates calcifications outlining the gall-bladder wall (arrows).

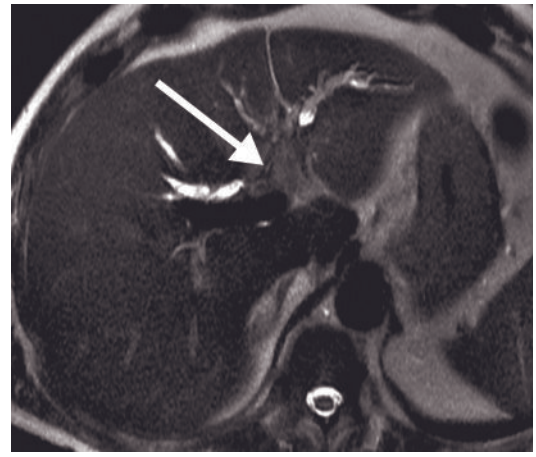
Progressive biliary dilatation on serial exams and relative increased length of the obstructing lesion are helpful findings in differentiating malignant from benign strictures [74].

Primary Sclerosing Cholangitis

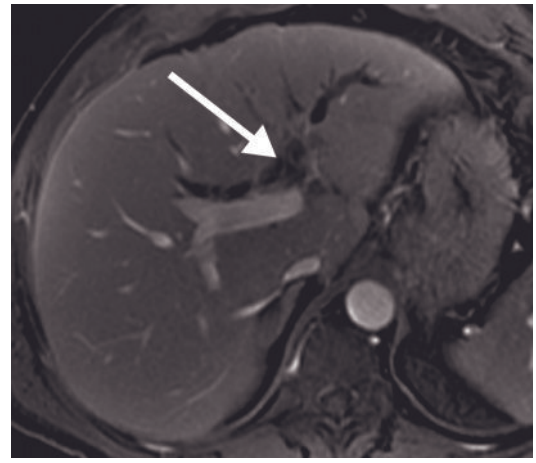
Primary sclerosing cholangitis (PSC) is characterized by progressive inflammation and fibrosis of the liver and bile ducts, resulting in an increased risk of cholangiocarcinoma in 10–15% of patients [75] and eventual liver failure. PSC is a disease of unknown etiology, but is often associated with ulcerative colitis. The CT and MR findings include focal duct wall thickening and stricture, with scattered areas of "skip" biliary dilatation. MRCP can be complementary to ERCP for directly visualizing associated biliary changes of PSC, such as stenosis, dilation, beading, and pruning (Figure 5.16); however, like ERCP, it has limited ability in depicting the duct wall itself or hepatic parenchymal diseases [76]. As this is best



(a)



(b)



(c)

Figure 5.15 Cholangiocarcinoma. (a) 3D MRCP image demonstrates dilated right and left intrahepatic ducts abruptly terminating at the hepatic hilum (arrows). (b) Axial T2-weighted and (c) contrast-enhanced images show the same dilated ducts occluded by an intermediate T2 signal, irregularly enhancing cholangiocarcinoma (arrows).

Figure 5.16 Primary sclerosing cholangitis (PSC). 3D-MRCP image demonstrates random, multifocal intrahepatic biliary duct strictures with intervening mild dilatation (i.e., "beading"); characteristic findings for PSC.

depicted after contrast administration, contrast-enhanced CT or MR sequences are beneficial in the examination of patients with suspected PSC. Imaging features that suggest superimposed cholangiocarcinoma in PSC patients include irregular high-grade ductal narrowing with asymmetric margins and proximal marked ductal dilatation; rapid progression of strictures/duct dilatation; and direct visualization of an underlying polypoid mass, especially those larger than 1 cm in diameter [77].

Take-home points

- MRCP and US are more sensitive for the detection of gall stones than CT.
- MRCP is more sensitive for the detection of choledocholithiasis than either US or CT.
- Gall-bladder adenomyomatosis can be differentiated from gall-bladder carcinoma with either US or MRCP.
- A delayed-enhancing mass and biliary duct dilatation are imaging features of cholangiocarcinoma.

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6

CHAPTER 6

Endoscopic Techniques in Management of the Liver and Biliary Tree: Upper Gastrointestinal Endoscopy

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Summary
Upper gastrointestinal endoscopy is very useful in the management of patients with cirrhosis. Hepatology units should have experienced endoscopic personnel available on call to address variceal (esophageal or gastric) bleeding and preventive measures should be incorporated into standard operating procedures for the care of the patient with cirrhosis. Over the last 10 years, more data have emerged suggesting that active endoscopic management has a role next to accepted pharmacologic intervention for the management of portal hypertension.

Introduction

Upper gastrointestinal endoscopy (UGIE) plays a pivotal role in the management of patients with chronic liver disorders. International guidelines recommend the use of screening UGIE to evaluate patients with cirrhosis for the presence of esophageal varices [1–4]. The ultimate goal is to prevent the index bleeding episode (primary prophylaxis) and, in those who present with bleeding, to control the bleeding episode (active bleeding management) and subsequently proceed to prevent recurrent bleeding (secondary prophylaxis) [2,4]. Gastric varices and portal hypertensive gastropathy are also problems that benefit form judicious use of gastrointestinal imaging. In this chapter the utility of UGIE is discussed in each step of the preventive care of the patient with cirrhosis.

Detection of Esophageal Varices and Primary Prophylaxis

On initial diagnosis of cirrhosis all patients should undergo UGIE to evaluate the stage of portal hypertensive complications [4–6] (Figures 6.1 and 6.2). Recently, the introduction of esophageal capsule endoscopy has led to consideration of this tool as a potential screening modality, despite limitations [7]. The likelihood of diagnosing esophageal varices at this management point is approximately 50%, with a greater incidence in those who have more advanced liver disease [4]. The risk of index variceal bleeding increases as the severity of the

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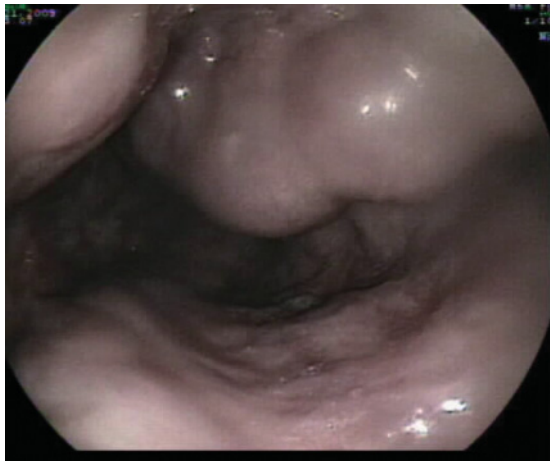

Figure 6.1 Large esophageal varices.

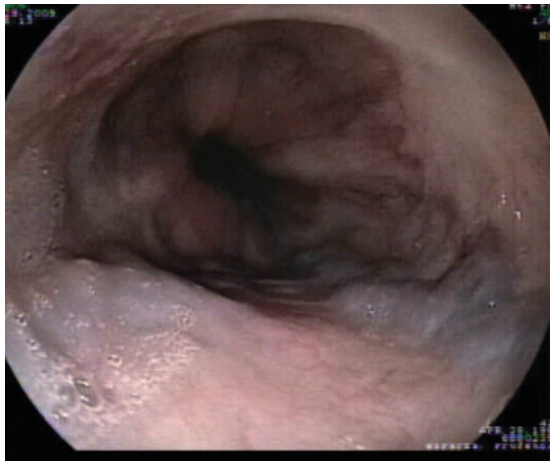

Figure 6.2 Small esophageal varices.

liver disease increases [4,5]. In addition, morphologic features of the varices, such as hematocystic spots and red weals, add predictive value to the endoscopic evaluation [5]. As the value of β blockers in prevention of variceal bleeding has been confirmed [1,4,6] and liver transplantation becomes widely used, the impact of endoscopic modalities in the prophylaxis of variceal bleeding has received more attention [6,8–10].

On detection of varices, the aim of therapy becomes prevention of bleeding, because the event itself, even when controlled hemostatically, can lead to decompensation of the patient with cirrhosis [4,6]. β Blockers have a long and well-established track record of effectiveness, particularly in patients with large varices who can adhere to this regimen [1]. However, many practical problems arise due to the inability of a significant percentage of the target population to tolerate this pharmacologic approach (10–20%) [4–6]. UGIE-driven therapies then take a primary role in the management of these patients. It is now acceptable to proceed to a therapeutic maneuver endoscopically if patients have large, high-risk varices when pharmacologic approaches fail [4].

Esophageal Sclerotherapy

Direct (variceal) or indirect (paraesophageal) injection of sclerosing agents has been extensively studied [1]. Although this technique remains a valuable rescue modality when treating active bleeding, prophylactic treatment using it has not held up well to scrutiny. A large multicenter Veterans' Administration Medical Center trial comparing sclerotherapy with sham treatment was stopped because there was higher mortality in the treatment group [11]. Meta-analytic reviews have been mixed, yet the latest data suggest that β blockers are preferable to esophageal sclerotherapy (ES) when primary prophylaxis is the aim [12,13].

Variceal Ligation

The use of esophageal band ligation (EBL) has revolutionized the management of esophageal varices [1]. In the prophylactic approach, this technique has far fewer local complications than sclerotherapy and as such its use in randomized trials has translated into significantly lower primary bleeding rates and very acceptable bleeding-related morbidity and mortality [14,15]. In direct comparison of the two endoscopic modalities, EBL and ES have not yielded significant differences in clinical outcomes. A European trial found that the number of sessions to eradication of varices was lower in the EBL group and the recurrence of varices was significantly higher in the ES arm. Efficacy was not different [16].

Compared with observation, EBL clearly changes the incidence of bleeding and may improve survival [17,18]. Pharmacologic approaches have been compared with EBL and the outcomes have been favorable [18–20]. Starting with the landmark work of Sarin and colleagues, β blockers have been found to be less effective

in preventing index bleeding in patients with cirrhosis with similar overall mortality [19,20]. A three-arm randomized study has been conducted, comparing nitrates, β blockers, and EBL [21]. This study found that the rates of bleeding were higher in those patients receiving the β blockers and nitrates, with high rates of discontinuation of pharmacologic therapy in favor of EBL. The mortality in all three groups was comparable but EBL was superior to nitrates and at least as good as β blockers [21].

When EBL is compared with observation, a recent meta-analysis favors its use [18]. The benefit is evident with respect to first bleed, mortality related to bleeding, and overall mortality. The benefit of EBL is not as significant when β blockers are added to the mix [18]. Analysis of four randomized trials revealed that only first variceal bleeds were reduced by the use of EBL compared with propranolol. The on-trial benefit of propranolol has to be studied carefully because there appears to be a significant failure rate of pharmacologic management, as evidenced by use of EBL in prophylactic efforts, and possibly better results with EBL [18,22].

In practical terms, UGIE should be used to evaluate the esophagus for varices on diagnosis of cirrhosis. If varices are seen on endoscopy, an effort has to be made to classify them as large, medium, or small, and to attribute the presence of stigmata of high risk [3,4]. In those patients with decompensated liver disease and large, high-risk varices, β blockers should be used if appropriate [3,4]. If β blockers cannot be used long term or if decompensation occurs, EBL should be pursued to increase the chance of bleeding-free survival [3,4]. The interval between banding episodes has been suggested as frequently as every 2 weeks [4], although, in the author's experience, every 4 weeks is more likely to lead to safe eradication without bleeding from shallow ulcers created by banding. This issue has also been raised in the literature [23] (Figure 6.3).

Active Bleeding from Esophageal Varices

Endoscopic treatment for known or suspected variceal bleeding is a must in a modern liver unit [2–4]. There is ample evidence that arrest of bleeding can be achieved without increased mortality from bleeding if endoscopic therapy is used [2]. However, the basics in bleeding management apply in this setting as they do in all cases of gastrointestinal bleeding [3,4]. First and foremost, the patient's airway, cardiorespiratory resuscitation, and spontaneous bacterial peritonitis prophylaxis have to be addressed promptly to maximize survival rates and decrease the impact of the bleeding episode on the cirrhotic liver [2–4,24].

Adjuvant pharmacotherapy to support endoscopy, either by arrest of active bleeding or by a decreased rebleeding rate, remains a widely used approach, although the practice varies widely. In the USA, octreotide and vasopressin remain approved by the Food and Drug Administration (FDA) (although off label) for this purpose. Elsewhere, arginine vasopressin, somatostatin, and other analogs of somatostatin such as vapreotide can be used for this purpose [2–4,25]. Generally, most endoscopists like to start treatment with a continuous infusion of the adjuvant agent before initiation of endoscopic treatment, and the agent of choice is maintained until discharge from the hospital or 5 days from index endoscopy, whichever comes first. β Blockers should be initiated as soon as the patient achieves hemodynamic stability [2–4,25]. Patients with impaired renal function and cardiovascular disease should be monitored closely in the intensive care unit (ICU) setting to prevent comorbid complications. There is still significant controversy about the preventive use of endotracheal intubation to prevent aspiration, yet the assessment of the patient by the ICU team before initiation of endoscopy is prudent if intubation is not being performed.

Endoscopic Technique

Endoscopic Band Ligation

Ligation has become the leading modality for management of acute variceal bleeding. Its major disadvantage is the possibility of limited visibility due to the constraints of the ligator set-up, particularly in the setting of torrential bleeds [26]. However, under most circumstances, EBL is very useful and very likely to control active bleeding. The endoscopy support team should be prepared to switch to sclerotherapy as needed to control bleeding circumstances where ligation fails. The advantages of ligation include the rapid healing of the mucosa

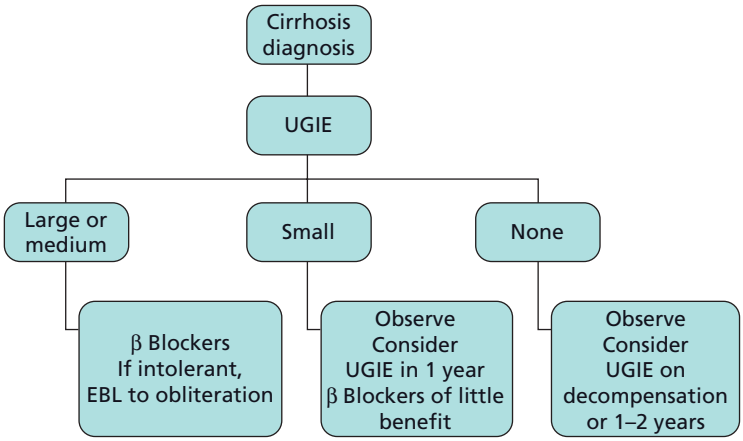

Figure 6.3 Algorithm for the management of patients diagnosed with cirrhosis with respect to portal hypertension. EBL, endoscopic band ligation; UGIE, upper gastrointestinal endoscopy.

and the much lower risk of perforation and deep ulceration frequently encountered when ES is used as the primary modality [26].

Many small studies have compared EBL with ES and the techniques are comparable in arrest of bleeding. Compared with vasoactive agents, a meta-analysis found EBL superior to vasopressin/arginine, vasopressin, or somatostatin analogs used alone [27].

Secondary Prophylaxis

As with the primary prophylaxis setting, the use of EBL is felt to be superior to sclerotherapy. The most compelling argument in favor of EBL compared with sclerotherapy is the very limited incidence of esophageal complications, which include ulceration structuring and perioperative chest pain and perforation. The number of sessions required to obliterate varices with EBL been reported to be much lower. The incidence of re-bleeding when EBL is the primary modality is lower than when ES is used.

The management of these patients should include β blockers (if tolerated) until the varices are felt to be eradicated. The sessions should be spaced every 2–3 weeks in order to prevent re-bleeding, and at the same time avoid iatrogenic injury to recently treated areas. Most of these interventions require an average of three sessions to eradicate varices and this is a significant advantage over the use of ES. It is prudent to re-evaluate the esophagus 6–12 months after completion to ensure eradication of the varices. Clinical judgment may dictate yearly assessment, particularly if the liver disease worsens. β Blockers can be stopped once eradication has been achieved.

Gastric Varices

The incidence of gastric varices is approximately 20% in the setting of portal hypertension, with an expectation of bleeding in 20–25% of those affected [5] (Figure 6.4). Recurrence and mortality from bleeding from gastric varices are felt to be higher than in patients with esophageal varices, although the data on these patients are scanty [28]. Injection of sclerosants and ligation carries prohibitive risk and thus has limitations. Primary prophylaxis is not generally recommended because there are no data to support this practice. There is significant excitement about injection of two cyanoacrylate compounds into varices as an intervention on the active bleeding setting or as a secondary prophylactic measure [28].

N-Butyl-2-cyanoacrylate and 2-octyl-cyanoacrylate have been studied in small series, with conclusions that control of acute bleeding and gastric variceal obliteration are achieved in a large percentage of patients [29,30]. Cost analyses have been limited, but may point toward a reasonable impact on resource expenditure if transjugular intrahepatic portal shunt can be avoided [31]. There are risks of embolization of cyanoacrylate and these risks should be discussed with the patient before the use of these compounds, particularly in the USA where these agents are not approved for this indication by the FDA.

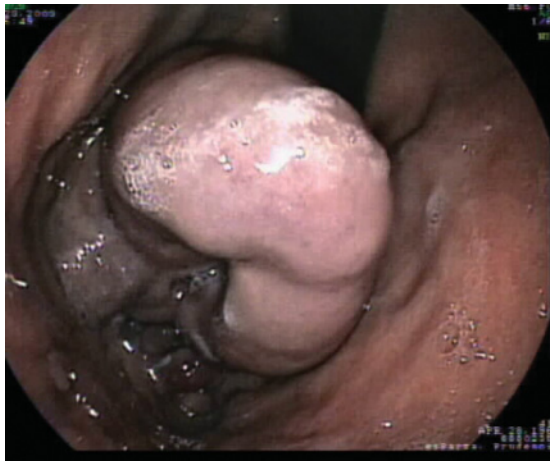

Figure 6.4 Large gastric varix.

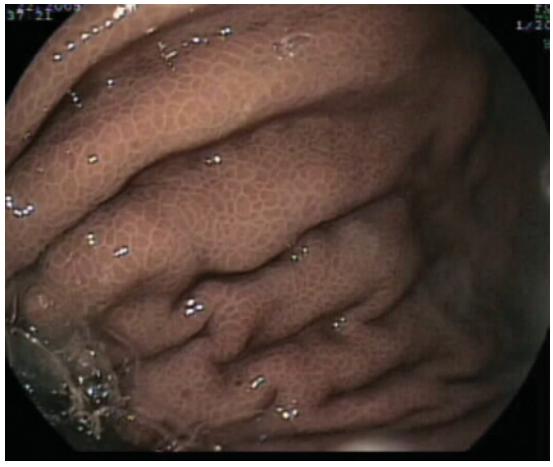

Figure 6.5 Portal hypertensive gastropathy.

Gastric Antral Vascular Ectasia

This entity is commonly encountered in patients with cirrhosis and commonly blamed for bleeding complications [32] (Figure 6.5). The reality at this time is that this entity may either coexist with portal hypertension-related gastropathy or be a separate entity that complicates the management of portal hypertension [32].

The management of anemia related to gastric antral vascular ectasia (GAVE) and portal hypertensive gastropathy (PHTNG) may involve plasma argon coagulation or ligation, both well tolerated and, despite limited data, successful in those treated [33]. Liver transplantation appears to be the best approach to eliminate this complication of chronic liver disease; shunting procedures have been less than successful in reducing bleeding from GAVE when performed in efforts to address chronic bleeding, adding value to histologic data that PHTNG and GAVE may be distinct entities [34].

Take-home points

- All patients diagnosed with cirrhosis should undergo a baseline upper endoscopy.
- If varices are diagnosed, their size should be assessed. Large and medium-sized varices should lead to initiation of β blockers (when appropriate). If variceal bleeding has already occurred, esophageal band ligation should be used to promptly eradicate varices.
- Active variceal bleeding necessitates careful management, usually in the ICU, with active endoscopic management but also with optimal upper endoscopy management to minimize bleeding and prevent morbidity.
- Secondary prophylaxis of varices should be carried out after index bleeding. Esophageal band ligation is the safest modality and usually requires three sessions to eradicate varices.

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7

CHAPTER 7

Endoscopic Techniques in Management of the Liver and Biliary Tree: Endoscopic Retrograde Cholangiopancreatography and Biliary Manometry

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Summary

Endoscopic retrograde cholangiopancreatography (ERCP) is both an endoscopic and a radiological procedure. Although ERCP was once used as a diagnostic procedure, it is now performed almost exclusively for therapeutic purposes. The main therapeutic applications in the biliary tree are palliation of malignant biliary obstruction by biliary stent placement and removal of bile duct stones. There are, however, many other biliary applications. Biliary manometry, performed at the time of diagnostic ERCP, allows the diagnosis of specific types of sphincter of Oddi dysfunction and directs treatment toward endoscopic biliary sphincterotomy.

Case

A 35-year-old woman underwent cholecystectomy 2 years before intermittent upper abdominal pain and evidence of gall-bladder sludge by abdominal ultrasonography. She was pain free until months ago when symptoms recurred. A magnetic resonance cholangiopancreatography (MRCP) is normal. During attacks of pain she was seen in the emergency room where serum transaminases were elevated more than three times. The lab results returned to normal between attacks. An ERCP with biliary sphincter of Oddi manometry is performed. The mean basal sphincter pressure is 85 mmHg (normal ≤40 mmHg). A biliary sphincterotomy is performed. She has been asymptomatic for 6 months.

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Equipment and Review of Technology

Endoscopic retrograde cholangiopancreatography (ERCP) has evolved from a purely diagnostic to an almost exclusively therapeutic procedure. The diagnostic applications of biliary ERCP are:

- Primary sclerosing cholangitis
- Sphincter of Oddi dysfunction.

The therapeutic applications of biliary ERCP are:

- Palliation of malignant biliary obstruction
- Removal of bile duct stones
- Treatment of bile duct leaks
- Treatment of benign biliary strictures
- Endoscopic resection of ampullary adenomas.

ERCP is commonly performed using moderate sedation, although in patients with greater severity of illness and

in anticipated complex cases, involvement of an anesthesiologist is often necessary. ERCP is performed with a side-viewing endoscope that has an elevator to allow identification of the major papillae. ERCP is performed in a fluoroscopically equipped room. Catheters and guidewires are passed into the bile duct under endoscopic and fluoroscopic guidance. A variety of catheters, guidewires, stone extraction balloons and baskets, dilating balloons, and stents are available to allow therapeutic interventions to be performed. In addition, small-caliber endoscopes (cholangioscopes) are available that can be passed into the bile duct for direct visualization of biliary pathology. Diagnostic ERCP is used for the diagnosis of primary sclerosing cholangitis (PSC) when other imaging techniques have been non-diagnostic and for diagnosis of suspected sphincter of Oddi dysfunction through the use of manometry. There are a variety of biliary indications for ERCP, as indicated above.

How to Perform ERCP

The side-viewing endoscope is passed transorally to the level of the major papillae. At this point the endoscope is in a long position with a loop in the stomach and is reduced to a shortened position. The catheter is passed through the working channel and directed toward the bile duct access with the elevator. Contrast and guidewires are used to selectively cannulate the bile duct. After the catheter has passed deeply into the biliary tree, endoscopic therapy can be undertaken. For bile duct stones a biliary sphincterotomy is almost always performed (see Bile Duct Stones below) to enlarge the papillary opening. This is performed using a sphincterotome and electrocautery. Strictures are traversed with a guidewire and stents placed across the stricture. For benign strictures, balloon dilation using rigid balloons is undertaken.

Bile Duct Stones

ERCP is usually performed in patients with known choledocholithiasis or in those with at least a moderate clinical suspicion of choledocholithiasis. In those with a low clinical suspicion, it is recommended that alternate, non-invasive imaging studies be undertaken (MRCP, multidimensional computed tomography – MDCT) or less-invasive endoscopic ultrasonography (EUS) be performed to minimize the potential for ERCP complications. In patients with low clinical suspicion for choledocholithiasis in whom cholecystectomy is planned, intraoperative cholangiography can be performed and, if stones are identified, laparoscopic exploration and stone removal can be carried out. ERCP can then be reserved for those in whom stones are not extracted.

The standard method for stone removal is endoscopic biliary sphincterotomy to allow enlargement of the papilla opening and subsequent extraction of stones using balloons or baskets (Figure 7.1 and Video 1). Using this approach, more than 80% of all stones can be successfully removed [1]. Larger stones (discussed separately) may require additional techniques for removal.

An alternative to biliary sphincterotomy is dilation of the papilla which can be performed using small-diameter balloons (4–8 mm). This method was introduced as a way to preserve sphincter function, especially in young patients. The stones are removed using standard balloon or basket techniques. Most of the literature regarding the use of balloon sphincteroplasty originated from outside the USA. Meta-analyses of randomized trials of balloon sphincteroplasty and sphincterotomy showed that the rate of pancreatitis and need for mechanical lithotripsy is significantly higher in the sphincteroplasty group, but the bleeding complication is significantly lower in the sphincteroplasty group (almost 0%) [2]. One randomized trial in the USA comparing sphincteroplasty and sphincterotomy was prematurely closed due to two deaths in young patients from post-ERCP pancreatitis in the sphincteroplasty group [3]. However, sphincteroplasty still remains an alternative for patients with coagulopathy underlying cirrhosis (particularly Child C type) and in those patients with altered anatomy (e.g., Billroth II procedure) where sphincterotomy is technically difficult. Placement of a prophylactic pancreatic duct stent (see Complications) may prevent pancreatitis following a sphincteroplasty.

Removal of large bile duct stones (≥1.5 cm in diameter) may require additional techniques, one of which is lithotripsy. Lithotripsy can be in the form of mechanical lithotripsy where the stone is captured in a specialized large basket and crushed. The fragments are removed using standard baskets or retrieval balloons. Lithotripsy can also be performed using laser or electrohydraulic catheters to fragment stones within the bile duct. Laser or electrohydraulic lithotripsy is performed under direct endoscopic visualization by passing a choledochoscope

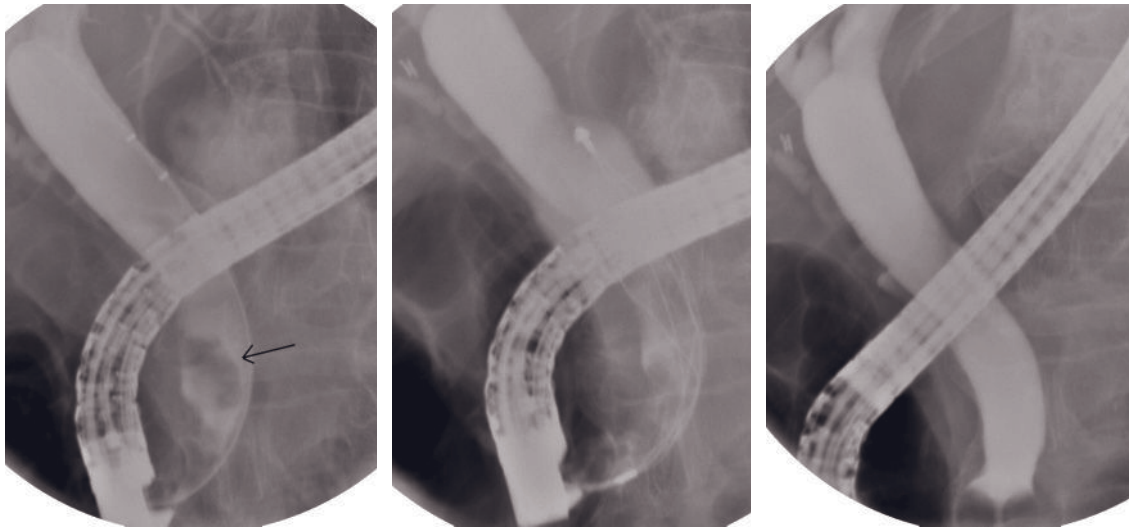


Figure 7.1 Removal of bile duct stones. (a) Radiographic image shows stone in distal bile duct (arrow); (b) Basket with stone captured; (c) follow-up cholangiography without bile duct stones.

into the bile duct. This is necessary to prevent injury to the bile duct wall by ensuring that the energy is directed at the stone. A relatively new technique to facilitate removal of large bile duct stones is biliary sphincterotomy followed by dilation of the lower bile duct and sphincterotomy site using a large-diameter dilating balloon (≥12 mm). This is performed because the limitation to large stone removal is the diameter of the distal bile duct and the size of the sphincterotomy. This technique allows removal of large stones and decreases the need for mechanical lithotripsy [4]. This large-diameter dilation method appears to be safe without an increased risk in post-ERCP pancreatitis [5], as occurs with primary sphincteroplasty. If large stones cannot be cleared from the bile duct, a biliary stent is placed to ensure relief of obstruction. Additional procedures are performed electively to remove residual stones and/or fragments.

Bile Leaks

Bile leaks arise after surgery and trauma. The most common surgery that results in bile duct leaks is cholecystectomy. These leaks arise from either the cystic duct or the duct of Luschka, a small intrahepatic duct that runs though the gall-bladder fossa. These smaller leaks can usually be managed with biliary sphincterotomy alone and/or by placement of small-diameter (7 French or 7 Fr) plastic biliary stents. This diverts bile away from the leak and into the duodenum and relieves the effect of the an otherwise high-pressure biliary sphincter. More complex leaks usually require placement of one or more large-diameter plastic biliary stents (10 Fr) in combination with biliary sphincterotomy.

Primary Sclerosing Cholangitis

PSC is a fibrosing disease of the bile ducts. Some patients develop dominant strictures and/or biliary stones, and such patients usually present with worsening biliary obstruction and/or cholangitis. Patients with PSC are at elevated risk of developing cholangiocarcinoma, which should be considered in any PSC patients with dominant strictures. Biliary brush cytology is performed at the time of ERCP in these patients, but has a low sensitivity in the setting of PSC. Recently, fluorescence *in situ* hybridization (FISH) of cytologic specimens has been shown to have a high sensitivity for the detection of underlying cholangiocarcinoma in PSC patients [6]. Cholangioscopy

may also improve the detection of cholangiocarcinoma in these patients [7].

Endoscopic treatment of dominant strictures involves the use of balloon dilation, often in combination with short-term (≤8 weeks), large-bore (10 Fr) stent placement [8]. Endpoints after endoscopic therapy have included clinical, biochemical, and radiologic improvement and ranges from 65% to 100% [9].

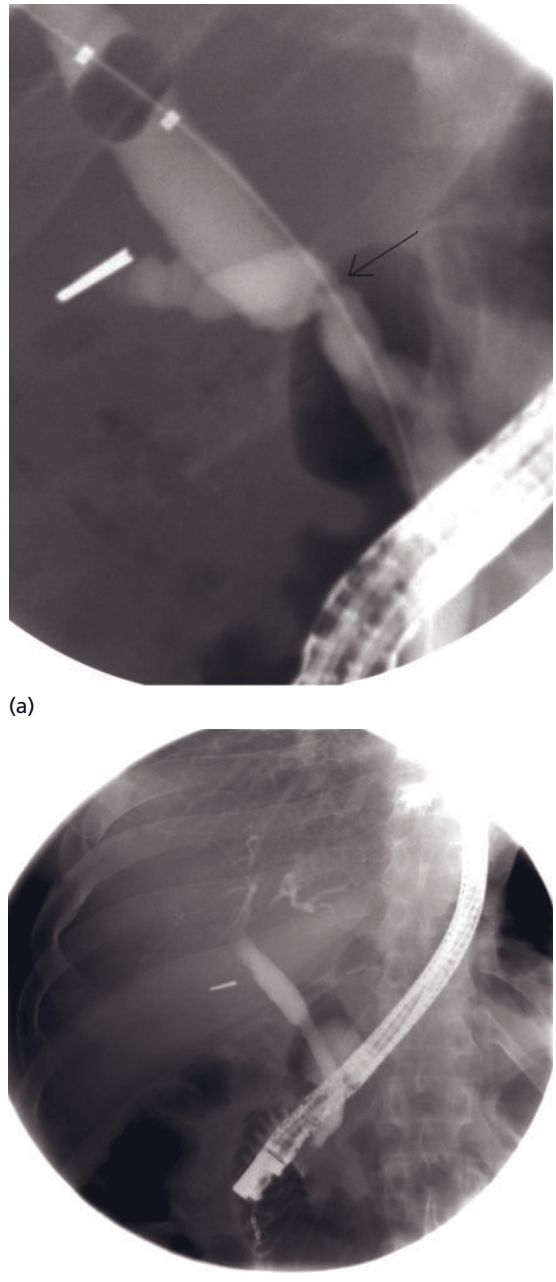
Benign Biliary Obstruction

Benign biliary strictures are caused by a variety of disorders and thus the response to endoscopic therapy varies. Endoscopic therapy consists of balloon dilation followed by placement of plastic biliary stents (Figure 7.2). It is now accepted that, for most causes of benign strictures, placement of multiple side-by-side large-bore plastic stents over the course of several endoscopic sessions, with stent exchanges and replacement for up to 1 year, allows a higher rate of successful stricture resolution than when only one or two plastic biliary stents are placed [10].

Chronic pancreatitis produces distal bile duct strictures that are usually refractory to endoscopic therapy with single plastic stents, particularly in those patients with chronic calcific pancreatitis. Multiple side-by-side plastic stents can also be used in these patients. However, recently covered, self-expandable metal stents (SEMS) have been used for the treatment of chronic pancreatitis-induced bile duct strictures [11]. The large diameter of these stents (10 mm) dilates the stricture. These stents are potentially removable because the covering prevents the stent from embedding in the tissue. The stent is endoscopically removed 3–6 months later. Results using this approach are promising, although these devices are not approved for use in benign disease by the Food and Drug Administration (FDA).

Indeterminate Biliary Obstruction

Some patients with biliary strictures cannot be readily classified into benign or malignant based on imaging studies and tissue sampling. Tissue sampling techniques during ERCP consist of wire-guided biliary brush cytology and intraductal forceps biopsy [12]. Additional techniques to assess strictures include intraductal ultra-



(a)

(b)

Figure 7.2 Treatment of benign biliary stricture with multiple biliary stents. (a) Anastomotic stricture (arrow) after transplantation; (b) after balloon dilation, multiple 10 French plastic stents were placed as seen. The stricture resolved on follow-up cholangiogram.

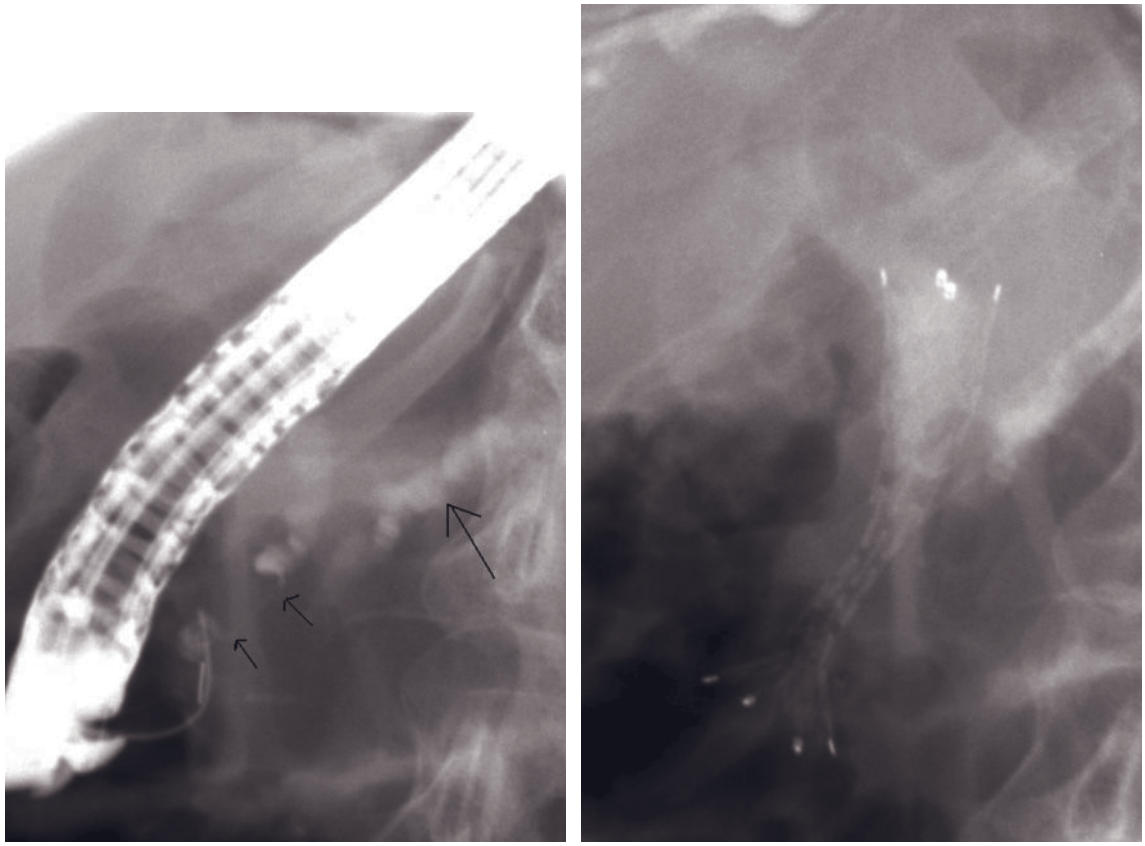
sonography and direct cholangioscopy with or without directed biopsy. Recently, the use of intraductal confocal endomicroscopy probes has demonstrated promise [13]. In a small percentage of patients the diagnosis still remains unclear and in some cases the final diagnosis can be established only during long-term follow-up or at surgical exploration and resection.

Malignant Biliary Obstruction

Endoscopic relief of malignant biliary obstruction is achieved by placement of large-bore plastic or self-expandable metal stents across the malignant stricture (Figure 7.3 and Video 2). The approach to the patient depends on whether the stricture is distal to or involves the bifurcation.

Distal Bile Duct Obstruction (Non-hilar): Preoperative Use

Carcinoma of the head of the pancreas is the most common cause of distal bile duct obstruction. In patients with known pancreatic cancer who are to undergo surgical resection (pancreaticoduodenectomy or Whipple procedure) within a short time, the routine use of preoperative ERCP for biliary decompression is discouraged. There are several studies showing that this approach does not improve surgical outcome and may cause postoperative morbidity, and complications from ERCP may delay or prevent surgical resection. The indications for



(a) (b)

Figure 7.3 Expandable metal biliary stent placement for unresectable pancreatic cancer. (a) Initial injection reveals tight distal bile duct stricture (two arrows). A dilated pancreatic duct is seen (large arrow, right). (b) Immediately after placement of a self-expandable metal stent.

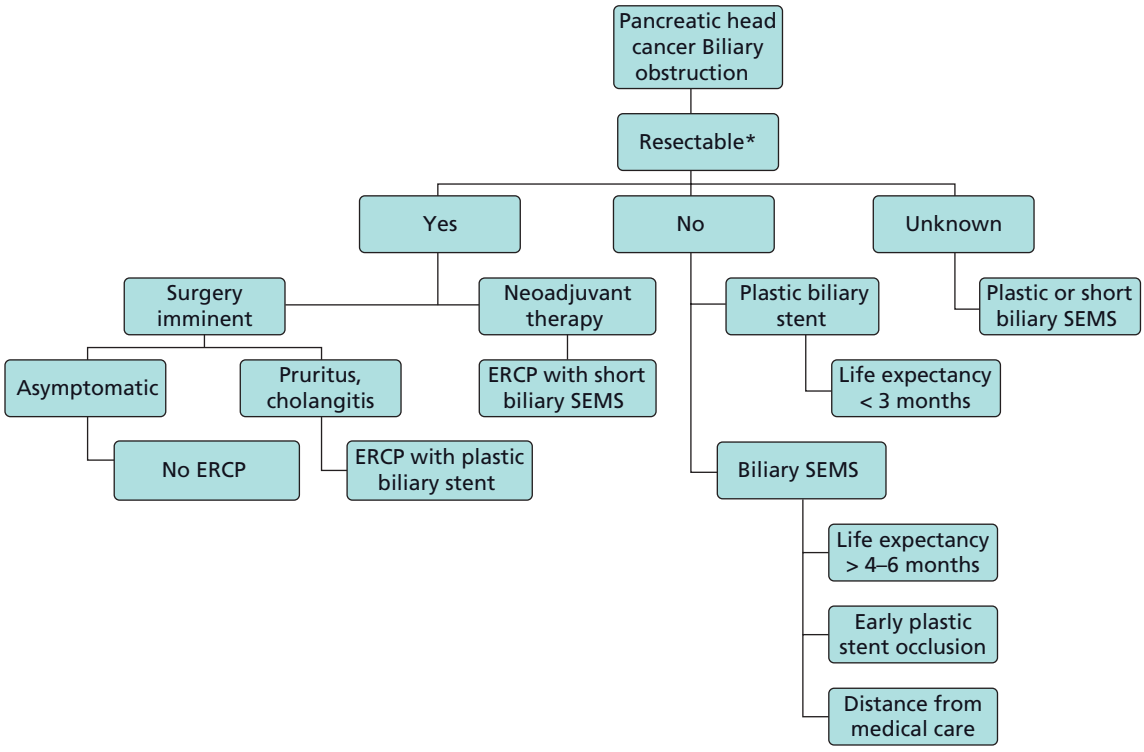


Figure 7.4 Algorithm for biliary stenting. *After staging, with or without tissue acquisition based on local expertise and practice. ERCP, endoscopic retrograde cholangiopancreatography; SEMS, self-expandable metal stent (covered or uncovered).

preoperative ERCP include cholangitis and pruritus with delay in operation. In addition, in centers where neoadjuvant chemoradiation is administered, stent placement is indicated because the time to resection is usually prolonged. If this approach is undertaken, the use of a short-length SEMS (covered or uncovered) appears to be the best option because one study showed a high rate of plastic stent occlusion compared with those who received SEMS in patients with pancreatic cancer undergoing preoperative chemoradiation [14]. Uncovered SEMS are resected along with the tumor at the time of resection. In one study, covered SEMS were placed in all patients with pancreatic cancer regardless of respectability; this was found this to be a cost-effective approach over plastic stents [15]. An algorithmic approach to biliary stenting is presented in Figure 7.4.

Distal Biliary Obstruction—Palliative

ERCP and biliary stent placement has been shown in randomized trials to provide equal palliation to surgical bypass (Table 7.1) [16]. Biliary stents can be safely placed in an outpatient setting. The comparative studies of endoscopy and surgery for palliation of distal biliary obstruction were performed using plastic stents, before the advent of SEMS. The main limitation to plastic stent placement is stent occlusion as a result of bacterial biofilm and/or reflux of vegetable matter. Larger-diameter plastic stents have a longer patency than smaller stents, but the channel of the endoscope is a limitation to further increasing the diameter of the stent. SEMS, which have a small pre-deployment delivery system and a larger diameter, have superior patency rates to plastic stents (Table 7.1) [16]. However, the comparative trials of surgery and endoscopy were performed with plastic biliary stents before the advent of metal stents. The lower initial hospital stay in the endoscopy group was offset by the need for subsequent hospitalization and subsequent ERCP to manage stent occlusion. The median time for stent occlusion for standard large-bore stents is approximately 3 months. Stent occlusion results in recurrent

Table 7.1 Evidence-based therapeutics.

- ERCP is effective as surgical bypass in the palliation of distal malignant biliary obstruction
- Self-expandable metal biliary stents have a significantly longer patency than plastic biliary stents for distal biliary obstruction
- Covered metal stents have not been definitely proven to prolong patency over uncovered metal stents but have a higher rate of migration and possibly a higher rate of cholecystitis
- Endoscopic biliary balloon sphincteroplasty for removal of bile duct stones is associated with a significantly higher rate of post-ERCP pancreatitis but a significantly lower rate of bleeding than biliary sphincterotomy
- Sphincter of Oddi dysfunction clinical type II patients who have abnormally high biliary pressures respond to endoscopic biliary sphincterotomy significantly more than those with normal biliary sphincter pressures

jaundice, usually with cholangitis. SEMS have overcome the problem of bacterial biofilm and randomized controlled trials have shown superior patency rates to plastic stents [16]. As the costs of SEMS are much greater than the cost of plastic stents, SEMS are cost-effective only if the patient lives more than 3–6 months. Therefore, projected life expectancy is taken into consideration when choosing between plastic stents and SEMS. Other factors to be considered include patient compliance, ability to return for care, and the development of early plastic stent occlusion. Uncovered SEMS occlusion is generally easily managed with placement of a plastic stent or another SEMS within the existing one. More recently, covered metal stents have been developed in an attempt to overcome occlusion due to tumor overgrowth and tissue hyperplasia. Some early comparative studies showed prolonged patency with covered compared with uncovered SEMS, although this has not been firmly established (Table 7.1) [17]. Covered SEMS are associated with higher migration rates and possibly an increased risk for acute cholecystitis.

Endoscopic Palliation of Hilar Biliary obstruction

Hilar strictures may be due to cholangiocarcinoma or metastatic diseases. The clinical success rates for achieving adequate palliation for hilar tumors is less than that for distal tumors. In addition, technical success rates for placing stents into both sides of the liver (right and left hepatic ducts, bilateral placement) and endoscopic stent placement are lower. It has been shown that most patients with hilar biliary obstruction will be adequately palliated when only one side of the liver (unilateral drainage) is drained, assuming that only one side has been accessed and contaminated [18]. Patients who have had contrast instilled in both systems require stenting of both systems to prevent cholangitis. Recent studies suggest that SEMS are also superior to plastic stents in patients with hilar biliary obstruction. In a recent prospective observational cohort study in patients with hilar tumors treated with plastic stents or SEMS, patients with SEMS had significantly less post-procedural complications and need for percutaneous drainage [19]. This suggests that metal stents may offer the same benefits in hilar biliary obstruction as in distal biliary obstruction.

In some centers, percutaneous management of hilar tumors is preferred over endoscopic management because hilar tumors are more difficult to stent endoscopically than distal tumors. There are few comparative studies of endoscopic and percutaneous approaches to hilar tumors. In one study the outcome after endoscopic and percutaneous approaches to hilar cholangiocarcinoma using only SEMS found that the rate of successful biliary decompression was significantly higher in the percutaneous SEMS group than in the endoscopic SEMS group [20]. Median survival of patients in whom biliary drainage was initially successful, regardless of which procedure was used, was much longer than that of patients who had failed biliary drainage. In addition, once successful biliary decompression had been achieved, median survival and stent patency duration were similar.

In summary, in most patients with unresectable hilar cholangiocarcinoma who are undergoing ERCP for palliation, it is recommended that minimal contrast injection be confined to one side of the liver and followed by unilateral stenting of that side. A pre-ERCP abdominal CT may reveal atrophy of one lobe, and this lobe should not be manipulated or stented because contamination will require drainage to prevent cholangitis, but will not likely add to effective reduction in bilirubin and subsequent palliation. Also magnetic resonance imaging can define the anatomy before ERCP. One stent, plastic or metal, is usually sufficient to achieve palliation. Expandable metal stents appear to offer superior palliation. Finally, from an endoscopic perspective, hilar tumors are

more technically difficult to drain successfully than nonhilar tumors.

Photodynamic therapy (PDT) is the intravenous infusion of a drug that is inactive until exposed to light of a specific wavelength. Endoscopically, laser fibers are passed into the bile duct to the site of the obstruction and light is delivered to the tumor. PDT has been used for palliation of patients with unresectable hilar cholangiocarcinoma who did not improve their jaundice by at least 50% after adequate endoscopic placement of bilateral plastic stents [21]. Significant improvement in cholestasis, quality of life, and survival (compared with historical controls) has been demonstrated using PDT and can be maintained for an extended period. The main side effect of PDT is photosensitivity to ambient light. PDT for cholangiocarcinoma is generally performed in selected centers where this expertise is available.

Sphincter of Oddi Dysfunction

Biliary sphincter of Oddi dysfunction (SOD) is classified clinically into types I, II, and III [22,23]. All three types are defined by characteristic intermittent biliary abdominal pain. Sphincter of Oddi manometry (SOM) is traditionally performed during ERCP by passing water-perfused catheters into the bile duct and/or pancreatic duct to allow measurement of the biliary and/or pancreatic sphincter pressure, respectively. The pressure across the sphincter is compared with intraduodenal pressure. More recently, solid-state catheters have been introduced, although water-perfused catheters are still widely used. Type I SOD is associated with objective abnormalities in laboratory tests during attacks and an abnormally dilated extrahepatic bile duct on imaging studies, and can be considered synonymous with papillary stenosis. Type II SOD has either an abnormal laboratory test or a dilated bile duct. Type III SOD has pain only. Type I SOD patients almost invariably respond to endoscopic biliary sphincterotomy and do not require SOM for diagnosis [22]. Type II SOD patients who have high basal sphincter pressures (>40 mmHg) at SOM have a higher response to biliary sphincterotomy than those without elevated pressures (see Table 7.1) [22]. Type III SOD patients do not appear to respond to biliary sphincterotomy at a greater rate than placebo and thus the role of ERCP in these patients is unclear [23]. Indeed, it has been suggested in one study that post-cholecystectomy pain may be explained by persistent hyperexcitability of the nociceptive neurons in the central nervous system and may be unrelated to objective motility disorders of the sphincter [24].

Complications of ERCP

There are five major types of complications of ERCP: sedation, pancreatitis, bleeding, perforation, and infection. Rates of post-ERCP pancreatitis (PEP) vary because of variations in patient selection, and operator technique and experience. The patients at highest risk are young otherwise healthy women, especially those with known or suspected SOD. Elderly patients, and those with chronic pancreatitis or pancreatic cancer have lower rates. It has become clear that placement of prophylactic stents into the main pancreatic ducts reduces the risk of PEP in high-risk patients, and almost eliminates the risk of severe PEP [25]. These stents are expected to pass spontaneously within several weeks after the procedure. Bleeding complications occur only after performance of biliary sphincterotomy [26], which is not necessary in most cases of biliary stent placement. Risk factors for post-sphincterotomy bleeding include coagulopathy and institution of anticoagulation within 72 h of sphincterotomy. Perforation occurs in less than 1% of patients and may require surgical management. Infection occurs primarily in patients in whom there is inadequate drainage of the biliary tree after ERCP. These types of patients include those with extensive intrahepatic PSC or advanced hilar tumors, and after failed stent placement for biliary obstruction. Not surprisingly, data are accruing that lower procedural volume is associated with lower success rates and higher complication rates [27].

Combined Percutaneous and Endoscopic Approaches (Rendezvous)

In some situations where ERCP fails, and yet the bile duct still needs to be accessed endoscopically, a combined percutaneous–endoscopic approach can be taken. This is referred to as a rendezvous procedure. The patient is then brought to the ERCP suite and an ERCP is repeated. The

wire is grasped and pulled back through the endoscopic channel and accessories are passed over the wire, allowing sphincterotomy and stone extraction.

Ampullary Adenomas

Traditionally, ampullary adenomas have been removed surgically. Endoscopic resection at the time of ERCP has emerged as a viable non-surgical option in these patients [28]. EUS and ERCP are used to determine extension into the bile duct, which, if extensive, precludes endoscopic resection. Endoscopic resection is performed using polypectomy snares. Pancreatic duct stents are placed to prevent post-ERCP pancreatitis.

Take-home points

- ERCP is rarely used solely as a diagnostic modality.
- Therapeutic applications of biliary ERCP include palliation of malignant biliary obstruction, removal of bile duct stones, and treatment of bile duct leaks and benign strictures.
- Biliary sphincter of Oddi dysfunction (SOD) is divided clinically into three types (I, II, II) based on the presence or absence of objective findings.
- SOD types II and III are diagnosed by biliary manometry at the time of ERCP based on high sphincter pressures.
- SOD is treated by endoscopic biliary sphincterotomy.

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8

CHAPTER 8

Endoscopic Techniques in Management of the Liver and Biliary Tree: Endoscopic Ultrasonography

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Summary
Endoscopic ultrasonography (EUS) has evolved over the last few decades from an experimental test to a diagnostic and therapeutic procedure for several gastrointestinal and non-gastrointestinal diseases. The development of linear echoendoscopes has allowed for acquisition of cells/tissue for cytologic and histologic assessment using fine-needle aspiration and Tru-Cut biopsies respectively. In biliary disease, the use of transpapillary intraductal ultrasonography has improved the imaging of biliary strictures and staging of biliary tumors. Future potential EUS applications in the area of hepatobiliary disease include coil embolization for refractory variceal bleeding and EUS-guided delivery of radiofrequency ablation of liver lesions. In this chapter, the authors illustrate the current role of EUS in hepatobiliary disease, including choledocholithiasis, biliary strictures, cholangiocarcinoma, cholelithiasis, gall-bladder polyps, metastatic liver disease, and liver cirrhosis.

Case

A 51-year-old woman presented with a 3-month history of intermittent nausea and right upper quadrant abdominal pain. Past history was significant for a laparoscopic cholecystectomy. Pathology showed chronic cholecystitis with stone disease. Physical examination was unremarkable. Liver biochemistry values showed a mildly elevated alkaline phosphatase of 150 IU/L (normal = 45–115 IU/L), with normal aspartate transaminase (AST) and bilirubin. A transabdominal ultrasound scan and abdominal CT revealed a dilated common bile duct (8 mm) and were otherwise unremarkable.

What is the next step in this young patient with persistent abdominal pain, prior history of cholelithiasis, indeterminate dilated common bile duct, and mildly elevated alkaline phosphatase?

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Introduction

Based on the clinical scenario there was an intermediate suspicion of choledocholithiasis. Either endoscopic ultrasonography (EUS) or magnetic resonance cholangiopancreatography (MRCP) is recommended as being highly effective for confirming the presence of choledocholithiasis. The selection process between the two modalities depends on patient suitability, accessibility to diagnostic testing, and local expertise. The authors' patient in the case proceeded to EUS and several small common bile duct stones were observed. The patient then underwent endoscopic retrograde cholangiopancreatography (ERCP) with biliary sphincterotomy and stone extraction, with resultant symptomatic relief.

Equipment and Review of Technology

EUS represents one of the most significant developments in gastrointestinal endoscopy over the past 25 years. It provides high-resolution images of structures within or just beyond the wall of the gastrointestinal tract, which allows the detection of lesions as small as 3–5 mm in diameter [1]. This, in turn, permits assessment of hepatobiliary disease, pancreatic lesions, mediastinal disease, and locoregional staging of gastrointestinal malignancy and non-small-cell lung cancer [2].

Echoendoscopes are available in two varieties: radial scanning and curvilinear array devices. Radial scanning devices contain either a rotating mechanical ultrasound transducer or a wraparound, non-rotating, electronic, ultrasound transducer that generates an ultrasound image perpendicular to the long axis of the endoscope, using a frequency of 5–20 MHz. Higher frequency scanning allows greater resolution of details at the expense of depth of penetration. The radial systems use circumferential views that range from 270° to 360°. In contrast, linear array echoendoscopes produce an ultrasound image in a single plane parallel to the long axis of the endoscope via an electronic ultrasound transducer with a frequency range of 5–7.5 MHz. The linear design makes it possible to perform direct fine-needle aspiration (FNA), Tru-Cut biopsies (TCBs), and fine-needle injection under real-time ultrasonographic visualization. Therapeutic echoendoscopes with channels ≥3.8 mm allow passage of larger-diameter devices to include large-bore biliary stents. The radial and linear echoendoscope transducers are non-flexible so the echoendoscope tip has a more rigid segment (up to 4 cm) than their corresponding standard flexible videoendoscope counterparts, which may lead to difficulty in echoendoscope passage in patients with luminal narrowing or angulation, and in maintaining access within the second portion of the duodenum.

The endoscopic luminal view obtained of the gastrointestinal tract is similar to views obtained with a side-viewing duodenoscope, implying that intubation and advancement of the echoendoscopes are in a semi-blind fashion. EUS views permit a highly detailed assessment of the five uninterrupted gastrointestinal tract wall layers based on histology:

- The first and second layers correspond to the superficial (hyperechoic) and deep mucosa layer (hypoechoic).
- The third layer corresponds to the submucosa (hyperechoic).
- The fourth layer is the muscularis propria (hypoechoic).
- The fifth layer corresponds to the adventitia in the esophagus and serosa in the stomach, duodenum, and rectum (hyperechoic).

Examination of the bile duct from the ampulla to the liver hilum can be performed with either radial or linear echoendoscopes. However, visualization of the entire liver is incomplete by EUS. The majority, but not all, of the left lobe liver parenchyma and, to a much lesser extent, the right lobe of the liver are visualized. From the proximal stomach, the left lobe of the liver, portal vein/confluence, common bile duct (CBD), common hepatic artery, hepatic vein, and inferior vena cava may be visualized. The gall bladder is imaged from the antrum and the duodenal bulb. Within the duodenum the portal vein, CBD, cystic duct, common hepatic duct, common hepatic artery, and right hepatic artery may be seen, in addition to the ampulla.

Innovative design of equipment and devices has broadened the utility of EUS as a diagnostic and therapeutic tool over the last decade. The latest generation of electronic radial and linear echoendoscopes provide excellent imaging and do not vary significantly between model types. EUS and EUS-FNA or TCB may be performed with moderate sedation as an outpatient procedure.

Fine-needle Aspiration and Tru-Cut Biopsy

FNA is performed using a 25, 22, or 19 gauge needle. The FNA needle is passed through the working channel of a linear echoendoscope and, under direct endosonographic visualization, advanced into the target lesion. Minimal negative pressure aspiration is usually applied to facilitate acquisition of cells. The aspirated sample is submitted for cytologic evaluation. Performance of FNA is not limited by lesion size. The TCB device (20 mm tissue tray with a 19 G outer cutting sheath) contains a spring-loaded mechanism built into the handle that permits automated procurement of biopsy specimens. The target biopsy area needs to be ≥20 mm. There are challenges to the transduodenal approach when attempting to acquire tissue.

Ideally the echoendoscope needs to be in a straight/unangulated position for the TCB needle to deploy correctly. The angulation of the duodenum therefore precludes satisfactory TCB deployment due to the natural curvature of the duodenum, so performance of TCB is preferred via the transgastric approach; this in turn allows for tissue acquisition of structures such as the liver. Clinical experience is limited but available preliminary data suggest that EUS-TCB is safe. TCB should be considered when FNA is non-diagnostic or when core tissue is needed. Distinct echo features are discernible with FNA and TCB, which allows imaging of the needle and tissue tray within the target lesion, so permitting continuous visualization of each step.

Intraductal Ultrasonography

The technical evolution of EUS has led to the development of small-caliber intraductal ultrasound (IDUS) mini-probes (approximately 2 mm), which can be inserted through the working channel of the duodenoscope. The tip of the probe is radiopaque to aid fluoroscopic visualization. These probes can be passed selectively into either the biliary or the pancreatic ducts. The transducer rotates on the end of the probe and generates 360° images in a plane perpendicular to the axis of the catheter (similar to the radial echoendoscope). Ultrasound frequencies of 20 or 30 MHz generate a high-resolution image, enabling penetration of up to 2 cm. The normal bile duct appears as either a two- or three-layer structure with an inner hypoechoic layer accompanied by an outer hyperechoic layer, which is similar to that seen during standard EUS. The small caliber, flexibility, and excellent image quality produced by these catheters make them ideal for evaluating a variety of disorders, including:

- choledocholithiasis
- microlithiasis
- bile duct strictures: wall thickness and extrinsic compression at the stricture site
- bile duct wall thickening
- cholangiocarcinoma staging.

Intraductal ultrasonography may add to the diagnostic sensitivity of ERCP with brushings when no mass is seen on cross-sectional imaging or EUS, or when EUS with FNA is negative and suspicion of cancer persists [3].

EUS Evaluation of Hepatobiliary Disease

EUS Evaluation of Biliary Tree Disease

Suspected Choledocholithiasis

The major advantage of EUS in suspected choledocholithiasis compared with transabdominal ultrasonography is the ability to position the ultrasound transducer within the duodenal lumen, thereby allowing visualization of the adjacent biliary tree with no interference from intestinal gas or abdominal fat. Endosonography is particularly important in correctly identifying patients with acute biliary pancreatitis from other causes of pancreatitis.

Choledocholithiasis on EUS is seen as echo-rich areas with typical post-acoustic shadowing within the CBD or the ampulla (Figure 8.1). These areas may be mobile, multiple, and of variable size. On occasion stones do not demonstrate acoustic shadowing, and may be associated with a thickened bile duct wall. Bile duct sludge is seen as variably shaped and easily distorted echo-rich structures without acoustic shadowing.

In the setting of suspected choledocholithiasis, EUS detection of CBD stones has a sensitivity of >90% [4,5].

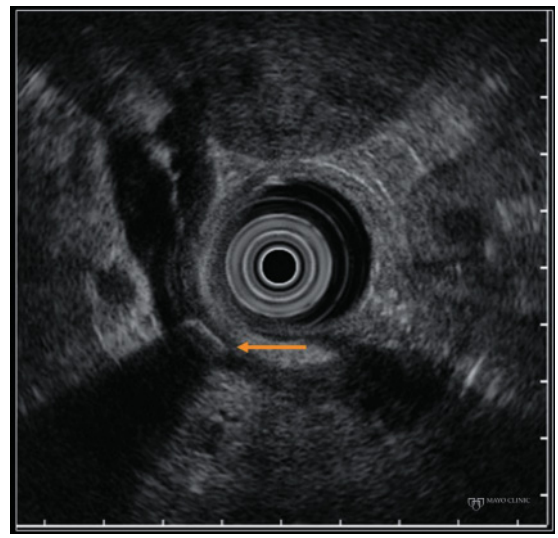

Figure 8.1 Radial endoscopic ultrasound view of a common bile duct stone (arrow) with associated post-acoustic shadowing.

The findings compare favorably with ERCP and are superior to transabdominal ultrasonography, without the associated post-procedural ERCP risk of pancreatitis. For patients with a low or intermediate risk of bile duct stones it is a cost-effective initial screening study [6]. Comparative controlled trials of EUS and MRCP have demonstrated that EUS has a comparable or higher accuracy than MRCP in the diagnosis of obstructive jaundice and detection of CBD stones [7,8].

A recent systematic review suggests that EUS be reserved for the evaluation of patients with an intermediate suspicion of choledocholithiaisis [9]. Although EUS does not have the therapeutic capacity of ERCP for stone removal, algorithms have been developed that incorporate its use into clinical practice [10]. Ultimately, the choice of modality should be based on clinical suspicion, availability of resources, experience, and costs [11–13].

Biliary Strictures

Using EUS, the differentiation between extrinsic compression and ductal pathology of biliary strictures can usually be determined. An extrinsic mass is typically seen as a hypoechoic lesion, causing compression of the ductal system with proximal dilation. Primary biliary malignancy is usually associated with a bile duct wall thickness ≥3 mm with hypoechoic changes [14]. It is important to remember that, during the evaluation of biliary strictures, the presence of biliary stents can impede adequate visualization as a result of stent-induced shadowing, and furthermore may lead to thickening and asymmetry of the bile duct wall. Although not routinely adopted as standard clinical practice, EUS-FNA may be performed and is a sensitive method for the diagnosis of proximal biliary strictures after negative or unsuccessful ERCP brush cytology. An EUS meta-analysis of 555 patients estimated sensitivity of 78% (95% confidence interval [CI], 69–85%) and a specificity of 84% (95%CI 78–91%) in detecting malignant biliary strictures, which is similar to that for MRCP [15,16]. Molecular cytologic techniques, including digital image analysis (DIA), fluorescent *in situ* hybridization (FISH), and IDUS, enhance the accuracy of standard techniques in evaluation of indeterminate bile duct strictures, allowing diagnosis of malignancy in a substantial number of patients with false-negative cytology and histology [17].

Cholangiocarcinoma

The EUS T-staging accuracy for CBD malignancy is reported as 83% in contrast to a lower N-stage accuracy of 55% [18,19]. Although not standard practice, the clinical impact of EUS-FNA in regional lymph node staging, in patients with unresectable hilar cholangiocarcinoma before liver transplantation, identifies lymph nodes in virtually all patients. Importantly, in this setting, lymph node morphology and echo features do not predict malignancy, and FNA of lymph nodes irrespective of appearance is recommended. In one study, confirmation of malignant lymph nodes by EUS-FNA precluded 17% of patients from transplantation [20]. In the authors' practice, EUS-FNA of the primary lesion is not performed due to the risk of peritoneal seeding, and aspiration of the primary tumor is now considered a contraindication to proceeding with neoadjuvant therapy and liver transplantation.

Ampullary Tumors

There is controversy as to whether all patients with ampullary adenomas should undergo EUS before therapy [21]. Some experts suggest that lesions <1 cm in diameter or those that do not have suspicious signs of malignancy (ulceration, induration, bleeding) do not require EUS evaluation before endoscopic management [22]. EUS is more accurate than computed tomography (CT) or magnetic resonance imaging (MRI) in the overall assessment of the T-stage of ampullary neoplasms (EUS 78%, CT 24%, and MRI 46%), but there is no significant difference in N-stage accuracy between the three imaging modalities [23]. Other studies suggest that tumor extension and locally metastatic lymph nodes are more accurately assessed by means of EUS than with other imaging methods and may decrease the need for exploratory laparotomy [24,25]. In the presence of a transpapillary endobiliary stent EUS, T-stage accuracy may be reduced. Tumor extension along the CBD or main pancreatic duct is particularly important when considering endoscopic resection in the setting of ampullary adenomas. At EUS it is possible to detect small intra-ampullary tumors and segmental thickening of the wall of the prepapillary biliary duct when standard white light endoscopy is normal. Patients with a T1-weighted lesion (disease limited to the ampulla) may benefit from endoscopic ampullectomy as the treatment of choice.

Primary Sclerosing Cholangitis

Transduodenal EUS may detect thickening (>1.5 mm) of the CBD wall in patients with primary sclerosing cholangitis (PSC); however, the role of EUS and IDUS in the diagnosis of PSC is limited [26]. Lymphadenopathy is commonly demonstrated by EUS and radiological imaging in these patients. and does not necessarily imply malignancy. EUS-guided FNA of such nodes is helpful to exclude malignant lymphadenopathy.

Gall-bladder Disease

Cholelithiasis

EUS can reliably identify cholelithiasis, particularly in the setting of small stones and obese patients. The EUS appearance is that of a hyperechoic structure within the gall bladder, sometimes associated with an acoustic shadow. In patients with suspected gall-bladder stone disease, but with negative conventional transabdominal ultrasound examinations, the EUS sensitivity and specificity are 96% and 86%, respectively, when compared with the corresponding cholecystectomy specimens or long-term clinical follow-up [27].

Microlithiasis

A portion of biliary sludge contains comparatively large particles (1–3 mm) called microliths, the formation of which is an obligatory intermediate step in the development of all types of gall stones (Figure 8.2). Microscopic examination of bile under polarized light can detect cholesterol crystals, which are a surrogate marker for biliary sludge and gall stones. EUS has been shown to be as accurate as crystal analysis for the detection of microlithiasis [28]. At EUS, the crystals appear as floating hyperechoic foci that move with abdominal pressure when applied to the right upper quadrant. In approximately 20% of patients with acute pancreatitis, a cause is not established by history, physical examination, routine laboratory testing, or abdominal imaging. Recent studies suggest that microlithiasis may be the explanation in up to 75% of patients with an unexplained attack with a gall bladder *in situ*. Sphincter of Oddi dysfunction is most prevalent in patients with recurrent attacks who have previously undergone cholecystectomy. Therefore, EUS is an important diagnostic tool in patients with unexplained biliary colic. Transduodenal EUS-guided FNA of gall-bladder bile using a 22-G needle carries a significant risk of bile peritonitis and should be avoided [29].

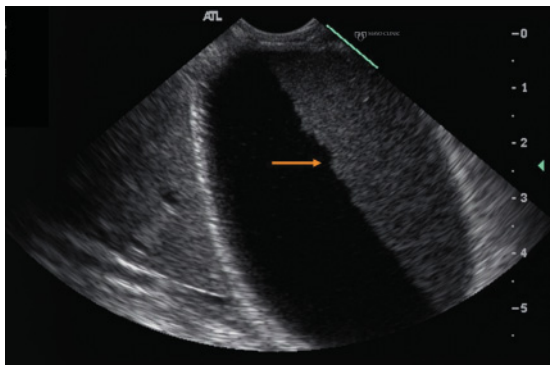

Figure 8.2 Linear endoscopic ultrasound image of a gall bladder with dependent non-shadowing sludge (arrow).

Polyps

The normal gall-bladder wall is seen as a two- or three-layer structure at EUS: the inner hypoechoic layer and the outer hyperechoic layer, which correspond to the muscularis propria layer and an adipose layer, respectively. Polypoid lesions of the gall bladder are typically incidental findings. The majority are benign non-neoplastic lesions, which include cholesterol polyps (usually pedunculated), adenomyomatosis, and inflammatory polyps. Cholesterol polyps are usually <10 mm and appear as tiny echogenic spots or echogenic pedunculated masses without acoustic shadowing on ultrasonography. Multiple microcysts, seen as anechoic areas or a comet tail artifact, are considered to be pathognomonic for adenomyomatosis [30]. An EUS scoring system aiming to differentiate between neoplastic and non-neoplastic polypoid lesions of the gall bladder highlighted three useful variables associated with an increased risk of a neoplastic polyp: (1) polyp maximum diameter >1 cm, (2) absence of hyperechoic spots, and (3) a heterogeneous type of internal echo pattern [31].

Gall-bladder Carcinoma

Gall-bladder carcinoma can be staged by EUS, although the data are considerably limited [32,33]. Loss of the gall-bladder wall layer pattern is thought to be the most specific finding for gall-bladder carcinoma. The overall EUS T-stage accuracy is reported as 77%

and N-stage accuracy as 90% [34]. However, most gall-bladder cancers present at a relatively advanced stage and EUS may add little to the overall evaluation. EUS-guided FNA of gall-bladder carcinoma is controversial due to the increased risk of bile leaks [35,36]. When performed, every attempt should be made to maintain an intramural position of the needle and not to advance into the lumen in order to minimize the potential of a bile leak.

EUS Evaluation of Abnormal Liver Parenchyma

Liver Metastases

The ability of ultrasonography to detect a focal liver lesion depend on the size, location, echogenicity, and mass effect. Small hyperechoic lesions in the liver found incidentally are usually hemangiomas. EUS can detect small (2 mm) focal liver lesions primarily of the left hepatic lobe. Liver metastases have similar appearances to the transabdominal equivalent examination [37]. Features on EUS suggestive of malignant hepatic masses include hypoechoic or hyperechoic lesions with a regular outer margin, hypoechoic halo, and the detection of two or more lesions (Video 3) [38]. Endosonography may detect occult liver metastases in 7% of patients with esophageal or gastric cardia cancers [39–41]. Early experience suggests that EUS-FNA is comparable to CT-FNA in terms of diagnostic utility for hepatic lesions [42]. An EUS-FNA may be useful when a patient is at increased risk of percutaneous biopsy complications (coagulopathy, cirrhosis, ascites, aspirin intake) and the presence of small liver tumors <2 cm [43].

Hepatocellular Carcinoma

Imaging of the entire liver typically cannot be obtained by EUS and as such EUS is generally not used in the staging of hepatocellular carcinoma (HCC). Nonetheless preliminary studies show an increase in the accuracy of intrahepatic staging of HCC by delineation of lesions, which are missed by CT and MRI [44–46]. An EUS-FNA can also confirm additional HCC liver lesions or liver metastases, in deep-seated locations, again in the setting of poor liver function and coagulation disorders, thus upstaging patients and changing clinical management [41].

Liver Cirrhosis and Portal Hypertension

Although EUS is not an established approach to evaluate liver cirrhosis, a TCB of the left lobe of liver via a transgastric approach may provide adequate numbers of complete portal tracts and connective tissue for evaluation to establish a histopathologic diagnosis [47]. In patients with portal hypertension, both esophageal and gastric varices, and periesophageal and perigastric collateral veins, can be visualized. Esophageal and gastric varices appear as submucosal anechoic vascular structures and collateral veins are found adjacent to the esophageal/gastric wall. In portal hypertensive gastropathy, there is increased thickness of the gastric mucosal and submucosal layers due to venous and lymphatic outflow obstruction.

Lymphadenopathy

Malignant infiltration and enlargement of periportal, portacaval, and hilar lymph nodes can occur in patients with cancers of the liver, gall bladder, and biliary tree. In one study, 19% of patients with periportal lymph nodes 10–40 mm in size were due to a malignant etiology [48]. EUS-guided FNA of lymphadenopathy should be considered for tumor staging or in patients with suspected malignancy without a diagnosis.

Therapeutic Applications

Biliary Tree Access

In the mid-1990s, the concept of combining therapeutic ERCP with interventional EUS technology led to endoradiosonographic–cholangiopancreatography (ERSCP) [49,50]. Since then, the practice has expanded and EUS-guided intrahepatic or extrahepatic drainage may be performed via a transhepatic or an extrahepatic (transenteric–transcholedochal) approach. Various accessories may be used to create the fistula between the gut lumen and bile duct to facilitate passage of other accessories and/or for dilation of strictures. Longitudinal data are still needed to determine the long-term outcomes and role of EUS-guided biliary intervention. The limited data available (most of which are retrospective) preclude an accurate assessment of the technical success of EUS-guided biliary tree intervention. However, evaluating the collective literature to date (1996–2008), it

appears that EUS-guided biliary access, either transhepatic or extrahepatic, has a 77% technical success rate.

The indication for attempted EUS-guided biliary tree access and therapy is a failed ERCP, which may be due to:

- technically challenging postoperative gastrointestinal anatomy (Billroth II gastric resection, pancreaticoduodenectomy, gastrectomy with Roux-en-Y reconstruction)
- an inaccessible major or minor papilla
- gastric outlet obstruction.

Future Therapies

Selective embolization of the portal vein by EUS guidance using Enteryx (ethylene–vinyl alcohol copolymer) appears to be feasible and a potential minimally invasive preoperative treatment for patients undergoing extensive hepatectomy [51]. Successful EUS-guided injection of cyanoacrylate at the level of the perforating veins in the treatment of gastric varices, and EUS coil embolization for refractory variceal bleeding, have been described in case reports [52,53]. Selective EUS-guided transgastric cryotherm ablation of the liver and spleen shows promising preclinical results, potentially opening the field for radiofrequency ablative therapies [54]. EUS-guided portal vein catheterization for portal angiography and pressure measurements are other areas of evolving interest [55,56].

Complications

EUS is a safe procedure with an overall complication rate of <1% [2]. The perforation rate associated with EUS is comparable to standard endoscopy (<1%). The majority of complications are associated with EUS-FNA. The risk of bacteremia after EUS-FNA is low and comparable with that of diagnostic endoscopy (0–8%). Mild bleeding after EUS-FNA has been reported to occur in as many as 4% of patients [57]. Early experience suggests that complications associated with the use of TCB are no more frequent that FNA. Complications have been reported to occur in approximately 15% of patients undergoing EUS-guided biliary intervention, including bile leak, cholangitis, hemorrhage, pneumoperitoneum, and pancreatitis.

Take-home points

- EUS has an established role in the evaluation of suspected choledocholithiasis.
- EUS and intraductal ultrasonography have complementary roles in the evaluation of biliary strictures and cholangiocarcinoma.
- EUS may be reliably used in the diagnosis of cholelithiasis, microlithiasis, and polypoid lesions of the gall bladder.
- EUS evaluation of liver metastases, hepatocellular carcinoma, and non-malignant hepatic parenchyma has an evolving clinical role.
- EUS-guided therapeutic intervention to aid access to the biliary tree and injection therapy of varices or coil embolization for refractory bleeding are promising new methods of endoscopic intervention for the future.

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CHAPTER 9
Liver Biopsy and Paracentesis

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Summary

Liver biopsy remains the most definitive test in assessing the severity of liver disease. The most important complication of liver biopsy is bleeding which occurs in 0.1–0.3% of patients. Exchange of information between the clinician and the pathologist is imperative in liver biopsy interpretation because the findings on liver biopsy are often not specific for a diagnosis. Paracentesis is the most efficient way of determining diagnosis in patients presenting with ascites. Bleeding occurs in 0.3% of patients undergoing paracentesis. Intravenous albumin should be administered to patients undergoing removal of more than 5 L of ascites fluid.

Introduction

Liver biopsy and paracentesis are frequently used in the management of patients with acute and chronic liver disease. This chapter reviews the indications, complications, technical aspects, and interpretation of percutaneous liver biopsy and paracentesis.

Liver Biopsy

Indications

The most common indication for liver biopsy is in the assessment of patients with chronic liver disease for either diagnosis or, more commonly, assessment of fibrosis in a patient with a known diagnosis such as non-alcoholic fatty liver disease or hepatitis C. It is estimated that a liver biopsy, in combination with blood tests to identify causes of chronic liver disease, will provide an accurate diagnosis in about 90% of patients with unexplained liver test abnormalities; however, findings on liver biopsy are often non-specific, e.g., a common descriptive pathology report might be that of a lymphoplasmacytic portal infiltrate consistent with viral, drug, or autoimmune hepatitis. Clinical information is then required to help differentiate a cause. To further complicate the interpretation, many patients are on multiple drugs, most of which can cause liver test abnormalities. Finally, tests such as antinuclear antibody are often positive in low titers and therefore not specific. When the liver biopsy is done for diagnostic reasons, the pathologist and clinician should communicate when possible to allow an exchange of relevant information. This kind of dialogue is much more effective than the clinician merely relying on the biopsy report or the pathologist relying on printed clinical information, much of which may be incomplete. The finding of otherwise clinically unsuspected cirrhosis will trigger surveillance for esophageal varices and hepatocellular carcinoma.

In patients with acute liver disease, a diagnosis is usually forthcoming with the help of the clinical history and blood tests for infections and inherited and metabolic disorders; therefore, a biopsy is generally not performed. Occasionally liver biopsy is needed to

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help in the diagnosis of acute presentation of autoimmune hepatitis, diffuse intrahepatic malignancy not identified on imaging, Wilson disease, alcoholic liver disease when clinical history is uncertain, and unusual infections such as herpes or histoplasmosis. Occasionally liver biopsy may detect clinically unsuspected chronic liver disease in a patient presenting with acute hepatitis. Biopsy in patients with acute liver disease is generally not needed for prognosis as the severity of the acute hepatitis is usually clinically apparent using examination findings such as encephalopathy and biochemical tests such as bilirubin, prothrombin time, and albumin. In addition, the severity of histologic changes in patients with acute liver disease can be surprisingly patchy.

A typical percutaneous liver biopsy will sample about 1/50 000 (0.002%) of the total liver mass and therefore sampling error can be a concern. In patients with chronic hepatitis C, up to 30% of patients will have a difference of one histologic stage in two specimens obtained from the liver. Sampling error is probably even greater for cholestatic liver diseases, especially primary sclerosing cholangitis. It is minimized when larger specimens are obtained and the ideal biopsy specimen is about 2.5 cm long and 1.4 mm wide, and contains more than six portal tracts.

Technique and Safety

Most percutaneous liver biopsies are performed guided by imaging such as ultrasonography. The use of ultrasonography helps to avoid inadvertent biopsy of adjacent structures such as the gall bladder and, in some studies, has shown a lower rate of complications than "blind" biopsy. In many centers, all liver biopsies are done by radiologists. The diminishing involvement of gastroenterologists in carrying out a liver biopsy is illustrated by the fact that liver biopsy is no longer a requirement of gastroenterology training programs. Biopsies are usually done transthoracically, although a subcostal approach can be used (only with imaging guidance) if an approach to the left lobe is desired. At our institution liver biopsies are done either by a radiologist or a hepatology physician assistant. We have demonstrated that a physician assistant, trained by hepatologists and using a portable ultrasound device for guidance, can obtain quality liver biopsy specimens with minimal morbidity and no mortality. Light sedation with midazolam and/or fentanyl may be employed although most patients in the authors' institution do not require sedation.

Risks of Liver Biopsy

The most common complication of liver biopsy is pain, which occurs in up to 50% of patients. Pain often radiates to the right shoulder. Analgesics are required in 10–30% of patients after percutaneous liver biopsy. We typically use oral agents for analgesia unless pain is severe, at which time parenteral opiate agents are administered. Prolonged pain may be due to persistent bleeding or bile leak and may lead to imaging with computed tomography (CT) or ultrasonography. The most important risk of liver biopsy is serious bleeding which occurs in 0.1–0.3% of patients. Bleeding does not usually require transfusions and generally subsides spontaneously. In rare cases, transarterial embolization or even surgery is required to stop bleeding. Clinically significant infection after liver biopsy is unusual unless there is concomitant biliary obstruction. Prophylaxis against infectious endocarditis is not recommended. Pneumothorax and perforation of the gall bladder or colon have become increasingly uncommon with the widespread use of ultrasound guidance. The risk of death from liver biopsy is about 0.03%.

Pre-procedure Assessment

Laboratory and clinical requirements for liver biopsy vary but we generally require a hemoglobin >8 g/dL, platelets $>50 \times 10^9$/L, and prothrombin time or international normalized ratio (INR) <1.5. We do not routinely perform a bleeding time before liver biopsy unless the patient has a history suggestive of a bleeding disorder. The use of aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) is not considered a contraindication to biopsy although, when possible, aspirin is held for 1 week and NSAIDs for 24 hours before percutaneous liver biopsy. The use of the antiplatelet agent clopidogrel is considered a contraindication to liver biopsy and should be stopped for at least 5 days before the procedure. In patients with coagulopathy, as well as those with marked perihepatic ascites, biopsies can be obtained transvenously, usually via the right jugular vein. This technique usually produces specimens of excellent quality. If open or laparoscopic abdominal surgery is necessary for another indication, biopsies may also be obtained under direct visualization.

Absolute contraindications to percutaneous biopsy include inability to cooperate, uncorrected coagulopathy, marked ascites, and mechanical biliary obstruction with dilated intrahepatic bile ducts. Before biopsy, imaging should be obtained to exclude large masses or multiple cysts. Bleeding risk may be higher in patients with amyloidosis, diffuse hepatic malignancy, and sickle cell disease; therefore, some have suggested that transjugular liver biopsy be performed when one of these is known or highly suspected. Percutaneous biopsies may be obtained in patients with hemophilia after appropriate factor replacement.

Various needles are used for percutaneous biopsy. The choice is left to the operator. In patients with cirrhosis, cutting devices, such as the Tru-Cut or Vim–Silverman needle, may give less fragmented specimens than suction devices. Biopsy with a cutting needle is often done using a spring-loaded device ("gun") which is simpler to use than manual cutting needles. Suction devices, such as the Jamshidi, Menghini, or Klatskin needles, are simple to use and can obtain longer biopsy specimens than cutting needles.

Almost all liver biopsies are done in an outpatient setting unless the patient requires hospitalization for other reasons. Acceptable hematologic parameters and absence of contraindications must be ensured. Some centers advise an overnight fast although we permit a light breakfast which may be advantageous in patients with a gall bladder. A light meal before biopsy enhances emptying of the gall bladder which may decrease the risk of gall-bladder puncture. We establish intravenous access in almost all patients, although some liver transplant recipients who have undergone repeated biopsy may not need intravenous access. We do not perform a pre-procedure transfusion crossmatch, although this is done in some centers.

Technique

Although the specifics about liver biopsy will vary according to the type of needle used and whether ultrasound guidance is employed, the overall procedure should include the following:

1 The risks of biopsy are reviewed with the patient and a consent form signed. The explanation of risks should include bleeding, perforation of adjacent organs, and pain.

2 The procedure should be explained to the patient.

3 Intravenous access is established in some patients, particularly those at highest risk for bleeding, such as inpatients.

4 Conscious sedation may be used if requested by the patient.

5 The site of needle entrance should be identified between the anterior and midaxillary lines using either ultrasound guidance (preferred) or percussion.

6 Most biopsy kits will have a sterile drape and iodine swabs to maintain a sterile field.

7 Local anesthesia is administered using 1% lidocaine. A 22-gauge spinal needle allows safe infiltration of the intercostal area and liver capsule, but minimizes the risk of bleeding that might occur with sudden unexpected movement. The spinal needle should be inserted superior to the rib, oriented parallel to the floor, and aimed toward the contralateral shoulder (intact gall bladder) or xiphoid (absent gall bladder). When the 22 G needle reaches the liver capsule, the thoracic wall will act as a fulcrum, causing the syringe side of the needle to swing superiorly on inspiration. This gives a good measurement of depth and direction of approach of the liver.

8 A 3–4 mm nick is made in the skin. This is particularly important with suction needles which have a duller edge than cutting needles.

9 Practice patient breathing. Have the patient take an easy breath and hold at end-expiration, when the biopsy will be performed.

10 Perform the biopsy.

11 Send the specimen to the pathology laboratory ensuring that it is appropriately labeled. The authors' pathology department requests that the specimen be sent in formalin.

Post-biopsy Monitoring

Most complications will occur within 3 h of biopsy. After the biopsy, patients are observed in the liver biopsy room with blood pressures done every 5 min for 15 min. If the patient is stable, they are then transferred to an outpatient nursing unit where they are observed for 3 h. If the patient remains stable, he or she is then dismissed. Patients are advised to have a traveling companion and stay within 30 min of the hospital for 24 h in case late complications occur. The major complications, bleeding or perforation of an adjacent organ, are usually heralded by abdominal pain and/or hypotension. Should such

symptoms occur and persist after biopsy, cross-sectional imaging, usually with CT, should be performed.

Interpretation

The clinical pathologic correlation is of paramount importance in liver biopsy interpretation. Histologic findings are often non-specific and the clinician must communicate to the pathologist clinical information including laboratory data, results of blood tests used to establish an etiology of liver disease, and imaging tests including whether the biopsy is directed at a liver mass or is from the general liver parenchyma. Routine staining techniques vary with institution but all will perform hematoxylin and eosin (H & E) staining as well as a stain for connective tissue such as Masson trichrome. In addition, many pathologists will also do stains for iron, periodic–acid Schiff with diastase (PAS-D), and reticulin. H & E stain allows assessment of hepatic inflammatory change, presence of abnormal cells that might indicate malignancy or inflammation, and vascular changes. The use of Masson trichrome will allow an assessment of fibrosis, which, if present, implies chronicity. A semi-quantitative assessment of inflammatory change is called "grade" and that of fibrosis is called "stage." The most commonly used staging systems are demonstrated in Table 9.1.

Iron staining is generally used to assess for iron overload conditions, particularly genetic hemochromatosis, although a diagnosis of hemochromatosis is now more frequently established with genetic testing. Excessive iron staining may also be seen in hematologic disorders characterized by ineffective erythropoiesis, chronic hemolysis, and/or the need for periodic transfusions. In addition, patients with advanced fibrosis due to chronic liver diseases such as viral hepatitis, alcohol, or steatosis may have excessive iron staining in the liver. In general iron staining due to genetic hemochromatosis is largely found in hepatocytes whereas those with secondary iron overload will have more prominent staining in Kupffer cells.

PAS-D is used to assess for globules that are seen in α_1-antitrypsin deficiency although it will also stain lipofuscin, which is a pigment that appears in hepatocyte cytoplasm due to non-specific damage to intracellular organelles. Globules of α_1-antitrypsin tend to be most prominent in periportal hepatocytes or in those on the periphery of a regenerative nodule. The PAS-D positive globules are most prominent in patients with the ZZ phenotype although can also be seen with the MZ phenotype. Reticulin staining is useful to assess the thickness of hepatocyte cords which can be helpful in the diagnosis of nodular regenerative hyperplasia or, when assessed on biopsy from a liver mass, in the differentiation of hepatocellular adenoma from hepatocellular carcinoma. Stains for copper are not generally routinely employed because of a lack of sensitivity or specificity. Even patients with Wilson disease can lack a positive stain for copper. In addition, a positive copper stain is not specific for Wilson disease because it can also be seen in cholestatic liver conditions such as primary sclerosing cholangitis or primary biliary cirrhosis.

Table 9.1 Commonly used staging systems to assess hepatic fibrosis.

Chronic hepatitis: Batts and Ludwig
Stage 0: no fibrosis
Stage 1: portal fibrosis
Stage 2: periportal fibrosis
Stage 3: septal fibrosis
Stage 4: cirrhosis
Chronic hepatitis: Ishak
Stage 0: no fibrosis
Stage 1: fibrous expansion of some portal areas
Stage 2: fibrous expansion of most portal areas
Stage 3: fibrous expansion of most portal areas with occasional portal to portal bridging
Stage 4: fibrous expansion of portal areas with marked bridging
Stage 5: marked bridging with occasional nodules (incomplete cirrhosis)
Stage 6: cirrhosis
Non-alcoholic fatty liver disease: Clinical Research Network
Stage 0: no fibrosis
Stage 1: perisinusoidal or periportal fibrosis
Stage 2: both perisinusoidal and portal/periportal fibrosis
Stage 3: bridging fibrosis
Stage 4: cirrhosis
Non-alcoholic fatty liver disease: Brunt
Stage 0: no fibrosis
Stage 1: perisinusoidal/periportal fibrosis; focally or extensively present
Stage 2: perisinusoidal/pericellular fibrosis with focal or extensive periportal fibrosis
Stage 3: perisinusoidal/pericellular fibrosis and portal fibrosis with focal or extensive bridging fibrosis
Stage 4: cirrhosis

New Alternatives to Assessing Liver Fibrosis

The problems with liver biopsy include expense, risk, and sampling variability. Various combinations of biochemical blood tests and percutaneous ultrasound- or magnetic resonance imaging-guided measurements of liver "stiffness" with elastography are therefore being studied as alternatives to liver biopsy, but have not replaced histopathologic assessment. These techniques are being actively pursued and may become more accepted in the future.

Paracentesis

Ascites is the most common complication of end-stage liver disease. In patients with decompensated cirrhosis, ascites is the initial manifestation in about 60%, more common than variceal bleeding or hepatic encephalopathy. In addition, patients with heart failure and peritoneal carcinomatosis may present with ascites. Paracentesis represents a relatively simple, safe, and relatively inexpensive diagnostic step in patients with ascites.

Indications

Paracentesis is indicated in the initial assessment of patients presenting with ascites although, in many patients, there will be clinical evidence or a prior history of liver diseases, cardiac disease, or malignancy. Paracentesis is also used in the exclusion of infection in patients with pre-existing ascites. Paracentesis should generally be performed in all patients with new-onset ascites and whenever infection of pre-existing ascites is suspected. Large-volume paracentesis is indicated for symptomatic relief of those patients with respiratory compromise or abdominal discomfort.

Contraindications for paracentesis are less strict than those for liver biopsy. Paracentesis can be performed safely in patients with significant coagulopathy or thrombocytopenia. In the absence of renal failure or evidence of fibrinolysis or disseminated intravascular coagulation, the authors' group will proceed with paracentesis if INR <2.5 and platelets >20 $\times$ 10^9/L. Patients with renal failure, especially if on dialysis, appear to have an increased risk of paracentesis-associated bleeding, perhaps related to platelet dysfunction. In such patients, an INR <2.0 is optimal. Bleeding is more of a concern in patients undergoing therapeutic paracentesis with large-bore needles or catheters than in paracentesis performed only for diagnosis, when a small-bore needle can be used. Other contraindications to paracentesis are inability of the patient to cooperate, pregnancy, intestinal obstruction with dilated bowel loops, and abdominal wall infection that prohibits unimpeded access to ascites fluid.

Risks of Paracentesis

The most severe complication of paracentesis is bleeding. Serious bleeding occurs in about 0.3% of patients although abdominal wall hematoma is more common, occurring in about 2% of patients. Intestinal perforation is unusual and probably without clinical consequence in most cases although inducing infection is a concern. Ascites fluid leak is most common in patients with incomplete removal of ascites when intra-abdominal pressure remains high. The use of a "z-track" technique (Figure 9.1) may minimize the risk of ascites fluid leak.

Post-paracentesis circulatory dysfunction is a dreaded complication of large-volume paracentesis. It is characterized by renal insufficiency caused by activation of the renin–angiotensin system perhaps related to hypotension or exacerbation of intravascular volume depletion during the procedure. For those patients anticipated to have more than 5 L of ascites removed, the authors advise replacement with 6–8 g of albumin, given as 25% albumin, per liter of ascites removed. It is probably not necessary to replace albumin when less than 5 L of ascites is removed.

Pre-procedure Assessment and Technique

Most clinical facilities where paracentesis is performed will have a commercial tray that is used for the procedure. The tray we use has an 8 French catheter that is inserted over an 18 G introducer needle. The technique for paracentesis is as follows:

1 Explain the risks of the procedure. Included in the discussion should be a risk of bleeding of about 0.3% (1 in 300 procedures) and a very small risk of infection or perforation of intra-abdominal organs.

2 Intravenous access should be available for patients who are undergoing therapeutic paracentesis so that albumin may be administered.

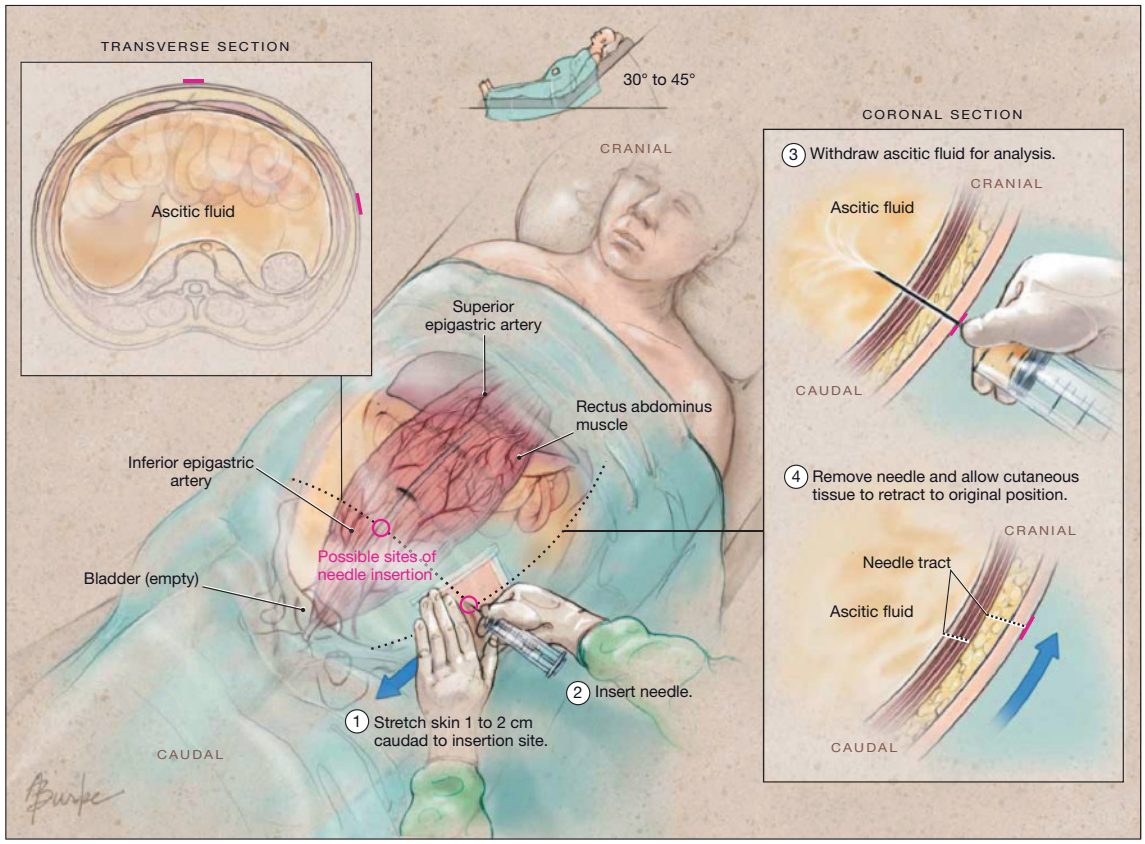

Figure 9.1 Positioning of patient and needle for diagnostic paracentesis using the "z-track" technique. (From Wong et al. [1], with permission. Copyright © 2008 American Medical Association.)

3 Position the patient supine with the head of the bed minimally elevated. Put the patients hand above the head to help maintain a sterile field.

4 Choose a site for needle insertion. It is best to use ultrasound guidance, especially for patients undergoing paracentesis for the first time. Either a midline position, 2 cm inferior to the umbilicus, or a lateral (usually left to avoid the cecum) position can be used. When using the lateral approach, it is advised to select a spot 5 cm cephalad and medial to the anterosuperior iliac spine, staying lateral to a midpoint between the anterosuperior iliac spine and the umbilicus. It is best to avoid incisional scars where there may be additional blood vessels or adherent bowel loops.

5 Prepare the site in a sterile fashion using drapes (usually supplied in the kit) and swab with iodine solution.

6 Use lidocaine for local anesthesia at the skin site and then make a 2- to 3-mm superficial incision.

7 Insert the catheter, at the incision site, parallel to the abdominal wall, aspirating on the syringe until ascites fluid is retrieved. Use of a "z-track" approach diminishes the chances of ascites fluid leakage after the procedure (see Figure 9.1).

8 The catheter is then advanced over the needle.

9 Use of large-volume vacuum containers or apparatus using wall suction facilitates therapeutic paracentesis.

Table 9.2 Use of ascites fluid protein and serum ascites–albumin gradient to determine etiology.

Serum ascites–albumin gradient (g/dL)	Ascites protein ≤2.5 g/dL	Ascites protein >2.5 g/dL
≥1.1	Cirrhosis	Budd–Chiari syndrome, right heart failure, sinusoidal obstruction syndrome
<1.1	Nephrotic syndrome	Peritoneal carcinomatosis, tuberculous peritonitis

10 When cultures are requested, we inoculate bottles at the bedside to enhance sensitivity.

Post-procedure Instructions

Most patients are dismissed directly from the paracentesis procedure suite. The authors' group advises that they lay on the opposite side of the paracentesis for 2–3 h to minimize leakage from the site.

Interpretation

Tests ordered at the time of paracentesis will vary according to presumed etiology. Most patients should have the following tests done at the time of initial paracentesis: total protein, albumin (with simultaneous measurement of serum albumin to allow calculation of the serum ascites–albumin gradient), total cell count, differential cell count, and cultures for bacteria and fungi. We have demonstrated that incidence of infection in outpatient cirrhotic patients undergoing paracentesis is very low and routine cell count and differential may not be necessary, especially in those undergoing repeated large-volume paracentesis. Depending on the clinical condition and indication for paracentesis, the following tests may also be necessary: cytology, cell count, lactate dehydrogenase, amylase, and bilirubin. The utility of ascites fluid analysis is discussed in Chapter 14 but an overview of the interpretation of ascites fluid protein and serum ascites–albumin gradient is shown in Table 9.2.

Take-home points

- Liver biopsy remains the most definitive test to determine the amount of hepatic fibrosis.
- The most severe complication of liver biopsy is bleeding, which occurs in 0.1–0.3% of patients.
- Exchange of information between the clinician and the pathologist is imperative in liver biopsy interpretation because the findings on liver biopsy are often not specific to a diagnosis.
- Paracentesis is the most efficient way of determining diagnosis in patients presenting with ascites.
- Bleeding occurs in 0.3% of patients undergoing paracentesis.
- Intravenous albumin should be administered to patients undergoing removal of >5 L of ascites fluid.

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PART 3

Problem-based Approach to Liver Disease

10

CHAPTER 10
Jaundice and Pruritus: A Diagnostic Approach

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Summary
The evaluation of the patient who presents with jaundice and pruritus is complex. Multiple potential causes must be considered, and a thorough diagnostic evaluation should be completed in a timely fashion. The symptoms, particularly the pruritus, can be tremendously bothersome to the patient and measures to increase patient comfort must be used. Details of the patient's clinical presentation, including concurrent symptoms, medication use, and underlying disease, are important and can be particularly instrumental in guiding the diagnostic work-up. This underscores the critical importance of taking a thorough history at presentation.

Management of jaundice and pruritus should focus on the underlying cause. In the absence of hemolytic conditions, efforts should be directed toward evaluation of the biliary tree. Diagnostic studies including ultrasonography, computed tomography, endoscopic retrograde cholangiopancreatography (ERCP), and magnetic resonance cholangiopancreatography may all play a role in the evaluation of these patients. In addition, blood work can prove to be extremely valuable in determining the presence of underlying hepatic disease.

Antipruritics can be beneficial and include diphenhydramine, cholestyramine (or other resins), rifampin, naltrexone, naloxone, and ondansetron. For some patients, a single agent works well at relieving the symptoms. For others, multiple agents may be employed. If obstruction is the primary cause of pruritus, ERCP may provide improvement in symptoms once the obstruction has been relieved.

The presence of bile duct malignancy provides significant challenges for the clinician, and may require surgical or oncologic consultation. Finally, if end-stage liver disease is the underlying source, referral for orthotopic liver transplantation should be considered.

Introduction

Jaundice and pruritus in combination are cutaneous symptoms representing an underlying pathology, typically of the hepatobiliary system. The evaluation of the patient who presents with these symptoms must be comprehensive and timely (Figure 10.1). The symptoms can be quite aggravating for patients, particularly pruritus, and may represent serious pathology. Jaundice is the yellowish-green hue to the skin and sclera that develops when there is excess bile in the bloodstream. Pruritus is the cutaneous sensation that provokes the intense desire to scratch. It is one of the most prominent and disturbing of skin conditions.

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Jaundice

The etiology of jaundice is varied. One Swedish study evaluated 173 patients over a 3-month period of time and

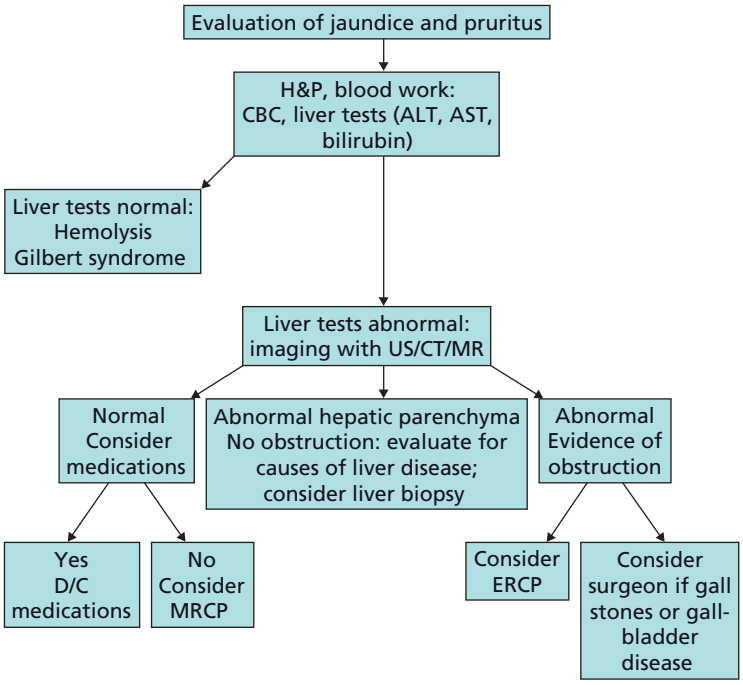

Figure 10.1 Evaluation of jaundice and pruritus. ALT, alanine transaminase; AST, aspartate transaminase; CT, computed tomography; D/C, damage/cirrhosis; ERCP, endoscopic retrograde cholangiopancreatography; H&P, history and physical exam; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; US, ultrasonography.

found that malignancy and alcoholic liver disease were the most common causes (67% and 17% respectively), with viral hepatitis a less common reason for jaundice (3%) [1]. In another study of 732 patients with new-onset jaundice, a hepatic cause made up 55% of the cases with an extrahepatic cause such as sepsis or gall-stone disease making up the other 45%. The most common cause overall was sepsis or an altered hemodynamic state resulting in presumed ischemic hepatic injury (37%) [2]. Decompensation of pre-existing liver disease was the cause in 21% and gall-stone disease in 14%. Acute liver disease as a result of non-alcoholic etiologies caused new-onset jaundice in 13%, with acute viral hepatitis causing 9% and a drug-induced liver injury causing 4%. Acetaminophen (paracetamol) was the most commonly implicated drug.

Jaundice is probably the most commonly recognized marker of hepatobiliary dysfunction. Due to the central role of the liver in bilirubin metabolism, the onset of jaundice localizes the abnormality to the hepatobiliary system in most patients. Hemolysis and Gilbert syndrome are common non-hepatobiliary causes of jaundice.

Jaundice may develop with any type of underlying liver disease, but tends to occur more commonly with diseases that are cholestatic, such as primary biliary cirrhosis and primary sclerosing cholangitis. The actual skin color ranges from a light yellow to dark green. The basis for the discoloration is typically the bilirubin. In general, until the total bilirubin level exceeds 2.5 mg/dL jaundice will not be evident [3]. Hyperbilirubinemia develops when there are abnormalities in the complex process that balances bilirubin formation with bilirubin clearance. Not only is jaundice evident in the skin, but it also involves the mucosal surfaces and sclera, with scleral icterus frequently being the first manifestation of jaundice. Hypercarotenemia, which can occur with excessive β-carotene supplementation, can cause yellow discoloration of the skin but not of the sclera [4].

Pruritus

Generalized pruritus may be a manifestation of a variety of systemic conditions including atopic dermatitis, end-stage renal disease, iron deficiency, pregnancy, and chronic liver disease. A number of pathologic processes can lead to pruritus: inflammation, hypersensitivity,

degenerative changes, malignant tumors, and even psychiatric abnormalities. Pruritus is prevalent in the setting of hepatobiliary obstruction and cholestasis, and remains one of the most debilitating and poorly understood phenomena of hepatic failure. Pruritus is an extremely frustrating symptom for all those who experience it.

Multiple dermatologic conditions can contribute to pruritus and typically manifest as a rash or dermatitis of some type. Pruritus associated with an underlying liver condition tends to have a different quality. Typically, there is no obvious rash nor is a potential cause, such as a contact agent, identified. There may, however, be diffuse excoriations from scratching. Pruritus related to liver disease is frequently most noticeable during sleep and is not easily relieved with topical creams, although they may provide some mild, temporary relief.

Pruritus is a well-recognized manifestation among patients with liver diseases and intrahepatic or posthepatic cholestasis. Hepatic diseases leading to pruritus include primary biliary cirrhosis, viral hepatitis B and C, primary sclerosing cholangitis, carcinoma of the bile ducts, alcoholic cirrhosis, and autoimmune hepatitis. Pruritus may occur in any patient with cirrhosis but is most common in cholestatic liver disease. The presence and severity of pruritus in cholestasis do not necessarily correlate with the degree of cholestasis.

Typically, pruritus is generalized, but may be more intense on hands and feet, and around tight-fitting clothes. The face, neck, and genital area are rarely involved [5]. The pathogenesis is still poorly understood, as the precise substance responsible for it is not known. Some authors believe that it is caused by the bile acids in the blood (cholemia) or skin [6], but there is a poor correlation between the skin concentration of bile salts and intensity of pruritus. Others believe that the pruritus is related to endogenous opiates [7,8]

Infection can also cause jaundice through extrahepatic obstruction, granulomatous inflammation as with tuberculosis, or intrahepatic cholestasis leading to cholangitis.

Evaluation

The patient who presents with jaundice and pruritus requires a detailed interview to help identify the potential cause. Questions to consider include the following:

- Does the patient have pain, particularly in the right upper quadrant of the abdomen?
- Have there been gastrointestinal symptoms?
- Is the patient systemically ill?
- Has the patient recently started a new medication?
- Is there a history of cancer?
- Has the urine been dark or the stool light?

The answers to these questions may provide important clues to the etiology of jaundice and pruritus.

The physical examination plays an important role in the evaluation of the patient with jaundice and pruritus. The skin should be evaluated for the presence of a rash or excoriations from scratching. Superinfections of lesions should be ruled out. Parasitic infestations should be considered. The skin should also be evaluated for the presence of spider angiomas and xanthelasmas because these would suggest a more chronic condition. The presence of ascites, palmar erythema, muscle wasting. and/or splenomegaly would corroborate this supposition. The presence of fever, right upper quadrant pain, tenderness, and hepatomegaly is more suggestive of an acute condition.

The age of the patient can also provide important clues. In general, patients younger than 30 years are more likely to have acute parenchymal disease whereas patients between 30 and 50 are more likely to have chronic liver disease. Women over the age of 30 are more likely to have stone disease whereas, in men over the age of 50, carcinoma should be considered.

The evaluation of the patient presenting with jaundice and pruritus should include blood tests, such as an alkaline phosphatase level and white blood cell count, as well as total and direct serum bilirubin. Bile acids or bile salts are also sometimes measured. These are increased in nearly all types of hepatobiliary disease, however, and are therefore of limited value in determining the cause of jaundice.

When evaluating the patient with hyperbilirubinemia, consideration must be given to hepatic as well as nonhepatic causes of jaundice, the latter being:

- Hemolysis:
  - erythrocytosis
  - elliptocytosis
  - spherocytosis
- Gilbert syndrome.

In order to do this, the clinician must first differentiate between conjugated and unconjugated

hyperbilirubinemia by using total and direct bilirubin assays. Normally, serum bilirubin is almost entirely unconjugated, reflecting a balance between bilirubin production and hepatic elimination. If primarily unconjugated hyperbilirubinemia is present, the patient should undergo an evaluation for hemolysis. Of note, chronic hemolysis does not typically produce elevations of serum bilirubin >5 mg/dL. Evaluation would include a reticulocyte count, peripheral smear, and haptoglobin levels. Serum level of lactic dehydrogenase may also be checked. An abnormality in any of these tests should lead the clinician to consider ineffective erythropoiesis, such as with vitamin B_{12} deficiency, lead toxicity, thalassemia, or sideroblastic anemias. Conditions leading to hemolysis include erythrocytosis, hereditary spherocytosis, and elliptocytosis. Most patients with hemolysis will not be pruritic.

As conjugated bilirubin is excreted in urine, plasma levels >30 mg/dL are uncommon in the absence of renal failure. When hemolysis is excluded in patients with unconjugated hyperbilirubinemia, the diagnosis of Gilbert syndrome must be considered. This is an inherited defect in bilirubin metabolism that affects up to 7% of the population and is benign. Typically, the total serum bilirubin level in this condition does not exceed 3 mg/dL.

In the patient with conjugated hyperbilirubinemia, serum transaminase levels including aspartate transaminase (AST) and alanine transaminase (ALT) as well as an alkaline phosphatase (ALP) level should be measured. These tests help distinguish between primary hepatocellular disease and biliary tract or cholestatic diseases.

Abdominal imaging should also be performed to evaluate the hepatobiliary system. Abdominal ultrasonography is often the first modality utilized. The advantages include wide availability, non-invasive nature, lack of ionizing radiation, and relatively low cost. Ultrasonography is good at differentiating intra- and extrahepatic biliary tract disease, and at identifying gall-bladder pathology [9]. In a comparative study of 131 patients, ultrasonography had a diagnostic accuracy of 80% with a sensitivity of 71% and a specificity of 96% for cholelithiasis [10]. The accuracy declined when abnormalities were noted in the distal common bile ducts or when the patient was obese. Gall-stone disease and malignancy are potential causes and should be considered particularly in the older population.

Computed tomography (CT) may also be used to determine whether the intra- or extrahepatic biliary system is dilated and may be preferred when more precise information about location is desired. Furthermore, CT is less operator dependent, which may provide an advantage over ultrasonography. Of note, the presence of dilated ducts in a patient who has undergone cholecystectomy does not necessarily indicate pathology.

More sophisticated testing to evaluate the cause and level of obstruction, and, to fully evaluate the biliary tree, may include cholangiography. This is particularly important if dilated ducts are indeed noted. The gold standard is endoscopic retrograde cholangiopancreatography (ERCP). This modality not only allows for diagnostic information, but also provides the option for therapeutic intervention. ERCP involves passing an endoscope into the duodenum, introducing a catheter into the ampulla of Vater, and injecting contrast medium into the distal common bile duct and/or pancreatic duct. Percutaneous cholangiopancreatography is reserved for patients in whom ERCP is precluded for anatomic reasons, yet access to the biliary tree is required. This procedure is performed by passing a needle through the hepatic parenchyma and injecting contrast medium into the proximal biliary tree through a peripheral bile duct. Due to its non-invasive nature, magnetic resonance cholangiopancreatography (MRCP) may also be considered. This modality allows for diagnosis, but not intervention, so it is ideal when intervention is not anticipated. CT cholangiopancreatography is another acceptable alternative, but is used less frequently. Endoscopic ultrasonography can also provide a low-risk way to evaluate the distal biliary tree and surrounding tissue. The decision about which modality to utilize should depend on the presumed site of obstruction, the presence of coagulopathy or ascites, and the local expertise of the radiologists and gastroenterologists [11].

The role of liver biopsy is limited in the evaluation of the patient who presents with jaundice and pruritus, and is not indicated in the routine evaluation of suspected obstruction. If underlying hepatic disease is the suspected cause of hyperbilirubinemia, liver biopsy may prove helpful in establishing a specific diagnosis. In general, liver biopsy should be reserved for difficult or confusing cases.

A variety of medications can also contribute to the clinical picture of a patient with jaundice and pruritus. Drugs such as testosterone, chlorpromazine, oral contra-

ceptives, erythromycin, clavulanic acid, allopurinol, and rifampicin may provoke cholestatic jaundice and pruritus, and should be considered in the differential.

Management

The management of a patient who presents with jaundice and pruritus should focus on the offending cause. No specific therapy is recommended for hereditary disorders of biliary metabolism, such as Gilbert syndrome. Therapies in patients with increased bilirubin production should be directed at the underlying disorder, typically hemolysis. For the purposes of this chapter, the authors have focused on the hepatobiliary causes.

In the case of an obstructing lesion that is intrabiliary, ERCP may be of benefit. This modality allows removal of intrahepatic stones. In the case of biliary strictures, balloon dilation or biliary stenting may be performed. The development of strictures may occur in the setting of primary or secondary sclerosing cholangitis.

For those patients who have used a medication that may be to blame, interruption or discontinuation should be considered. If the cause was indeed the medicine, the liver tests should improve over 1–2 weeks. If end-stage liver disease or hepatic failure is the primary cause, consideration of liver transplantation may be appropriate.

Management of pruritus may include one or more medications. First-line therapy is typically diphenhydramine. This may provide relief from the itching while causing drowsiness, which may help the patient sleep through the night. Next, use of a non-absorbable anion exchange resin such as cholestyramine should be considered. The aim of this therapy is to increase the fecal excretion of the pruritogens [12]. Rifampin, although it has been implicated as a potential cause of cholestasis, has also been efficacious when used as treatment for pruritus [13–15]. Treatment with oral naltrexone, an orally bioavailable opiate antagonist, has been shown to be an effective therapy with few side effects [16–18]. Naloxone has also provided benefit in some patients [19,20]. Interestingly, some serotonin HT_3-receptor antagonists such as ondansetron, given intravenously or orally, have also been helpful in the treatment of cholestatic pruritus [21]. In addition, conservative measures such as avoiding hot showers, using topical creams and lotions, and avoiding harsh soaps may provide some benefit.

Take-home points

- Pruritus is a well-recognized manifestation among patients with liver diseases and intrahepatic or posthepatic cholestasis.
- The presence and severity of pruritus in cholestasis do not necessarily correlate with the degree of cholestasis.
- Management of jaundice and pruritus should focus on the underlying cause. In the absence of hemolytic conditions or offending medications, efforts should be directed toward evaluation of the biliary tree.
- Diagnostics to evaluate the cause and level of obstruction, to fully evaluate the biliary tree, and to provide therapeutic interventions may include percutaneous or endoscopic cholangiopancreatography.
- Liver biopsy is of limited usefulness in this setting.
- Medicines that may be of benefit include diphenhydramine, cholestyramine, rifampin, and naltrexone.

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CHAPTER 11
Liver Mass Found on Abdominal Imaging

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Summary
The discovery of a liver mass, whether incidentally or during the investigation of a clinical problem, is a relatively common scenario. Common benign entities include hemangioma, focal nodular hyperplasia, and hepatic adenoma. The diagnosis of adenoma is significant due to a risk of future hemorrhage or malignant transformation. Malignant conditions include hepatocellular carcinoma—to be suspected in the setting of cirrhosis—as well as cholangiocarcinoma and metastatic tumors. A stepwise approach to the liver mass will usually lead to an accurate diagnosis. Furthermore, the capabilities of modern imaging, although not without some risk of patient harm, permit a non-invasive diagnosis in a substantial percentage of cases.

Case
A 58-year-old woman, previously in good health, is referred to a gastroenterologist after presenting to an emergency room (ER) with left lower and suprapubic abdominal pain, with cramping and slight fever. At the ER she was afebrile, hemodynamically stable, alert, and without any cardiopulmonary findings or peritoneal signs. Pelvic exam was normal. Evaluation included urinalysis compatible with urinary tract infection, and she was prescribed an oral antibiotic. Before discharge she underwent a contrast-enhanced abdominal–pelvic CT scan, which was negative except for an incidental 3 cm mass in the left lobe of the liver which appeared to take up contrast. She presents for an opinion on the newly described liver mass.

Evaluation of Liver Masses

The prevalence of liver masses in the general population is unknown. Autopsy series suggest that common benign tumors such as hemangiomas are present in up to 20% of patients [1,2]. The widespread use of abdominal imaging has not surprisingly been accompanied by the frequent discovery of incidental liver lesions, which in turn commonly result in gastroenterology or hepatology referrals. Discovery of a liver mass, whether incidentally or during the investigation of symptoms, can lead to considerable patient anxiety. Physicians may also feel challenged because a gold-standard tissue diagnosis cannot be obtained without invasive liver biopsy and its attendant risks. Fortunately, clinical assessment combined with modern imaging can lead to an accurate diagnosis *without biopsy* in the vast majority of circumstances [3,4]. This chapter reviews diagnostic and management strategies for liver masses.

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Benign Liver Lesions

Liver Cysts

Any consideration of liver masses requires that they be categorized separately from liver cysts. Hepatic cysts may be simple or complex, single or multiple, and are readily distinguished from mass lesions by ultrasonography,

computed tomography (CT), or magnetic resonance imaging (MRI). Simple liver cysts—those without thickened septations or internal echoes—are rarely symptomatic and typically require no follow-up [5,6]. Occasionally large cysts may lead to abdominal pain. In this circumstance, aspiration with or without injected sclerosant may afford temporary relief, but recurrence is the rule [7,8]. Laparoscopic unroofing appears to provide much better long-term efficacy and has been proposed as a new standard by some groups [9]. This technique also allows for histologic analysis of the portion of cystic wall removed during the unroofing, in order to exclude biliary cystadenoma which has malignant potential and generally should be resected completely [6]. Cystadenoma should be considered when imaging suggests abnormally thickened walls or septa, or when there is evidence of dilated or obstructed biliary ducts adjacent to the cyst. Magnetic resonance cholangiopancreatography (MRCP) may be useful when suspicion of a cystadenoma exists (Figure 11.1).

Echinococcal cysts, although rare, should be considered in patients with cholestatic features either clinically or by imaging, or when there is a history of Mediterranean or South American travel. Occasional patients with echinococcal cysts present with longstanding unexplained episodes of urticaria or anaphylaxis; echinococcal serology is usually positive in affected patients [6]. Traditional treatment has been open surgical resection, but less invasive alternatives now exist that involve the use of albendazole or mebendazole before and after cyst aspiration [10]. Anaphylaxis remains a rare but serious potential complication of surgery or percutaneous drainage, although that risk appears to be diminished by the use of antiparasitic agents before intervention.

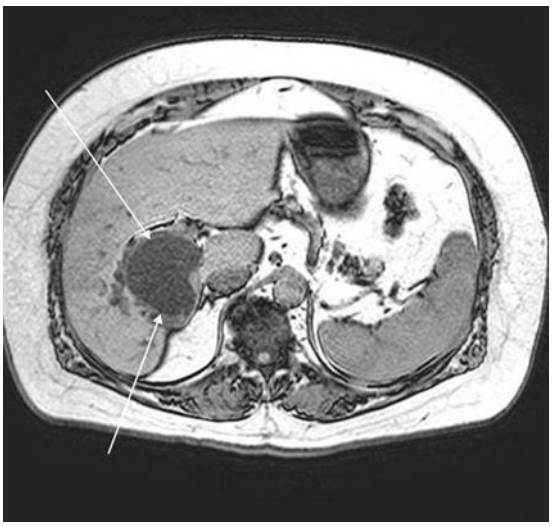

Figure 11.1 Magnetic resonance imaging demonstrates biliary cystadenoma with thickened walls (arrows), causing focal biliary dilation and displacement of a vessel.

Patients with polycystic liver disease, including those with associated polycystic kidney disease, may present with innumerable cysts occupying the entire liver, although hepatic function is typically normal. Patients may become symptomatic if cysts become enlarged and/or distort the hepatic contour. Echogenic material seen on ultrasonography within cysts may be a clue to prior spontaneous cyst rupture or hemorrhage, sometimes associated with sudden severe pain but rarely any hemodynamic compromise. Patients with massive cystic enlargement leading to distortion and painful distension of the abdomen should be referred for consideration of liver transplantation [11].

Hemangioma

Cavernous hemangiomas are the most common benign liver tumors and are usually discovered incidentally. Hemangiomas are usually <5 cm in size, have a slight female predominance, and exist as solitary lesions in 85–90% of cases [12]. When multiple liver hemangiomas are present, they may also be found in the lung, skin, and brain. Unless large and convincingly symptomatic, these tumors seldom require treatment. However, larger lesions, particularly "giant cavernous haemangiomas" in excess of 15 cm, are more likely to cause pain, in which case resection is an appropriate consideration [13]. Rare events of spontaneous or trauma-induced rupture may result in hemorrhagic shock requiring emergency surgery or arterial embolization [12]. For exceedingly large hemangiomas, a form of coagulopathy (Kasabach–Merritt syndrome) has been reported, which is presumably the result of hypofibrinogenemia from ongoing bleeding and clotting within the lesion [14]. There are extremely rare reports of successful liver transplantation for this occurrence [15].

The appearance of hemangioma varies according to imaging modality. On ultrasonography, hemangiomas are bright lesions with internal bright echoes reflecting pooled blood and partial thrombi [16]. Doppler analysis

may reveal supplying vessels but usually no circulating blood within the core of the lesion [4]. CT reveals a hypodense, well-demarcated mass with early phase globular areas of enhancement in the periphery, and sometimes more central puddling of contrast on delayed phases [17]. The use of timed CT contrast allows hemangiomas to be distinguished from metastatic lesions with a sensitivity and specificity over 85% [18]. MRI shows hemangioma to have a hyperintense T2-weighted appearance and hypointense T1-weighted signal, markedly distinct from surrounding normal liver, and often containing internal lobulations (Figure 11.2). MRI is the most accurate imaging modality for the diagnosis of hemangioma, with a sensitivity approaching 100% and a specificity over 90% [4]. For a suspected hemangioma with atypical appearance on CT or MRI, a tagged red blood cell scan may be useful as a confirmatory test, particularly for larger lesions.

Pathologically, hemangiomas are well-demarcated spaces lined by a single endothelial layer, with fibrous septations and pools of blood, as well as thrombi and occasional calcifications [19]. Hemangiomas can be reliably diagnosed in most cases by imaging, and biopsy is to be avoided except in cases of real doubt, due to the risk of bleeding. A confident radiographic diagnosis in an asymptomatic patient requires no follow-up if the lesion is small. Larger lesions, especially those >10–15 cm, may require periodic radiographic and clinical monitoring due to the higher risk of rupture.

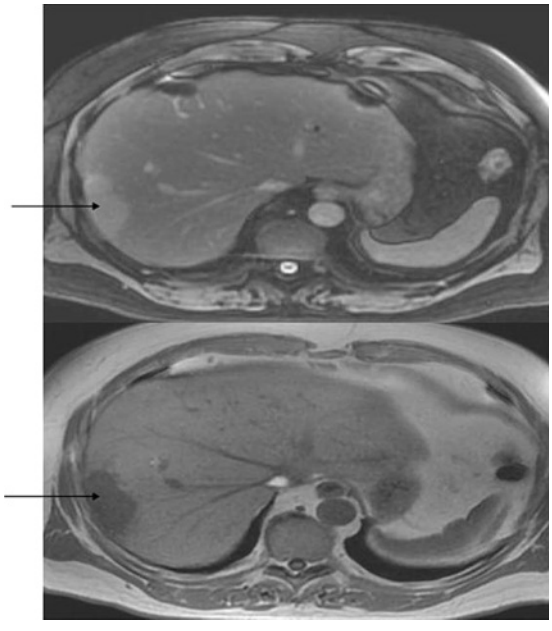

Figure 11.2 T2-weighted (upper picture) and T1-weighted magnetic resonance image of right lobe hemangioma.

Focal Nodular Hyperplasia

Focal nodular hyperplasia (FNH) is characterized by a benign nodular hyperplastic mass occurring in the liver. Tumors are usually <5 cm, unencapsulated, and exist as single lesions in 80% of cases [19]. There is a strong female predominance with at least a 6:1 female:male ratio [12]. Pathologically, FNH consists of a classic central fibrous scar, with peripheral radiations into the surrounding nodular tissue [20] (Figure 11.3). The nodular periphery of FNH contains sinusoids with Kupffer cells, but otherwise lacks typical hepatic architecture, with no portal triads or central veins, and a large amount of bile ductular proliferation [12].

FNH is usually an asymptomatic, incidental finding. However, hepatomegaly is sometimes noted and rarely a large FNH can result in a palpable mass [20,21]. Despite the strong female preponderance, published data have not yielded a consistent, convincing link between FNH and oral contraceptive (OC) use [12,22]. This suggests a different pathogenic process of FNH formation than that of hepatic adenoma, with which OC exposure is clearly associated.

On ultrasonography, FNH may appear hyper- or isoechoic compared with surrounding liver, and the

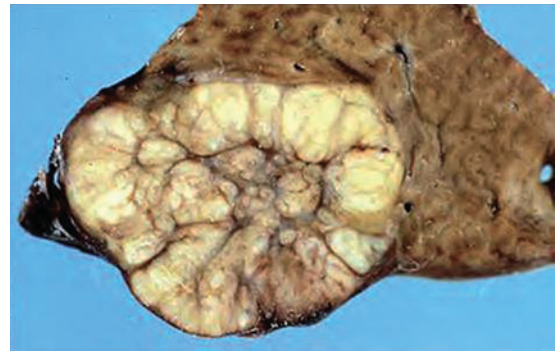

Figure 11.3 Resected 7 cm focal nodular hyperplasia demonstrating classic central scar with peripheral nodular radiation.

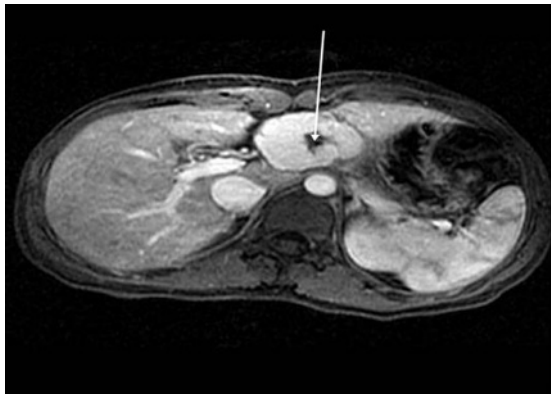

Figure 11.4 Left lobe focal nodular hyperplasia on delayed (1 h post-contrast) magnetic resonance image—retained enhancement around prominent central scar (arrow).

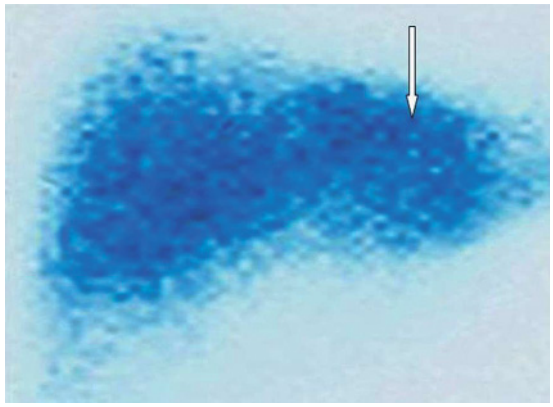

Figure 11.5 ^{99m}Tc-labeled sulfur colloid scan—prominent left lobe (arrow) uptake by focal nodular hyperplasia, distinguishing it from adenoma which would have appeared as a void.

classic central scar is not visible in 80% of cases [23]. Ultrasonography is therefore of limited utility for the diagnosis of FNH. Contrast-enhanced CT demonstrates FNH to have very early hyperenhancement peripherally and delayed enhancement centrally [24]. MRI reveals FNH to be iso- or hypointense on T1-weighted images, and iso- or mildly hyperintense on T2-weighted images [25]. After the use of gadolinium contrast, the enhancement pattern parallels that of CT, with early peripheral enhancement and more delayed central enhancement [4]. However, precontrast or real-time contrast-enhanced MR images may not distinguish FNH from hepatic adenoma (HA). Such differentiation may require delayed images, in which case the histologic features of FNH aid in its diagnosis. Contrast accumulates in the abundant biliary ductules of FNH such that 1–3 h delayed imaging can reveal persistent hyper- or isointensity (compared with the hypointense delayed appearance of adenoma) (Figure 11.4). One study of gadobenate dimeglumine-enhanced MRI using delayed imaging made possible the differentiation of FNH from HA with 97% sensitivity and 100% specificity [26].

Visualization of the central scar is the major advantage of both CT and MRI in the differentiation of FNH from HA and other conditions. But in cases where the central scar is poorly seen, scintigraphy with ^{99m}Tc-labeled sulfur colloid may be useful due to the presence of abundant Kupffer cells in FNH, which accumulate colloid. FNH nodules will appear hyper- or isodense to the surrounding liver on sulfur colloid scanning, as opposed to HA, which does not usually accumulate colloid and appears as a pale "void" in the liver [27] (Figure 11.5).

Except in cases of larger lesions causing pain, FNH does not require surgical removal, and patients can be reassured that data have not demonstrated a compelling risk of malignant transformation. Lesions may be periodically re-imaged at 6- to 12-month intervals for a period of 2 years to assure stability, although size may fluctuate slightly. The risk of spontaneous rupture and bleeding is exceedingly low [4]. Although OCs and other estrogen usage have not been causatively linked to FNH occurrence or size, individual FNH lesions may enlarge during pregnancy. For this reason, resection of larger (≥5 cm) lesions, especially those located near the liver capsule, may be considered in select cases of contemplated pregnancy. Liver biopsy is reserved for cases where imaging has failed to exclude FNH from adenoma or malignancy with reasonable confidence.

Adenoma

Adenoma of the liver is a benign mass neoplasm consisting of proliferating hepatocytes. This lesion is strongly associated with the use of OCs and androgen steroids, and certain types of glycogen storage disease [28–30]. The incidence of HA has increased in the past four decades, paralleling the increased use of OCs in this era [31–33]. Sheets of hepatic cords comprise the histology of HA, with cells the same size or slightly larger than

normal surrounding hepatocytes [19]. Kupffer cells are lacking in number compared with normal liver architecture and especially compared with FNH, which accounts for the voided appearance of HA on a sulfur colloid scan [12]. HA is fed by characteristic prominent arterial vessels that course along the periphery of the lesion, which usually lacks a true capsule [19,28]. Accordingly, the demarcation of HA from surrounding normal liver tissue may be vague. Equally problematic is the well-characterized difficulty in histologically distinguishing HA from well-differentiated hepatocellular carcinoma (HCC) [19]. For this reason, and because of the bleeding risk, biopsy is ideally avoided, being reserved for situations where radiological impression is uncertain and tissue results will determine management. When biopsy of possible HA is performed, it should be done with imaging guidance of the needle trajectory, using an approach that places sufficient liver parenchyma between the mass and the site on the capsular surface where the needle enters the liver. In this manner, if the lesion bleeds there is likely to be a tamponade effect from the surrounding parenchyma. A surface adenoma approached directly—with no parenchymal tissue between it and the site of needle entry into the liver—is more likely to bleed substantially into the peritoneal cavity.

HA is typically found incidentally in a woman of childbearing age with a significant duration of OC usage. Lesions are usually single tumors, but up to 30% of affected patients have multiple adenomas [12,34]. Adenomas rang from 3 cm to 8 cm in size, although larger lesions do occur [19]. The radiographic diagnosis of adenoma may be challenging. On ultrasonography, there are no specific features of adenoma that allow it to be easily distinguished from other benign or malignant lesions. HA may appear iso- or hyperechoic to surrounding hepatic parenchyma, and occasionally Doppler ultrasonography reveals peripheral arterial feeding vessels [4]. CT demonstrates HA to be hypodense on non-contrast images (Figure 11.6), with early and strong enhancement after contrast and rapid washout [35]. Larger lesions may be more heterogeneous with a peripheral-to-central pattern of enhancement and more delayed washout [4]. MRI demonstrates hyperintensity of HA on T2-weighted images, with variable T1-weighted appearance and early arterial enhancement after the use of gadolinium-based contrast [36]. The major differences between the MRI appearance of hemangioma and that of HA are the more heterogeneous composition and rapid washout pattern of the latter [4]. However, these same features may be seen in malignant lesions, particularly HCC occurring in a patient with cirrhosis. The clinical context must, therefore, guide the approach to a liver mass for which adenoma is considered within the differential diagnosis.

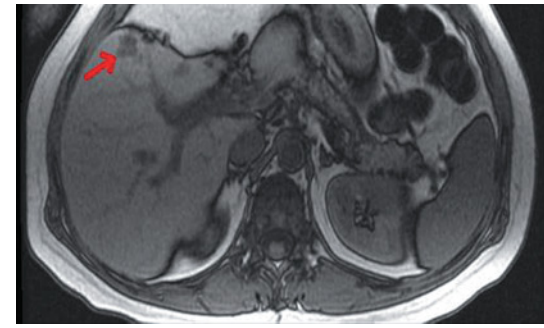

Figure 11.6 Non-contrast computed tomography scan obtained in 35-year-old woman with longstanding oral contraceptive use. Small hypodense mass consistent with adenoma (arrow).

The major clinical significance of HA is the potential for pain, spontaneous rupture with hemorrhage, and malignant transformation. Pain is more likely in larger lesions, although smaller lesions that have undergone intratumoral bleeding may also cause discomfort. The risk of bleeding from an adenoma is difficult to estimate. Published reports suggest that radiographic or surgical evidence of intratumoral bleeding is found in up to 29% of cases [37], with higher estimates for women who continue OCs [38]. However, the percentage of patients who present with hemodynamically significant bleeding is considerably less. Malignant transformation, based on published surgical and pathology reviews, appears to occur in 5% [37] to 18% [39] of cases, with most published data suggesting a risk near the middle of these parameters.

For the most common clinical scenario—that of an incidentally discovered HA in a reproductive-age woman with longstanding OC use—the first step is elimination of OCs. Adenomas may regress or even disappear after cessation of OCs [40,41]. For lesions that fail to disappear completely, ongoing monitoring or resection is required due to the potential for subsequent growth after a period of initial regression, including the potential for eventual hemorrhage [42] and malignant transformation [43,44]

long after OC withdrawal. There is debate about the management of small (<3 cm) asymptomatic adenomas, with some favoring resection due to the potential for bleeding and malignancy, and others favoring serial radiographic observation. Patients should be informed of the risks of both observation and resection, and advised to avoid OCs. This advice may not be followed by some patients, and it should be noted that pregnancy may also stimulate adenoma growth. As a result of this, stronger consideration for resection may be appropriate in the setting of contemplated pregnancy. The location of the adenoma also influences decision-making, as surface lesions pose concern for hemoperitoneum and greater blood loss. Larger adenomas, unless occurring in surgically unfit patients, should generally be resected [12,37,45]. The role of locoregional therapy (transarterial chemo- or bland embolization [TACE/TABE], radiofrequency ablation) in the treatment of HA is evolving. Arterially directed therapy appears to have a role in the treatment of bleeding or when imaging suggests impending rupture, particularly in cases where HA location or the patient's clinical status renders the surgery high risk [46].

Hepatic adenomatosis is a rare condition characterized by multiple (more than five) adenomas, and the term implies a disorder distinct from HAs associated with OC use, androgen steroids, or glycogen storage disease. A recent study suggests a link between hepatic adenomatosis and a form of maturity-onset diabetes of young people (MODY) [47]. Liver imaging to screen for adenomas in patients with newly diagnosed MODY should therefore be considered. Unless clustered in a single hepatic lobe, potentially facilitating resection of all lesions, the management of multiple adenomas is challenging. Liver transplantation has been successfully performed in this circumstance [48,49], but is controversial given that organs are scarce and most affected patients will *not* develop cancer or fatal bleeding. Some propose resection or TACE/TABE of the largest and/or most peripheral lesions, and successful treatment with both modalities has been reported [50,51]. Observation with serial imaging has also been advocated, reserving treatment for lesions that appear to be at risk of impending rupture or show other worrisome changes.

Nodular Regenerative Hyperplasia

Nodular regenerative hyperplasia (NRH) is a benign disorder characterized by the presence of multiple proliferative nodules of hepatocytes. The size of individual nodules ranges from a few millimeters to a few centimeters, and they may be sufficiently numerous and widely distributed to create a cirrhotic appearance on imaging, with a nodular liver contour [4]. Grossly, NRH may resemble cirrhosis (Figure 11.7) but histologic review can distinguish the two, mainly due to the absence of fibrous bands in the former. However, unless there is clinical suspicion the diagnosis may be missed on routine fine-needle aspiration or biopsy [12]. The use of reticulin stains on submitted biopsy tissue aids in the diagnosis [52]. Theories about the pathogenesis of NRH have centered on either obliterative changes affecting the portal microcirculation or a generalized proliferative hepatic process [12]. The disease is a leading cause of non-cirrhotic portal hypertension and may present with complications such as new-onset variceal bleeding. Alternatively, it may be found incidentally on imaging studies or during the work-up of splenomegaly and thrombocytopenia.

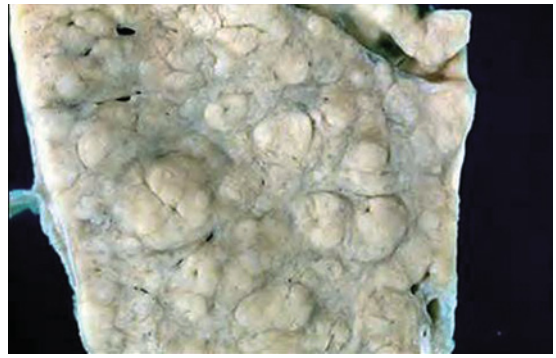

Figure 11.7 Explanted liver specimen from a patient with nodular regenerative hyperplasia.

NRH is often idiopathic, but the disorder has been linked to several rheumatologic and lymphoproliferative conditions as well as inflammatory bowel disease (IBD). The condition appears to be more common among patients previously treated with azathioprine [53] or 6-thioguanine [54], although there is a background incidence among thiopurine-naïve IBD patients [55]. Reversibility of NRH after cessation of azathioprine has been observed, although rarely [56]. The condition has also been recently described as a cause of new-onset portal hypertension in patients with HIV [57].

The treatment of NRH depends on the clinical presentation. Management of the underlying associated condition, if there is one, is necessary. Asymptomatic NRH can

be monitored observantly, with consideration given to screening for occult esophageal varices. When NRH presents with a manifestation of portal hypertension, the event is managed in the same manner as a patient with cirrhosis. The exception is that liver transplantation is seldom needed given the usually preserved synthetic hepatic function. Thus portal hypertension in NRH may be successfully managed with long-term radiological (transjugular intrahepatic portosystemic shunt) or surgical shunts [58]. Although there are rare case reports of HCC occurring in patients with NRH, in most cases there were changes to the liver microvasculature caused by the tumor or its treatment (TACE), suggesting that NRH was the result—not the cause—of HCC [59–61]. Rare patients with severe portal hypertension from NRH may experience clinical deterioration from hepatic insufficiency. In such cases liver transplantation is associated with favorable outcomes comparable to those for more common indications [62].

Macroregenerative and Dysplastic Nodules

Macroregenerative nodules (MRNs) and dysplastic nodules (DNs) are masses that occur in the setting of parenchymal liver injury or a vascular insult to the liver. The primary difference is that the former is considered to be a reactive phenomenon, whereas the latter is a neoplasm that has strong potential for becoming HCC [28]. Radiographic distinction between the two conditions may be difficult, and the clinical context must guide decision-making. MRNs have been described in association with biliary atresia in patients awaiting liver transplantation [63], and may generate false concern for a malignant process. The diagnosis of DN is often radiographically assigned to a mass found in a patient with cirrhosis who is under surveillance for HCC, when the mass lacks either the size or typical enhancement features of a hepatoma. Thus lesions >2 cm are rarely DNs because they are more likely to be malignant, an adenoma or FNH, or MRNs which can range in size from 5 mm to several centimeters [28].

Miscellaneous Benign Lesions

A host of less common liver lesions are encountered from time to time in hepatology practice. Bile duct harmartomas are small (<1 cm) nodules of biliary tissue separate or isolated from the biliary tree. Usually unseen on imaging studies, they are found incidentally in the surgical setting, usually located on the liver surface. The major clinical significance is that they may be mistaken grossly for metastatic disease even though they are benign, lack malignant potential, and do not typically require resection [12]. Histologic review (including operative frozen section) clarifies the diagnosis. An angiomyolipoma (AML) is a benign growth containing fat and smooth muscle cells in addition to vascular tissue. An AML is much more commonly found in the kidney, and thus when seen radiographically in the liver it may be misdiagnosed as sarcoma [19]. A hepatic AML may be associated with pain, in which case resection is appropriate [12]. Inflammatory pseudotumor (IPT) is a rare, benign, infiltrative liver process associated with fever, weight loss, and laboratory indicators of inflammation. Histologically, IPTs are made up of plasma cells, lymphocytes, and macrophages, as well as fibrous stroma [19]. The condition gets its name because it is difficult to distinguish from a malignant process radiographically, and clinically patients may present with cachexia and other symptoms encountered in cancer. When encountered, IPT is usually resected although spontaneous resolution may occur [64]. The cause of IPT is unknown.

Malignant Liver Lesions

Cancers of the liver are considered separately in this text, and a detailed review is thus not contained in this chapter. Important considerations include the doubling of HCC incidence over the last three decades in Western nations, almost certainly the result of the hepatitis C epidemic [65]. Thus, a hypervascular mass in a patient with cirrhosis should be considered a hepatoma until proven otherwise. There is debate about the utility of routine HCC screening in patients with cirrhosis and hepatitis B carriers. However, the preponderance of data as recently reviewed now indicates that screening such patients lowers mortality [66]. For unknown reasons, intrahepatic cholangiocarcinoma has been increasing in incidence over the past two decades [67]. As highly selected patients with hilar cholangiocarcinoma may benefit from liver transplantation after chemoradiation, vigilance for this tumor is also warranted [68]. Other malignant processes such as epithelioid hemangioendothelioma and neuroendocrine tumors without extrahepatic foci may also be successfully treated with liver transplantation, although the latter has an appreciable recurrence rate.

Metastatic cancer and lymphoma remain common liver entities, and an increasing array of surgical, radiological, and medical tools is being focused on these conditions.

Risks of Liver Imaging

Increasing attention is being devoted to the cumulative risk of radiation exposure associated with CT, particularly serial CT scans performed for HCC surveillance. In addition, the risk of nephrogenic systemic fibrosis (NSF) as a consequence of gadolinium-based MRI contrast has recently been highlighted in certain patients. NSF has a rapidly fatal course in a small percentage of patients. Patients at risk of NSF after gadolinium exposure include those with severe impairment of renal function, those in the perioperative period following liver transplantation, and those with hepatorenal syndrome of any severity [69]. The US Food and Drug Administration has issued a "black box" warning on the use of gadolinium-based MRI contrast in such settings. As with all medical decision-making, providers must carefully weigh the risks of liver imaging with the intended benefit.

Take-home points

- In most cases of liver masses, an accurate diagnosis can be made non-invasively.
- Hemangioma is the most common benign liver mass.
- Focal nodular hyperplasia is a benign entity that may be distinguished radiographically from other conditions by its classic central scar and its tendency to retain MRI contrast on delayed images.
- Hepatic adenomas have malignant potential and may cause serious bleeding.
- A hypervascular mass in a cirrhotic patient is cancer until proven otherwise.
- Physicians should recognize the risks associated with various imaging techniques.

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CHAPTER 12

Right Upper Quadrant Abdominal Pain

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Summary

Diseases of the liver, biliary organs, stomach, pancreas, and intestine can cause right upper quadrant (RUQ) pain. Disorders of other organ systems such as the heart, lung, kidney, adrenal glands, spine, lymphatic system, skin, and endometrium may also produce RUQ pain. The clinical history and symptoms of each disease process often have characteristics that can help clinicians formulate a working differential diagnosis. In order to offer appropriate, cost-effective, and timely care to patients with RUQ pain, physicians should take a stepwise approach in diagnosis and treatment.

Case

A previously healthy 50-year-old woman presents to the emergency department with severe pain in the right upper quadrant, which started 20 h earlier after eating a meal. In the waiting area, she had one episode of vomiting. She reports previous episodes of right upper quadrant and epigastric pain for up to 3 h but has not sought medical attention. On physical examination, her temperature is 39 C, and she has tenderness and guarding in the right upper quadrant. How should her condition be evaluated and treated?

Introduction

Abdominal pain is present on questioning 75% of otherwise healthy adolescent students [1] and about half of all adults [2]. It is one of the top ten outpatient complaints, and it is the chief complaint of 5–10% of patients presenting to emergency departments [3]. Due to the many organ systems in the abdomen, abdominal pain is a concern of general practitioners/family physicians, surgeons, internists, emergency medicine doctors, pediatricians, gastroenterologists, urologists, and gynecologists. Occasionally, patients with rare causes can see a number of specialists before being diagnosed correctly (e.g., chronic functional abdominal pain). Abdominal pain can be one of the symptoms associated with transient disorders or serious diseases. Establishing a definitive diagnosis of the cause of abdominal pain can sometimes be quite challenging because this symptom is shared by a variety of pathologic conditions.

Diseases of the liver, biliary organs, stomach, pancreas, and intestine certainly can cause right upper quadrant (RUQ) pain. Disorders of other organ system such as the heart, lung, kidney, adrenal glands, spine, lymphatic system, skin, and endometrium may also produce RUQ pain. One should not assume that if a patient presents with RUQ pain, she or he must have a problem with the GI tract. The differential diagnosis for RUQ pain is broad (Table 12.1). This chapter discusses

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Table 12.1 Causes of right upper quadrant pain.

Biliary	Calculi, infection, inflammation, neoplasm
Hepatic	Hepatitis, abscess, congestion, neoplasm, trauma, biopsy
Gastric	Peptic ulcer disease, pyloric stenosis, neoplasm, gastritis, hiatus hernia
Pancreatic	Pancreatitis, neoplasm, calculi
Intestinal	Retrocecal appendicitis, intestinal obstruction, high fecal impaction, Crohn disease
Cardiac	Myocardial ischemia (particularly inferior wall), pericarditis
Renal	Calculi, infection, inflammation, rupture of right kidney
Pulmonary	Pneumonia, pulmonary infarction, right-sided pleurisy
Lymphatic	Mesenteric adenitis, Hodgkin disease, lymphosarcoma
Cutaneous	Herpes zoster, cellulitis
Adrenal	Neuroblastoma
Thoracic spine	Tuberculosis, arthritis, herniated discus, neoplasm
Gynecologic	Fitz-Hugh–Curtis syndrome
Psychological	Functional abdominal pain

some of common causes for RUQ pain in clinical practice.

Biliary Diseases that Cause RUQ Pain

Biliary Colic

Biliary colic produces severe, deep, gnawing, constant pain that is localized in the RUQ or epigastrium. The pain occurs in distinct episodes and occurs without warning. It is usually caused by a stone pressed against the gall-bladder outlet or cystic duct opening during gall-bladder contraction in response to a meal. These pain attacks occur multiple times and usually go away one to several hours later as the gall bladder relaxes and the stone falls away from the area of compression.

Acute Cholecystitis

Acute cholecystitis produces persistent and severe pressure type of pain in the RUQ or epigastrium with radiation to the back or right shoulder. It occurs in the settings of chronic prolonged obstruction of the cystic duct by gall stones (calculus cholecystitis) or a non-functioning gall bladder in a very sick patient with systemic illness in the absence of gall stones (acalculus cholecystitis). Associated symptoms may include nausea, vomiting, anorexia, fever, and chills. Onset of all symptoms may be preceded by fatty food ingestion several hours earlier. The patient described in the clinical case above has the classic presentation of acute calculus cholecystitis. Most patients with acute cholecystitis have had attacks of biliary colic, but some have had no previous biliary symptoms [4–6]. After an initial attack of acute cholecystitis, additional attacks of pain or inflammation are common [7]. In a small proportion of patients, acute cholecystitis may coexist with choledocholithiasis, or gall-stone pancreatitis [8].

Acute Cholangitis

Acute cholangitis occurs when the main bile duct or intrahepatic bile ducts are obstructed, leading to bile duct dilation and bacterial superinfection. Common causes of obstruction include stone, mass, stricture, occluded bile duct stent, and parasites (e.g., ascariasis). Jaundice, clay-colored stools, cola-colored urine, and pruritus are common. The classic triad of Charcot—fever, RUQ pain, and jaundice—occurs in only 50–75% of patients with acute cholangitis [9]. RUQ pain is typically vague. Hypotension and mental status decline can occur in patients with suppurative cholangitis, producing the Reynold pentad, which is associated with significant morbidity and mortality [10]. Hypotension may be the only presenting symptom in elderly patients or those on corticosteroids [10].

Gall-stone Pancreatitis

Gall-stone pancreatitis is the most common causes of acute pancreatitis in the USA [11]. It occurs when the pancreatic duct is occluded by gall stones or biliary sludge, usually at the level of the papillary pancreatic ductal orifice, leading to activation of digestive enzymes within the pancreas. Pain produced by gall-stone pancreatitis can be in the RUQ but it is more commonly located in the epigastrium, with radiation to the back. Gall-stone pancreatitis should be suspected when there is a prior

history of biliary colic and absence of alcohol use in the setting of acute pancreatitis.

Sphincter of Oddi Dysfunction

Sphincter of Oddi dysfunction should be suspected in patients who have biliary-type RUQ pain without other apparent causes. It is also known as sphincter of Oddi (SOD) dyskinesia, a functional disturbance of the sphincter of Oddi, leading to intermittent biliary obstruction. SOD is most commonly recognized in patients who have undergone cholecystectomy (hence the name postcholecystectomy syndrome). The reasons for this are not well understood, but may be related to unmasking of preexisting SOD due to removal of the gall bladder, which may have served as a reservoir to accommodate increased pressure in the biliary system occurring during sphincter spasm [12]. However, SOD is an uncommon occurrence after cholecystectomy and SOD also occurs in patients whose gall bladders are intact, suggesting that other pathophysiologic mechanisms are involved [13].

Hepatitic Diseases that Cause RUQ Pain

Viral Hepatitis

Viral hepatitis can produce vague RUQ pain. In hepatitis A, prodromal symptoms, including fatigue, malaise, nausea, vomiting, anorexia, fever, and RUQ pain, are common. They usually diminish as jaundice appears [14]. Acute hepatitis B infection has a variable clinical course in different patients, ranging from minimal or no symptoms to hepatic failure. RUQ pain or discomfort can be a part of prodromal symptoms and usually disappears in 1–3 months. RUQ pain is rarely seen in patients with acute hepatitis C, chronic hepatitis B, or chronic hepatitis C.

Pyogenic Liver Abscess

Pyogenic liver abscess produces abdominal symptoms that occur in 50–75% of patients [15]. Abdominal symptoms are generally localized to the RUQ and may include pain, guarding, rocking tenderness, and even rebound tenderness. About half the patients with a liver abscess have hepatomegaly, RUQ tenderness, or jaundice [15]. Thus, the absence of RUQ findings does not exclude liver abscess.

Budd–Chiari Syndrome

Budd–Chiari syndrome is a pathologic condition in which thrombosis of the hepatic veins and/or the intrahepatic or suprahepatic inferior vena cava causes interruption or diminution of the normal blood flow out of the liver. Patients usually present with severe RUQ pain and hepatomegaly. Jaundice and ascites may not be apparent initially, but often develop rapidly. Variceal bleeding may also occur [16].

Liver Cancers

Liver cancers, including primary and metastatic tumors, rarely produce RUQ pain or discomfort in the early stages. When patients present with RUQ pain, usually there is significant liver congestion and/or mass effect on the liver capsule by the tumor.

Trauma

Trauma to the abdomen may cause liver laceration and sudden-onset RUQ pain. It can also produce delayed onset of RUQ pain by causing bleeding/hemobilia, and mass effect on the liver capsule. Although rare, *liver biopsy* can cause RUQ pain by inducing hemobilia, which may lead to mass effect on the liver capsule, obstructive cholangitis, or pancreatitis [17–19].

Erythromycin

Erythromycin is available to the clinician in several forms, each of which differs primarily because of a single substitution at the two-prime position of the desamine moiety. All commonly available forms can be associated with mild abdominal cramping, nausea and vomiting, diarrhea, and hypersensitivity reactions. Hepatotoxicity, presenting dramatically with fever and abdominal pain mimicking gall-stone disease, has been associated with the estolate and ethylsuccinate forms of the antibiotic. Transaminase serum levels are atypically increased less than 10 times normal, with mild elevation of alkaline phosphatase and total bilirubin. Increased peripheral eosinophils occur in up to 50% of cases [20,21].

Gastric and Intestinal Diseases that Cause RUQ Pain

Gastric and duodenal ulcer, duodenitis, colitis involving the hepatic flexure, diverticulitis of the right and trans-

verse colon, retrocecal appendicitis, and Crohn disease of the hepatic flexure may all produce RUQ pain and leukocytosis, although they can be differentiated by taking a careful history and performing imaging or endoscopic studies.

Pancreatic Diseases that Cause RUQ Pain

Patients with acute pancreatitis almost all have sudden-onset upper abdominal pain. The pain is generally persistent and locates in the epigastrium, RUQ, diffusely, or, rarely, in the left upper quadrant with band-like radiation to the back. Different from biliary colic, which lasts for only a few hours, the pain of acute pancreatitis can last for days or even weeks if large pseudocysts are formed. The patient's pain is frequently relieved by bending over because this maneuver can transiently decrease the irritation of the retroperitoneum.

Chronic Pancreatitis and Pancreatic Cancer

Chronic pancreatitis and pancreatic cancer can also produce steady epigastric and RUQ pain. Patients with this conditions often complain about weight loss, poor appetite, and loose stools.

Pulmonary Diseases that Can Cause RUQ Pain

Pneumonia and Pulmonary Emboli

Pneumonia and pulmonary emboli of the right lower lobes of the lung may produce RUQ pain by causing diaphragmatic irritation. Patients with these conditions may have fever and leukocytosis, so their symptoms can be very similar to those of acute cholecystitis. They may or may not have a cough or respiratory distress. RUQ pain can be the sole presenting symptom in some patients with lower lobe pneumonia or pulmonary emboli.

Cardiac Diseases that Can Cause RUQ Pain

Poorly localized epigastric and RUQ pain can be the presenting symptom for acute *myocardial infarction* and *myocarditis*. Elderly patients and patients with risk factors for these conditions should have appropriate cardiac work-up done such as a 12-lead EKG and cardiac enzymes.

Renal Diseases that Can Cause RUQ Pain

Pyelonephritis and *nephrolithiasis with obstruction of upper ureter or renal pelvis* often lead to flank pain or tenderness. They may also produce RUQ pain that waxes and wanes in some patients and should be considered if the patient has other associated urinary symptoms or prior history.

History and Physical Examination

History

The history should ideally be obtained from a patient with unaltered mental status. The physician should obtain general information about the pain's location, radiation, onset, duration, severity, and quality of pain, and about exacerbating and remitting factors.

Associated symptoms often allow the physician to further focus the differential diagnosis, e.g., in a setting of acute cholangitis, fever and jaundice are the associated symptoms with high positive predictive value. For right lower lobe pneumonia, productive cough and pleural chest pain are helpful in guiding the work-up for the RUQ pain.

Past medical history is often helpful, e.g., a history of peptic ulcer disease due to NSAIDs (non-steroidal anti-inflammatory drugs) or *Helicobacter pylori* infection should prompt the physician to think about perforated duodenal/gastric ulcer. A history of atypical angina should alert the physician to consider the possibility of inferior wall myocardial infarction. Kidney stones or pyelonephritis in the past should guide the physician to think about the renal causes of RUQ pain. A female patient with a history of pelvic inflammatory disease related to sexually transmitted infections presenting with RUQ should prompt the physician to include Fitz-Hugh–Curtis syndrome in the differential diagnosis.

Symptoms in patients with RUQ pain that suggest surgical or emergency conditions include fever, protracted vomiting, decrease in mental status, syncope or presyncope, and evidence of GI blood loss.

Physical Examination

The patient's general appearance, mental status, and vital signs can help formulate the differential diagnosis and initiate the appropriate work-up. Patients with myocardial infarction or peritonitis due to a perforated GI tract tend to lie very still, whereas those with renal colic or acute pancreatitis would frequently change their positions. Altered mental status can be observed in cholangitis, pyelonephritis, and myocardial infarction; however, it is not a clinical feature in patients with SOD or functional abdominal pain. Fever is very suggestive of infection; nevertheless, its absence does not rule it out, especially in elderly or immunocompromised patients. Orthostatic hypotension and tachycardia suggest hypovolemia.

Physicians should pay close attention to the cardiac and lung examinations in patients with risk factors for cardiopulmonary conditions that can be the cause of the RUQ pain.

Inspection of the abdominal wall without clothes is important and should not be skipped because infections such as herpes zoster and cellulitis, and trauma, may be the cause of the RUQ pain.

Hepatomegaly is suggestive of hepatic source for RUQ pain such as the Budd–Chiari syndrome, liver abscess, or liver cancer. The Murphy sign is indicative of acute cholecystitis, although it can be unreliable in older patients [22]; the psoas sign in patients is suggestive of retrocecal appendicitis.

The Carnett sign (i.e., increased pain when a supine patient tenses the abdominal wall by lifting the head and shoulders off the examination table) is helpful in diagnosing abdominal wall pain.

Diagnostic Testing

Laboratory Tests

Choosing the appropriate diagnostic tests is a clinical decision based on the working differential diagnosis for the RUQ pain. Basic metabolic panel (electrolytes, blood urea nitrogen, creatinine, and glucose) and liver-associated chemistries should be done for all patients with acute RUQ pain unless the cause is evident on physical examination, e.g., shingles from herpes zoster. A complete blood count is appropriate if blood loss or infection is suspected. If pancreatitis is clinically suspected, then both amylase and lipase measurements are recommended because an elevated lipase level with a normal amylase level is unlikely to be caused by pancreatitis [23]. A urinalysis should be obtained in patients with symptoms suggestive of kidney stones or pyelonephritis. A urine pregnancy test should be performed in women of childbearing age who have RUQ to determine whether certain imaging studies are appropriate. Testing for *Chlamydia* spp. and gonorrhea should be considered for women at risk of sexually transmitted infections. An EKG should be obtained if myocardial infarction or pericarditis is suspected.

Imaging Studies

Abdominal ultrasonography is the test of choice for most patients presenting with RUQ pain because its sensitivity for detecting gall stones, biliary dilation, and gall-bladder wall thickening is superior to that of CT [24]. Ultrasonography has similar sensitivity to CT for detecting choledocholithiasis. It is also the least invasive radiological modality for imaging the liver and biliary tract that applies no radiation, so it is the technique of choice in pregnant women, in patients with contrast allergies, or in those in whom CT or MRI is contraindicated.

Gas in the duodenum can obscure visualization of the distal common bile duct in transabdominal ultrasonography [25]. Cholangiography, magnetic resonance cholangiopancreatography (MRCP), or endoscopic ultrasonography (EUS) may be preferred in these circumstances.

Patients with a typical presentation of main bile duct stones may proceed directly to endoscopic retrograde cholangiopancreatography (ERCP), although a quick abdominal ultrasound before the procedure may clarify the diagnosis and provide useful guidance for the ERCP. If a patient is considered to have ascending cholangitis, transfer to a facility with ERCP capacity should take place as soon as the patient is stabilized.

CT of the abdomen is the test of choice if pancreatitis, perforated ulcer, appendicitis, transverse colitis/diverticulitis, Crohn disease, or hepatic abscess/tumor is clinically suspected.

A plain film is generally not useful for patients with RUQ pain, except in cases where pneumoperitoneum is suspected, or to detect gross pancreatic calcification. However, a chest radiograph should be ordered for patients with cough to rule out right lower lobe pneumonia.

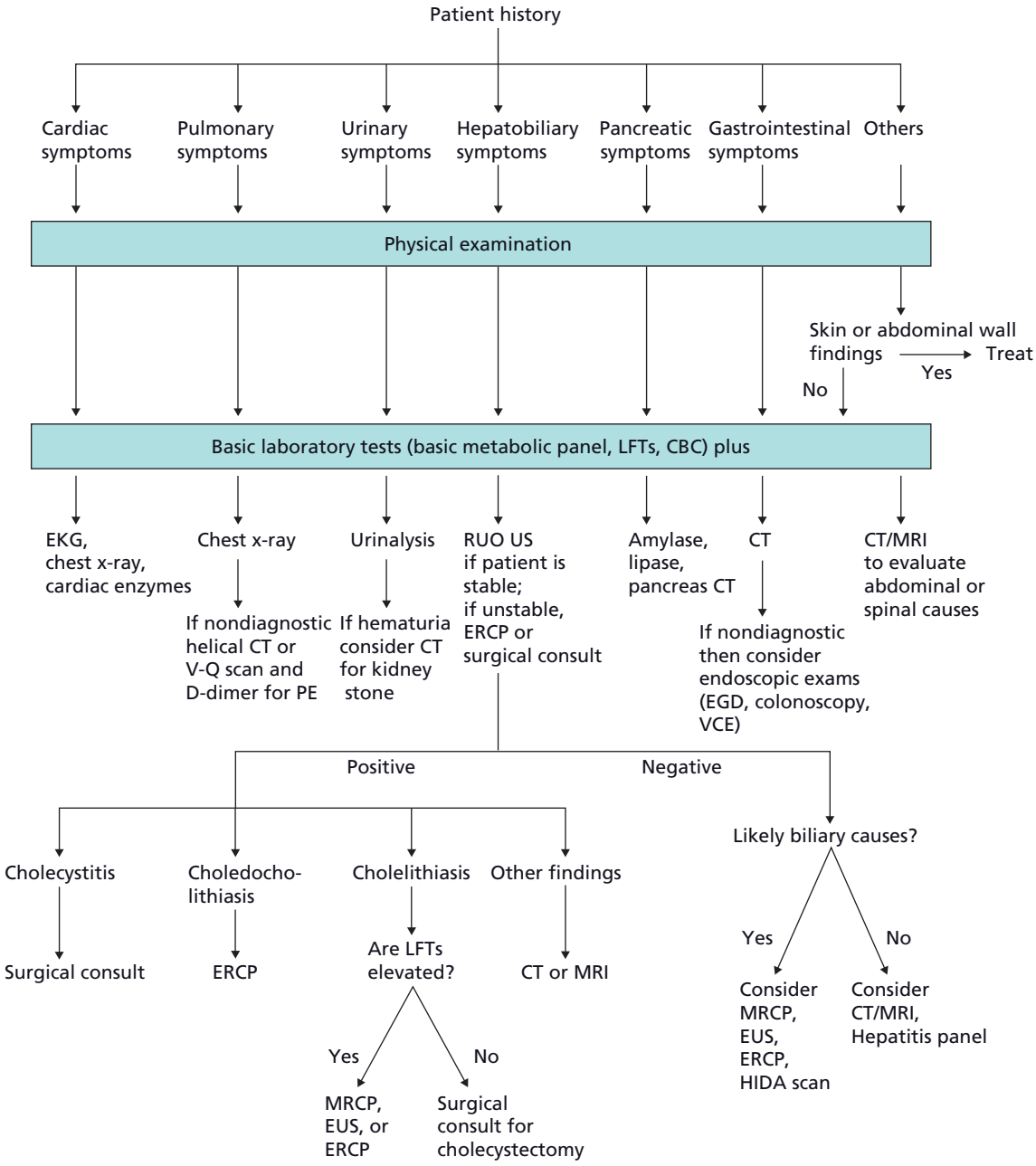

Figure 12.1 Algorithm for the evaluation of acute right upper quadrant abdominal pain. CBC, complete blood count; CT, computed tomography; EGD, esophagogastroduodenoscopy; EKG, electrocardiogram; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; HIDA, hepatobiliary scintigraphy; LFTs, liver function tests; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; PE, pulmonary embolism; RUQ, right upper quadrant; US, ultrasonography; VCE, video capsule endoscopy; V/Q, ventilation–perfusion.

Stepwise Approach to Patients

A stepwise approach to patients with acute RUQ pain is necessary for identification of specific high-risk populations and is essential in offering appropriate, cost-effective, and timely diagnostic testing and treatment (Figure 12.1).

- Abdominal ultrasonography is the test of choice for most patients presenting with RUQ pain.
- A stepwise approach to patients with acute RUQ pain is necessary for identification of specific high-risk populations and is essential in offering appropriate, cost-effective, and timely diagnostic testing and treatment.

Take-home points

- Many diseases of the gastrointestinal (GI) tract and non-GI tract systems can cause RUQ pain. One should not assume that, if a patient presents with RUQ pain, she or he must have a problem with the GI tract.
- Many diseases of the non-biliary GI systems can cause RUQ pain. RUQ pain can be the sole presenting symptom in some patients with lower lobe pneumonia or pulmonary emboli.
- One should not limit the differential diagnosis of RUQ pain to the biliary system.
- The classic triad of Charcot—fever, RUQ pain, and jaundice—occurs in only 50–75% of patients with acute cholangitis. RUQ pain is typically vague. Hypotension and mental status decline can occur in patients with suppurative cholangitis, producing the Reynold pentad, which is associated with significant morbidity and mortality. Hypotension may be the only presenting symptom in elderly patients or those on corticosteroids.
- Pain produced by gall-stone pancreatitis can be in the RUQ but it is more commonly located in the epigastrium with radiation to the back. Gall-stone pancreatitis should be highly suspected when there is a prior history of biliary colic and absence of alcohol use in the setting of acute pancreatitis.
- RUQ pain is rarely seen in patients with acute hepatitis C, chronic hepatitis B, or chronic hepatitis C. However, it is common in acute hepatitis A.
- In the Budd–Chiari syndrome, patients usually present with severe RUQ pain and hepatomegaly. Jaundice and ascites may not be apparent initially, but often develop rapidly. Variceal bleeding may also occur.
- Liver cancers including primary and metastatic rarely produce RUQ pain or discomfort in the early stage.
- Liver biopsy can cause RUQ pain by inducing hemobilia, which may lead to mass effect on the liver capsule, obstructive cholangitis, or pancreatitis.
- Erythromycin can occasionally cause hepatotoxicity, presenting dramatically with fever and RUQ pain mimicking gall-stone disease.

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CHAPTER 13
Acute Liver Failure

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Summary
Acute liver failure (ALF) is severe acute liver injury with coagulopathy that has progressed to encephalopathy within 8–26 weeks of illness in a patient with no chronic liver disease. This medical emergency of high mortality must be recognized without delay and demands rapid, complex management decisions for optimal patient outcome. The most common cause of ALF in the USA is acetaminophen (paracetamol) hepatotoxicity followed by indeterminate cases and idiosyncratic drug reactions. *N*-Acetylcysteine is given immediately to any case of suspected acetaminophen hepatotoxicity. Other etiologies with specific therapies must be recognized and treated appropriately. Supportive care, appropriate to the coma grade and complications, must be instituted and arrangements made for access to specialized intensive care and liver transplantation. Prognosis for spontaneous recovery and a decision on transplant candidacy must be made without delay to allow time for procurement of a donor organ in cases unlikely to survive spontaneously.

Case: Presentation

A 21-year old college student presents with increasing confusion. There is little history available. She is disoriented and uncooperative, and has no focal neurologic signs. She is hemodynamically stable and afebrile. Exam is otherwise normal; there is good nutritional status. Lab results are as follows:

- Hb 10.1 g/dL
- WBC 6.400 × 10^6
- Platelets 146 000 × 10^6
- INR 2.6
- AST 6829 U/L
- ALT 8265 U/L
- Bilirubin 2.2/1.5 mg/dL
- Creatinine 4.7 mg/dL

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Introduction

Acute liver failure (ALF) is an uncommon but devastating illness, often affecting children and young adults. Severe acute liver injury rapidly progresses to systemic multiorgan failure with altered mental status, vasodilation, renal failure, pulmonary failure, infections, and high mortality without liver transplantation. Deterioration in ALF can be rapid and optimal management requires the expeditious completion of multiple steps (Figure 13.1)—recognition of ALF, etiologic evaluation, consideration of specific therapies, and institution of optimal supportive care. However, for those with advanced disease and poor prognostic features, the only effective therapy is urgent orthotopic liver transplantation (OLT), the success of which requires early activation for OLT and rapid organ acquisition.

Definition

Acute liver failure (fulminant hepatic failure) is defined as severe acute liver dysfunction with coagulopathy and

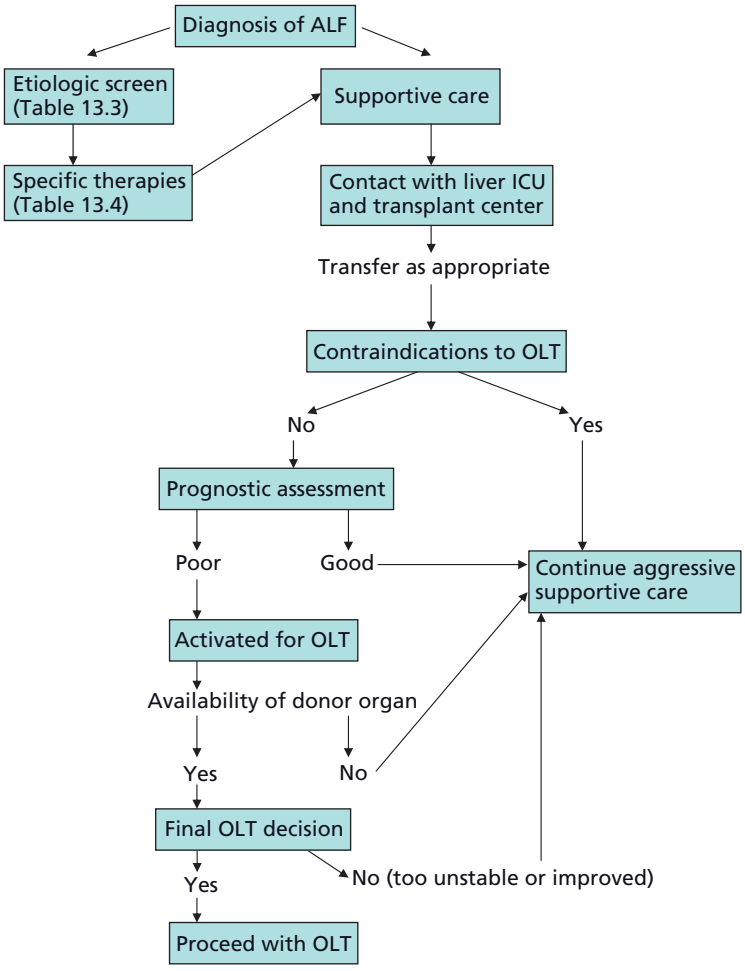

Figure 13.1 Management steps in acute liver failure. ALF, acute liver failure; ICU, intensive care unit; OLT, orthotopic liver transplantation.

encephalopathy occurring within 8–26 weeks of illness in the absence of chronic liver disease. Where encephalopathy develops within 7 days, the term "hyperacute" is sometimes used, a clinically useful designation because these patients can be expected to progress faster but also to have more likelihood of spontaneous recovery. Encephalopathy developing between 8 and 26 weeks may be termed "subacute hepatic necrosis" or "subacute liver failure."

Etiology

The etiology of ALF varies geographically and temporally [1]. Acetaminophen overdose is the leading cause of ALF in adults in the USA (Table 13.1), responsible for 46% of cases [2–4]. Cases of indeterminate etiology and idiosyncratic drug reactions are the next biggest groups. Many drugs, as well as herbal, complementary, and alternative medicines, are potential hepatotoxins; the most commonly implicated drugs leading to OLT for non-acetaminophen ALF in the USA are isoniazid, propylthiouracil, phenytoin, and valproate [5]. Fulminant viral hepatitis is less common than previously, with 7% ALF due to hepatitis B and 3% to hepatitis A. In many European countries, the etiology of ALF resembles that of the USA but, in Asia and Africa, fulminant viral hepatitis (B and E) predominates.

Autoimmune hepatitis is increasingly suspected as the cause of ALF in about 5% of cases; its diagnosis is difficult

without a liver biopsy and the response to steroids is uncertain. For ALF patients in the third trimester of pregnancy, a pregnancy-associated disease, either acute fatty liver of pregnancy or the **h**emolysis, **e**levated **l**iver tests, **l**ow **p**latelets (HELLP) syndrome is the most likely diagnosis. There are many rare causes of ALF including mushroom (*Amanita* sp.) poisoning, Budd–Chiari syndrome, heat stroke or rhabdomyolysis (occasionally from use of ecstasy), herpes hepatitis, ischemic hepatitis, malignant infiltration (especially lymphoma, breast cancer, and melanoma), Reye syndrome, varicella-zoster, leptospirosis, and dengue fever. With the same clinical presentation as ALF, fulminant Wilson disease, although a chronic liver disease, has to be considered in any young person with ALF.

The etiology of ALF has clinical importance for specific therapies, for prognostic evaluation, and, in some cases, to exclude the possibility of transplantation; however, it may be difficult, indeed impossible, to establish with speed and certainty in all patients.

Table 13.1 Causes of acute liver failure in the USA and their spontaneous survival.

Etiology	Percentage cases	Spontaneous survival (%)
Acetaminophen overdose	46	60–70
Indeterminate	15	10–20
Idiosyncratic drug reaction	12	10–20
Hepatitis B	7	20–25
Autoimmune	5	<10
Ischemic	5[a]	
Hepatitis A	3	60–70

Rare causes: mushroom poisoning, Budd–Chiari syndrome, heat stroke and rhabdomyolysis, malignancy, pregnancy-related, herpes.
[a]Prognosis depends on underlying cause of ischemia.

Pathophysiology

Severe acute liver injury rapidly progresses to affect many organs. Renal dysfunction is common, especially in patients with acetaminophen poisoning; it is usually reversible and due to acute tubular necrosis with or without a "functional" (hepatorenal) component. The most fatal complication of ALF is brain edema with increased intracranial pressure (ICP) and reduced cerebral perfusion, leading to brain herniation and death [6,7]. The main component is astrocyte swelling, with rapid accumulation of ammonia being of major importance. In ALF there is also loss of normal cerebral autoregulation, which keeps the ICP stable with fluctuations in hemodynamic status. Changes in systemic blood pressure are thus transmitted directly to the cerebral vessels with variable cerebral perfusion. Other factors that worsen cerebral edema are hyponatremia, cytokines, ischemia, seizures, and the systemic inflammatory response syndrome (SIRS) (Figure 13.2).

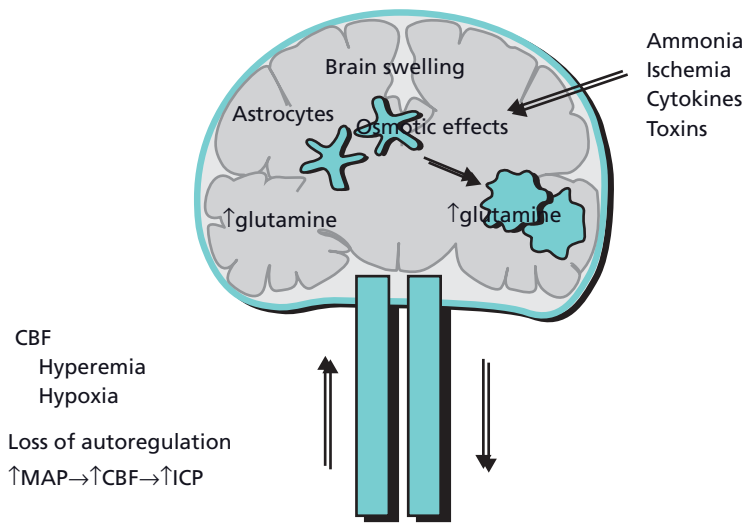

Figure 13.2 Pathophysiology of cerebral edema in acute liver failure. CBF, cerebral blood flow; ICP, intracranial pressure; MAP, mean arterial pressure.

Clinical Features

The clinical presentation of ALF varies widely depending on the etiology, severity, rapidity of progression, and timing of medical attention. Symptoms before encephalopathy vary from non-specific dyspeptic or flu-like symptoms to an acute hepatitis, with or without jaundice. Mental status may vary from subtle behavioral changes to full coma (Table 13.2). During the most acute early presentation, transaminases will be high and the coagulopathy and bilirubin increasing; later, transaminases may decrease but the coagulopathy, bilirubin, and encephalopathy continue to increase.

Acetaminophen ALF has a typical short course over a few days with rapid progression to advanced coma, very high transaminases, mild bilirubin elevation, metabolic acidosis, and renal failure [2,3]. Half of these cases are suicide attempts but the others are unintentional therapeutic misadventure, often with opiate–acetaminophen combinations taken for chronic pain. The minimum dose needed for liver injury is 4–10 g but often the actual ingested dose and its timing remain unknown. Idiosyncratic drug reactions and indeterminate cases of ALF typically have a more protracted course, sometimes over several weeks before the onset of encephalopathy, with lower transaminase levels but a progressive increase in bilirubin and coagulopathy, and a low likelihood of spontaneous recovery once encephalopathy occurs [5]. A high bilirubin and a prolonged latency period are poor prognostic signs in such cases.

Although reportedly higher in the past, about 32% patients with ALF will develop raised ICP. Cerebral edema occurs mainly in patients with coma grades III and IV, especially with a short interval between jaundice and development of encephalopathy (hyperacute ALF). An arterial ammonia level >200 µg/dL within 24 h of coma grade III or IV is predictive of cerebral herniation. Infection and SIRS, with or without infection, are implicated in the progression of encephalopathy and cerebral edema [8,9].

Table 13.2 Coma grade in acute liver failure.

Coma grade	Clinical features
I	Changes in behavior or slow mentation with minimal change in level of consciousness
II	Gross disorientation, drowsiness, asterixis, inappropriate behavior
III	Marked confusion, incoherent speech, sleeping most of time but arousable to vocal stimuli
IV	Comatose, unresponsive to pain, decorticate or decerebrate posturing

Case: Key Features and Clinical Diagnosis

Acute liver failure with:
- Short history (days)
- Rapid progression
- High transaminases
- Low bilirubin
- Renal failure.

Clinical diagnosis: acetaminophen hepatotoxicity
Specific therapy: *N*-acetylcysteine (give immediately)

Diagnosis

The etiologic screen in ALF must include a detailed history for drugs, herbal supplements, and toxins ,and a full clinical and laboratory evaluation (Table 13.3). For the acute presentation with very high transaminases, acetaminophen toxicity, or viral or ischemic hepatitis is suspected; negative viral studies, renal failure, and rapid disease progression over hours suggest acetaminophen toxicity; blood levels are often negative by the time the patient presents with ALF. Hopefully, testing for acetaminophen–protein adducts will soon be clinically available to allow a more definitive diagnosis. Serum and urine copper estimations and a slit-lamp examination for Kaiser–Fleischer rings should be obtained in any young patient in whom Wilson disease is suspected. Consideration should be given to rare causes of ALF with appropriate testing. Hepatic ultrasonography is performed to assess the hepatic parenchyma and patency of portal and hepatic vessels. A liver biopsy is generally done only in selected cases when there is suspicion of a diagnosis that would preclude OLT (malignancy) or when the diagnosis would require specific therapy (Table 13.4).

Table 13.3 Initial laboratory assessment in acute liver failure.

Hemoglobin, WBC, platelets, blood group
AST, ALT, bilirubin (total and direct), alkaline phosphatase, α-fetoprotein
INR, APTT, fibrinogen, factor V
Blood glucose, serum electrolytes, osmolarity, calcium, magnesium
Albumin, amylase, lipase, uric acid, creatinine, BUN, lactate
Arterial blood gases and ammonia
Serum acetaminophen level, urine drug screen
Hepatitis serology for hepatitis viruses A, B, C,[a] and E, herpes, Epstein–Barr virus
Ceruloplasmin and serum and urine copper[b]
Gamma-globulin and autoantibodies
Cultures of blood and urine: chest radiograph; HIV testing
Hepatic ultrasonogram
Head CT (if coma grade II or higher)

[a]Hepatitis C virus to define underlying liver disease.
[b]Eye check for Kayser–Fleischer rings if suspicion of Wilson disease.
ALT, alanine transaminase; APTT, activated partial thromboplastin time; AST, aspartate transaminase; BUN, blood urea nitrogen; CT, computed tomography; INR, international normalized ratio; WBC, white blood cell count.

Case: Diagnosis and Testing

Additional tests:

- Serum acetaminophen level undetectable
- Arterial ammonia 98 μmol/L, lactate 2.1 mmol/L, pH 7.40
- Drug screen negative
- Viral markers negative
- Ceruloplasmin normal at 15 mg/dL, serum copper normal
- Pregnancy test negative
- Ultrasonogram and head CT normal

Therapeutics

Supportive intensive care unit (ICU) management aims to provide the optimal environment for hepatic recovery and to prevent and treat complications of ALF. Urgent OLT is the only effective therapy for those with advanced disease, but some patients, with supportive care for their multiorgan failure, will adequately regenerate their hepatic mass and survive spontaneously. Supportive care is therefore needed for all cases of ALF—either for hepatic recovery or for donor organ acquisition—and should be initiated without delay. Unfortunately, in ALF, there are very few randomized clinical trials on which to base firm clinical recommendations and most practice is consensus driven [10,11]. Due to complexity and urgency of care for these patients, many centers find it advantageous to establish a standard management protocol. As a result of the high mortality of ALF, candidacy of the patient for OLT must be assessed early in the hospital course and any contraindications to OLT identified.

Table 13.4 Specific therapies in acute liver failure (ALF).

Cause of ALF	Therapy
Acetaminophen	*N*-Acetylcysteine (see Table 13.5)
Autoimmune	Corticosteroids
Herpes simplex	Acyclovir (30 mg/kg per day i.v.)
Hepatitis B	Antiviral agents[a]
Pregnancy related	Delivery of baby
Amanita poisoning	Benzylpenicillin (1g/kg per day i.v.) and *N*-acetylcysteine

[a]Controversial.

Specific Therapeutic Measures (see Table 13.4)

N-Acetylcysteine (NAC) is an effective antidote for acetaminophen overdose and is completely protective against hepatotoxicity if given in the first 8 h after ingestion. Despite its limited efficacy in late presentations, any patient with ALF should receive NAC promptly if there is any suspicion of acetaminophen hepatotoxicity, irrespective of the suspected time of ingestion. NAC is given orally only to those with coma grade I; in patients with more advanced coma or with other complications that preclude oral tolerability, it should be given intravenously (Table 13.5).

Corticosteroids are indicated only in autoimmune disease. For pregnancy-associated disease, immediate delivery of the baby is life saving. Also life saving is acyclovir in the very rare case of fulminant herpes hepatitis. The diagnosis of mushroom poisoning depends on a history of ingestion; therapy is most effective in the first

Table 13.5 Dosing of intravenous N-acetylcysteine (NAC).

Day	Dose of NAC (mg/kg)	Volume of 5% dextrose (mL)	Duration of infusion (h)
1	150	250	1 h
	50	500	4
	125	1000	19
2	150	1000	24
3	150	1000	24[a]

[a]Can repeat until international normalized ratio <1.5.
Oral dosing: 140 mg/kg loading dose, then 70 mg/kg every 4 h.

10 h after ingestion and consists of gastric lavage, activated charcoal (50 g) by nasogastric tube, intravenous penicillin (1 000 000 units/kg per day in divided doses) and intravenous NAC; if unsuccessful, OLT will be life saving. Antiviral therapy may be considered in fulminant hepatitis B, although its use is controversial. A diagnosis of fulminant Wilson disease or ALF secondary to Budd–Chiari syndrome should lead to consideration of immediate OLT because spontaneous recovery rarely occurs.

General Supportive Care for All Patients with ALF

Monitoring of Blood Tests and Avoidance of Medications

After the initial laboratory assessment of the patient with ALF (see Table 13.3), frequent monitoring (every 8–12 h) of hepatic and renal function, acid–base status, and blood glucose (hourly) is essential to assess disease progression and to stabilize the patient. All non-essential medications are avoided. A multicenter American trial to assess the efficacy of NAC in non-acetaminophen ALF has recently been completed; its use led to a survival benefit only in patients with early coma grades I/II [12].

Nutrition

Despite the loss of liver mass, caloric requirements have been shown to be markedly increased in ALF. Continuous intravenous infusion of glucose is used to avoid hypoglycemia. Enteral nutrition, with 20–25 kcal/kg per day, is recommended: adequate protein (1.0–1.5 g/kg per day) should be given with monitoring of arterial ammonia levels in those with severe dysfunction. Where arterial ammonia levels are high, protein can be reduced for several days. The ideal feed formula for these patients is unknown but branched-chain amino acid solutions confer no proven advantage. Parenteral nutrition should be considered if tube feeding is not tolerated. Multivitamin supplementation is generally recommended.

Management of Infection Risk

With complex immune dysfunction and the need for invasive monitoring and treatment, the patient with ALF is highly susceptible to both bacterial and fungal infections with an infection rate of about 50%; the SIRS is even more common with or without identified infection. Overt clinical signs of infection may be absent in these patients and daily screening with cultures of blood and urine (ascites, sputum, tracheal secretions if obtained) and a chest radiograph is important. Identified infection must be aggressively treated. The most common sites of bacterial infection are the lungs, urinary tract, and bloodstream, with Gram-positive cocci or enteric Gram-negative bacilli.

Prophylactic antimicrobial therapy in ALF is still controversial. Parenteral and enteral antibiotic prophylaxis reduce infections in ALF but no survival benefit is seen. Broad-spectrum antibiotics are widely used and are recommended in advanced coma grade, with invasive hemodynamic monitoring, with the presence of SIRS and in liver transplant candidates. Antifungal agents are also indicated, to prevent late death from fungal infections. Fluconazole (200 mg first dose, then 100 mg daily thereafter either orally or intravenously) is safe to use in ALF and will prevent most fungal infections.

Coagulation Abnormalities and Bleeding

Many hemostatic problems occur in ALF affecting platelets, coagulation factors and inhibitors, and the fibrinolytic system. Despite this, the risk of severe hemorrhage is about 10%, the major sites being the gastrointestinal tract, nasopharynx, lungs, puncture sites, and retroperitoneum. Prophylactic use of coagulation factors is not indicated and has the additional disadvantage of

eliminating a very important prognostic parameter. Although ineffective for ALF, vitamin K is given to prevent any coexisting deficiency and gastric acid suppression, by H_2-receptor blockade or proton pump inhibition, initiated.

Platelet transfusion, fresh frozen plasma (FFP), and cryoprecipitate are used only for bleeding, high-risk procedures and OLT. Recombinant activated factor VII (rFVIIa) may also be used for invasive procedures and OLT, but FFP and cryopecipitate must be given beforehand to replete other constituents of the clotting cascade; further studies are needed to define the clinical utility of rFVIIa. Plasma exchange may also be used to correct coagulopathy.

Intensive Care Depending on Coma Grade

Intensive management modalities of ALF are directed at prevention and early treatment of cerebral edema by hemodynamic stability, adequate oxygenation, normovolemia, and treatment of fever and agitation. The intensity of care will depend on the coma grade (see Table 13.2).

Coma Grades I and II

Experienced nursing in a quiet environment is satisfactory for coma grade I but, with progression to grade II, the patient is generally transferred to an ICU. Patients are nursed at head elevation of 30° to favor venous return. Management of volume status is essential to avoid overhydration but preserve renal function. Fluid resuscitation may be needed but no clinical trials provide guidelines about the optimal replacement fluid; both crystalloid and colloid are acceptable. No studies allow assessment of the efficacy of lactulose or rifaximin for the encephalopathy of ALF and their use is variable. Neomycin is avoided due to risk of nephrotoxicity. By coma grade II, head scanning by computed tomography (CT) is performed, mainly to exclude other intracranial pathology affecting mental status. Sedation is avoided in early coma grades because it prevents neurologic evaluation, but propofol or lorazepam may be needed for severe agitation, which will increase the risk of cerebral edema.

Coma Grades III and IV: Hemodynamic and Ventilatory Support

With progression to advanced coma grades, the Glasgow Coma Scale is used to more sensitively record progression of coma. Hemodynamic stability and euvolemia are essential with active management to control electrolytes, sodium, infection risk, temperature, and P_{CO_2}. The desired level for serum sodium is 145–155 mmol/L as this reduces ICP; low-rate infusion of hypertonic saline may be necessary. Fever is associated with poor outcome and, in intubated patients, a core temperature of 36 C is desirable, although there may be some beneficial effects from mild hypothermia. Randomized controlled trials of prophylactic hypothermia are ongoing at present.

Unfortunately there are few data on which to determine what constitutes optimal hemodynamic monitoring or markers of euvolemia. An arterial line, urinary catheter, and central line are placed, and often a pulmonary artery catheter will be needed. An inadequate cortisol response to a short Synacthen (tetracosatide) test may indicate relative adrenal insufficiency as a factor in hypotension and some advocate replacement doses of intravenous hydrocortisone in such patients.

With euvolemia, the mean arterial blood pressure is generally maintained at >65 mmHg, by norepinephrine (preferred by most centers) or phenylephrine if necessary. Cerebral perfusion pressure (CPP) of >60 mmHg is sought. Pressor therapy increases blood pressure but may worsen oxygen delivery. Dopamine has also been used but reduces splanchnic oxygen consumption. If jugular venous saturation monitoring is used, 55–75% is the desired level, with <55 indicating reduced cerebral blood flow and >75 indicating hyperemia. The use of low-dose, continuous vasopressin may be used with caution as an adjunct in vasopressor-resistant hypotension [10].

The usual indication for mechanical ventilation in ALF is progression to coma grade III for sedation and airway protection. Sedation is used to prevent agitation and surges in ICP, and propofol, with intravenous fentanyl, is often the choice of sedation. Cisatracurium is the preferred paralytic agent but is used only if necessary, as it may mask seizure activity. Prophylactic use of hyperventilation is not recommended. The patient's head is maintained at a 30° angle to improve jugular venous outflow. Endotracheal lidocaine should be used with suctioning to reduce patient stimulation. A nasogastric tube is placed for access for enteral nutrition and oral medications.

Renal Support

Renal failure and the need for dialysis are very common in ALF, especially in acetaminophen cases. Continuous venovenous hemodialysis (CVVHD), with less rapid fluid shifts and therefore less hemodynamic and metabolic instability, is the preferred method of dialysis. Bicarbonate-buffered hemofiltration fluids, rather than those containing acetate or lactate, are preferred to avoid hyperlactatemia and acidemia. CVVHD should be started as soon as renal failure is suspected; it will remove urea, glutamine, and ammonia, help correct metabolic abnormalities, especially metabolic acidosis, and can also be used to control core temperature.

Monitoring for raised ICP

Recognition of the clinical signs of elevated ICP—arterial hypertension, pupillary changes, marked hyperventilation, opisthotonus, hyperpronation–adduction of arms, seizures—demands experienced clinical monitoring and sedation with mechanical ventilation makes neurologic assessment difficult. ICP monitoring is the most reliable means of assessing changes in ICP and helps guide management decisions. However, its use has never been tested in a controlled clinical trial, although longer survival was seen in one study. Despite the risks of infection and bleeding, ICP monitoring is used in many centers, especially if OLT is likely. Correction of coagulation parameters is needed before catheter placement; epidural catheters are most commonly used, with the lowest complication rate of 3.8% and fatal hemorrhage in 1%. As a result of the risks of ICP monitoring, there is much emphasis at present to find a non-invasive method that will accurately identify the patients who are most likely to benefit from invasive monitoring. Some centers are now using jugular bulb venous saturation monitoring (jugular venous oximetry) to assess cerebral oxygen delivery and consumption. Other non-invasive modalities are transcranial Doppler, continuous electroencephalogram (EEG), and infrared spectroscopy.

With an ICP monitor, ICP will be measured directly and continuously; critically important is the CPP—mean arterial blood pressure minus ICP—and hemodynamic support may be needed to increase systemic blood pressure to achieve adequate CPP. Intracranial hypertension (ICH) is defined as an ICP >20–25 mmHg for >5 min or CPP <50–60.

Case: Initial Management Continued

- Intravenous *N*-acetylcysteine (72 h)
- Acid suppression, vitamin K
- Infection screen (blood, urine, chest radiograph)
- Cefotaxime and fluconazole
- Continuous venovenous hemodialysis
- Propofol for severe agitation
- Elective intubation (coma grade III) and ICP monitor.
- Enteral nutrition via feeding tube
- Assessment and activation for OLT

Treatment of Intracranial Hypertension

Therapies for ICH in ALF reduce ICP either by osmotic effects (mannitol, hypertonic saline) or by decreasing cerebral blood flow (hyperventilation, hypothermia, barbiturate coma, or indometacin).

First-line Treatment

Sedation should be optimized with or without neuromuscular blockade. An intravenous bolus of 0.5 g/kg mannitol is the first-line therapy for raised ICP; the dose can be repeated as long as serum osmolality remains <300–320 mosmol/kg. This is the only therapy proven in a controlled trial to be effective in reducing ICH and in improving patient survival. Unfortunately renal failure limits the use of mannitol.

Hypertonic saline boluses are increasingly used, as an alternative to mannitol, to treat ICH (30 mL of 23.4% saline or 2 mL/kg of 7.5% saline). An infusion of hypertonic saline (30%) to maintain serum sodium levels of 145–155 mmol/L reduces ICP levels but further studies are needed to confirm the optimal level for serum sodium in ALF. On the other hand, hyponatremia and the use of hypotonic solutions should be avoided.

Second-line Treatment

Hyperventilation to $Paco_2$ 3.33–3.99 kPa (25–30 mmHg) reduces cerebral blood flow by cerebral vasoconstriction, rapidly reduces ICP, and restores autoregulation of cerebral blood flow. It is safest used with jugular venous saturation control to prevent global cerebral ischemia. As a result of the latter problem, hyperventilation is restricted to acute, short-term situations of ICH, although some

programs now avoid its use altogether. Prophylactic continuous hyperventilation is not effective in reducing cerebral edema.

Mild-to-moderate hypothermia (32–33 C) has been shown in animals and humans to reduce ICP and normalize cerebral blood flow, perhaps by restoration of autoregulation, and has allowed successful OLT in some patients [13–16]. Induction of hypothermia by a cooling blanket is a simple bedside procedure in the vasodilated state of ALF and it can be continued during OLT to prevent ICH. Potential side effects are increased infection, coagulation abnormalities, and cardiac dysrhythmias.

Severe uncontrolled ICH

When severe ICH is completely unresponsive to all other available measures, it is reasonable to consider barbiturate coma (pentobarbital at 3–5 mg/kg loading dose, followed by 1–3 mg/kg per h or thiopental at 5–10 mg/kg, then 3–5 mg/kg per h), which decreases the cerebral metabolic rate and causes cerebral vasoconstriction: the resulting reduction in ICH has been shown to allow recovery of a few patients. Such therapy may cause myocardial depression and hypotension. An intravenous injection of 25 mg indometacin over 1 min will reduce cerebral blood flow but it may induce cerebral ischemia and this limits its routine use.

Seizure management in ALF

Untreated seizure activity will increase cerebral oxygen requirements and potentiate ischemia and cerebral edema. Seizures in ALF must be aggressively treated; intravenous phenytoin is the drug of choice with additional diazepam for ongoing seizures. Phenobarbital or sodium pentothal can be added if status epilepticus continues despite therapy. The use of continuous EEG monitoring and prophylactic intravenous phenytoin to reduce seizure activity is controversial.

Liver Support Devices

A device to support acute liver failure has long been sought, but there is as yet no effective bioartificial liver to replace the complex capabilities of normal hepatic metabolism [17]. A prospective, randomized, multicenter trial of an extracorporeal, porcine, hepatocyte-based, bioartificial liver in 171 patients with ALF showed the device to be safe; survival was improved in the subgroup of fulminant/subfulminant patients [18].

Case: Outcome (Day 2)

- ICP fluctuating: deep sedation, mannitol (1 dose)
- Temperature to 38 C: cooling blanket to 36 C
- Anuric: continued CVVHD
- Seizures on EEG: intravenous phenytoin
- Worsening coagulopathy and bilirubin
- Poor prognostic score
- Donor organ available: decision to proceed
- Successful OLT

Prognostic Assessment and Timing of OLT

Timing of OLT in ALF involves a balance between allowing time for hepatic recovery and avoidance of OLT and the development of fatal complications of brain herniation or multiorgan failure [19–21]. Unfortunately, some patients listed for OLT progress too quickly and die before a donor organ becomes available, especially in acetaminophen ALF where only 6% patients receive an OLT and there is an overall death rate of 27%. Acetaminophen hepatotoxicity is the most common cause of death from ALF in the USA. The ALF patient with no contraindications for OLT should be evaluated and activated immediately; the final decision about OLT is made when a donor organ is available.

With OLT, overall patient survival in ALF has increased in the present era to about 80%, especially with the use of low-risk grafts (whole, ABO compatible, non-steatotic) and if recipients are <50 years, with body mass index <30, creatinine <2 mg/dL, and no life support [20]. Overall survival after OLT for ALF is less than for chronic liver disease but superior to OLT outcomes in chronic liver disease patients of comparable severity. About 8% cadaver liver transplantations in the USA are performed for ALF. Experience with living donor liver transplantation for adults with ALF is very limited in the USA but may be considered in selected patients.

An accurate prognostic assessment for recovery or death without OLT is very important in ALF but there are no ideal criteria for prognosis or for proceeding to OLT [22,23]. Etiology is very important (see Table 13.2) with spontaneous survival higher in acetaminophen toxicity and hepatitis A. Fulminant Wilson disease or ALF due to Budd–Chiari syndrome is universally fatal and OLT should proceed without delay. Age, neurologic status on admission, and timing of OLT all influence survival.

The most widely used and most accurate prognostic criteria in ALF are the King's College Hospital (KCH) criteria developed in the 1980s from 588 patients [24]; these criteria predict survival of <20% and separate patients into acetaminophen toxicity (pH <7.3 24 h after overdose *or* creatinine >3.4 mg/dL plus international normalized ratio or INR >6.5 plus coma grade III or IV) and non-acetaminophen patients (INR >6.5 *or* three of the following criteria—INR >3.5, jaundice to encephalopathy >7 days, indeterminate or drug-induced hepatitis, age <10 or >40 years, bilirubin >17.5 mg/dL). Tested in the USA, KCH criteria accurately predicted poor outcome but were less accurate for predicting survival. In acetaminophen cases, arterial lactate levels of >3.5 mmol/L on admission or >3.0 mmol/L after fluid resuscitation were highly predictive of death with 97% specificity.

The French (Clichy) criteria for ALF [1], developed in patients with fulminant viral hepatitis, uses coma grade III or IV and factor V levels (<20% factor V level in patient <30 years or <30% factor V level in patient >30 years), and for non-acetaminophen patients very accurately predicts poor survival. The MELD score (as in Section 3.6.4, Table 1, of policies of United Network of Organ Sharing, www.unos.org) has not outperformed KCH criteria but may be part of a future prognostic score along with biomarkers that indicate degree of hepatic injury and/or capacity for regeneration. At present, more accurate criteria are needed.

Take-home points

- Acute liver failure (ALF) is defined as severe acute liver disease with coagulopathy and encephalopathy occurring within 8–26 weeks of illness in the absence of underlying chronic liver disease.
- Optimal patient outcome requires urgent diagnosis and management decisions and may be best affected by use of a standard management protocol.
- Acetaminophen hepatotoxicity is the most common cause of ALF in the USA; the next two etiologic categories are indeterminate cases and idiosyncratic drug reactions, with a small number of cases of viral hepatitis.
- Rare causes of ALF should always be considered.
- N-Acetylcysteine therapy must be given without delay to any case of suspected acetaminophen hepatotoxicity.
- Supportive care, appropriate to the coma grade and complications, must be instituted immediately and arrangements made for access to specialized intensive care and liver transplantation.
- Prognosis for spontaneous recovery and decision on transplant candidacy must be made without delay to allow time for procurement of a donor organ in cases unlikely to survive spontaneously.

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IV

PART 4

Problems Related to Chronic Liver Disease

14

CHAPTER 14
Portal Hypertension

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Summary
Clinical manifestations of portal hypertension include varices, ascites, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatic encephalopathy, and hepatopulmonary syndrome. Detailed management for each condition is reviewed in this chapter.

Introduction

Portal pressure is a product of portal resistance and portal blood flow. Increase in portal resistance may be due to fibrosis and nodularity of the cirrhotic liver, or intrahepatic vasoconstriction, which results largely from low levels of nitric oxide (NO), a vasodilator, and high levels of endothelin-1, a vasoconstrictor. Increased portal blood flow in cirrhosis is a result of splanchnic and systemic dilation, effected by NO [1].

The major complications of cirrhosis, which include variceal bleeding, ascites, and hepatic encephalopathy, are all consequences of portal hypertension. Portal hypertension is defined as an increase in hepatic sinusoidal pressure to ≥6 mmHg. The most common cause of portal hypertension in the Western world is cirrhosis. Other common causes include schistosomiasis, in the developing world, and extrahepatic portal vein thrombosis. Portal hypertension may be idiopathic, especially in patients from India and Japan. Other rarer causes of portal hypertension include polycystic liver disease, nodular regenerative hyperplasia of the liver, congenital hepatic fibrosis, myeloproliferative disorders, hepatic sarcoidosis, and hereditary hemorrhagic telangiectasia. Portal hypertension is classified as presinusoidal, sinusoidal, or postsinusoidal.

Cirrhosis is a histological diagnosis. Decompensated cirrhosis is diagnosed when the patient develops ascites, variceal bleeding, hepatic encephalopathy, and/or jaundice. Decompensated cirrhosis is associated with a median survival of only 1.6 years.

Other clinical features suggestive of cirrhosis include thrombocytopenia, impaired hepatic synthetic function (elevated international normalized ration [INR] and decreased serum albumin), palpable left lobe of the liver, splenomegaly, spider nevi, and palmar erythema. If these features are present with a suggestive history, a liver biopsy is not necessary to diagnose cirrhosis.

Varices

Case 1
A 62-year-old man presents to the emergency room (ER) at 6:00am with complaints of vomiting blood 1 hour ago. He denies any retching or abdominal pain. His last bowel movement was the previous night and was softer than his usual and dark in color.

Practical Gastroenterology and Hepatology: Liver and Biliary Disease, 1st edition. Edited by Nicholas J. Talley, Keith D. Lindor and Hugo E. Vargas.

He does have a past history of alcohol consumption up to six cans of beer a day for 30 years but he quit 6 months ago. He also has multiple tattoos, some of which he got when he was in the Far East. He denies ever being ill in the past and in fact does not even have a primary care physician.

On examination, he is afebrile, pulse 95, blood pressure 90/68. He appears mildly anxious. Skin examination reveals scleral icterus and multiple spider nevi on the front and back of the chest. Heart and lung examinations reveal no abnormality. In the abdomen, there is no palpable hepatomegaly. However, the tip of the spleen is palpable 2 cm below the costal margin. There is dullness to percussion in both flanks.

In the ER, he has another emesis and dark-red blood is noted in the pan.

What would be the next step?

Varices are dilated and tortuous veins that develop in an effort to decompress the elevated hepatic sinusoidal pressure.

Pathophysiology

Portal hypertension results in formation of new portosystemic collaterals as well as dilation of pre-existing collaterals. Flow in these collaterals is away from the liver into the systemic circulation. The gastroesophageal (GE) area is the main site of collateral formation [2]. At the GE junction there are longitudinal veins in the submucosa that drain into the short and left gastric veins. The fundus of the stomach drains into the splenic veins via the short gastric veins. Splenic vein thrombosis can cause isolated gastric fundal varices. At the umbilicus, the vestigial umbilical vein (systemic) communicates with the left portal vein (portal). The varices at the umbilicus are characteristically described as "caput medusae." In the rectum, the collaterals are between the inferior mesenteric vein (portal) and the pudendal vein (systemic).

Portal pressure must be at least 10 mmHg for GE varices to develop and at least 12 mmHg for varices to bleed. Increased wall tension, a risk factor for bleeding in varices [3], depends on the pressure within the varix (increased with higher blood flow through the varix), size of the varix (larger varices are more likely to bleed), and wall thickness. Varices in the lower third of the esophagus are more likely to bleed because of limited soft-tissue support for the varix.

Clinical Features

Variceal bleeding must be considered if a patient presents with gastrointestinal bleeding and features of chronic liver disease. Bleeding from gastric and esophageal varices manifests as either hematemesis or melena. The hematemesis is classically effortless with vomiting of dark-red blood. Portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE) manifest more commonly with anemia.

In patients with a splanchnic arteriovenous fistula, a bruit may be heard in the left or right upper quadrant. A venous hum in the epigastrium represents collateral flow in the falciform ligament. In Budd–Chiari syndrome, dilated collaterals may be seen in the flanks and back [4]. Abdominal ultrasonography or computed tomography (CT) may show ascites, collateral vessels, abnormal liver contour, and splenomegaly.

Diagnosis of Portal Hypertension

Portal venous pressure is measured either directly by portal venography or indirectly by the hepatic vein pressure gradient (HVPG). The HVPG is the difference between the wedged hepatic venous pressure (WHVP) and the free hepatic vein pressure (FHVP). As the HVPG is a measure of the hepatic sinusoidal pressure, in presinusoidal causes of portal hypertension, such as portal vein thrombosis, the HVPG is normal.

Ultrasonography

Changes of portal hypertension noted on ultrasonography include splenomegaly, reversal of flow in the portal vein, and portosystemic collateral blood flow. Ultrasonography can also demonstrate thrombosis in the portal or splenic vein.

Computed Tomography

The cirrhotic configuration of the liver, splenomegaly, portosystemic collaterals, and ascites may be demonstrated. CT can differentiate between submucosal and serosal surface varices [5], but is not as yet recommended as a screening modality for esophageal varices.

Magnetic Resonance Imaging

This provides an excellent view of the vascularity of the liver and the flow through the portal and azygous veins, but is still an investigational tool in the detection of esophageal varices.

Detection of Varices

Esophagogastroduodenoscopy

All patients with cirrhosis should be screened for varices with an esophagogastroduodenoscopy (EGD). Varices are graded during withdrawal of the endoscope with the esophagus maximally inflated after deflating the stomach. Large varices are >5 mm in diameter and small varices are <5 mm in diameter. If no varices are found on initial EGD, a repeat EGD should be performed in 2–3 years. If small varices are noted on initial EGD, a repeat EGD is performed in 1–2 years. Patients with small varices develop large varices at a rate of 8% a year.

Treatment

Management of esophageal varices includes prevention of the initial bleed (primary prophylaxis), control of acute variceal bleeding, and prevention of rebleeding (secondary prophylaxis).

Primary Prophylaxis

All patients with large varices should receive primary prophylaxis with either non-selective β-blockers or endoscopic banding.

β-Blockers must be non-selective, e.g., propranolol or nadolol. β_1-Receptor blockade decreases the cardiac output; β_2-receptor blockade in the mesenteric circulation allows unopposed action of α_1-adrenergic receptors, which results in vasoconstriction. The combination of decreased cardiac output and decreased splanchnic flow results in decreased portal blood flow. The advantages of nadolol over propranolol are predominantly renal excretion, low lipid solubility, and a lower risk of depression. The side effects of non-selective β-blockers include bradycardia and fatigue. A long-acting propranolol (60 mg daily) or nadolol (20 mg daily) is taken in the evening because the risk of bleeding is highest at night [6]. The dose can be gradually increased till the target heart rate of 25% below baseline, or 55–60 beats/min, is reached. Measuring the HVPG to monitor response to treatment is not routinely carried out.

If β-blockers are not tolerated or ineffective or contraindicated, or the patient does not wish to take them, endoscopic variceal band ligation is recommended. Although variceal banding is a more invasive procedure, it is associated with lower bleed-related mortality compared with β-blockers. The choice of therapy is best individualized to the patient.

Management of Acute Variceal Bleeding

Acute variceal bleeding is associated with a 6-week mortality rate of 20%. Treatment includes resuscitation of the patient, control of the bleed, and prevention of complications.

Two large-bore intravenous access lines should be established, and the airway protected with a low threshold for endotracheal intubation. Packed red blood cell (RBC) transfusions may be necessary to maintain the hematocrit between 25% and 30%; overtransfusion may worsen the portal hypertension.

A 7-day course of norfloxacin 400 mg orally, ciprofloxacin 400 mg intravenously, or levofloxacin 500 mg intravenously, all administered every 12 h, may be used to prevent spontaneous bacterial peritonitis (SBP) and bacteremia [7].

Pharmacotherapy

Vasopressin (0.2–0.4 units/min as an intravenous infusion) causes splanchnic vasoconstriction, and thus reduces portal venous flow and portal pressure. Side effects, including bowel necrosis, bradycardia, hyponatremia, and myocardial infarction, have reduced usage of this agent. Terlipressin, a vasopressin analog with lower risk of side effects, is widely used in Europe but is not available in the USA.

Somatostatin and its analogs decrease portal pressure by inhibiting release of glucagon [8]. They constrict the splanchnic arterioles and decrease postprandial portal blood flow. Octreotide is given as a continuous infusion of 25–50 μg/h.

Endoscopic Therapy

1 Band ligation, the preferred method of control of bleeding from esophageal varices, should be performed as soon as the patient is hemodynamically stable, and after the vasoactive agent has been infused for at least 30 min. Variceal ligation involves suctioning of a varix

into the channel of the endoscope and then firing a band around the base of the varix. The optimal site of ligation is at, or immediately distal to, the point of bleeding. If evidence of a recent bleed is seen, such as a white fibrin plug or RBC clot over a varix or any of the red signs described above, these sites should be banded. If active bleeding is not seen but large varices are present, the varices should be banded, starting at the GE junction and moving proximally in a spiral fashion at intervals of 2 cm. Complications of banding include esophageal ulcers, strictures, dysmotility, and rebleeding after the band sloughs off.

2 Sclerotherapy is no longer used as first-line treatment of variceal bleeding [9]. It involves injection of a sclerosant (e.g., sodium tetradecylsulfate) either into (intravariceal) or adjacent to (paravariceal) a varix. Complications include retrosternal discomfort, ulcers, strictures, and perforation.

If bleeding from varices cannot be controlled after two sessions of endoscopic therapy within a 24-h period, TIPS (transjugular intrahepatic portosystemic shunt) placement is recommended.

Prevention of Rebleeding

Following the first variceal bleed, up to 80% of patients rebleed at 2 years. Therefore, secondary prophylaxis with β-blockers, or variceal ligation, or the combination, should be initiated. Isosorbide mononitrate can be added to β-blockers to decrease the portal pressure further but nitrates are not usually well tolerated because of headaches and hypotension.

Endoscopic variceal ligation can be repeated first at 7–14 days after the initial banding. Thereafter, banding can be repeated at 3- to 4-week intervals till obliteration of the varices is completed. Patients who have a variceal bleed despite β-blockers and band ligation should be considered for a portosystemic shunt placement. If the patient has Child–Pugh class A cirrhosis, a distal splenorenal surgical shunt can be considered. In all other patients, a TIPS should be considered.

Transjugular Intrahepatic Portosystemic Shunt

A TIPS can be used to control refractory variceal bleeding and to prevent variceal rebleeding. TIPS creates a communication between the hepatic vein and an intrahepatic branch of the portal vein using an expandable metallic stent and decompresses the high portal pressures. The shunt is placed by an interventional radiologist via a transjugular approach, and dilated as needed to reduce the portacaval pressure gradient to below 12 mmHg. Nowadays, coated stents are more often used to reduce the frequency of shunt stenosis.

Immediate complications of TIPS placement include intraperitoneal hemorrhage, sepsis, and cardiopulmonary failure from excessive right heart volume. Early complications include shunt thrombosis or migration, hepatic encephalopathy, progressive hepatic failure, and pulmonary artery hypertension. Late complications include shunt stenosis, progressive hepatic encephalopathy, portal vein thrombosis, and heart failure.

The best indicator of failure of the TIPS is recurrence of gastrointestinal bleeding. TIPS should be avoided in patients with a MELD (model for end-stage liver disease) score >24 as these patients have a reduced survival [10]. In patients with a MELD score of ≤14, survival is excellent. Severe hepatic encephalopathy is a relative contraindication for TIPS. The best method to evaluate the patency of a TIPS is by hepatic venogram and measurement of the portacaval pressure gradient.

Varices at Other Sites

Gastric Varices [11]

- Type 1 GE varices (GOV1) extend 2–5 cm below the GE junction and in continuity with esophageal varices.
- Type 2 GE varices (GOV2) occur in the fundus of the stomach and in continuity with esophageal varices.
- Isolated gastric varices occur in the fundus (IGV1) or distal stomach (IGV2) in the absence of esophageal varices [11].

GOV1 comprise 70% of all gastric varices. IGV1 can result from splenic vein thrombosis but the most common cause is cirrhosis. Bleeding is most common from gastric fundal varices that are large (≥10 mm in diameter). β-Blockers may be used for primary prophylaxis, but endoscopic treatment is not currently recommended. Treatment of acute bleeding from gastric varices is similar to that of esophageal variceal bleeding except that the preferred endoscopic therapy is injection of polymers of cyanoacrylate into the varices [12]. Complications of cyanoacrylate injection include bacteremia, ulceration, and cerebral and pulmonary emboli. Ligation is safe if the varices are in the cardia of the stomach and <10 mm in diameter. Most patients with refractory

bleeding from gastric varices require a TIPS that controls 90% of bleeding [13,14].

Ectopic Varices

Ectopic varices are those other than in the esophagus and stomach, and account for <5% of all variceal bleeds. Ectopic varices usually present with melena. Cirrhosis is a cause of duodenal varices, but typically duodenal varices are associated with portal vein thrombosis [15]. Peristomal varices are especially seen in patients with primary sclerosing cholangitis and ulcerative colitis after a proctocolectomy [16]. They appear as a bluish halo around the stoma, with the stoma appearing dusky and friable. Anorectal varices are formed by dilated superior and middle hemorrhoidal veins. They collapse with digital pressure, as opposed to hemorrhoids, which do not.

Clinical evidence of bleeding from ectopic intra-abdominal varices includes a sudden increase in baseline ascites with abdominal pain, hypotension, and a fall in the hematocrit. A CT of the abdomen can help make the diagnosis but confirmation is by paracentesis of bloody fluid.

There is no evidence to support primary prophylaxis against bleeding from ectopic varices. Control of bleeding and secondary prophylaxis are essentially the same as with GE varices. To prevent rebleeding, β-blockers, surgery, or TIPS is considered.

Portal Hypertensive Gastropathy and Gastric Antral Vascular Ectasia

Mild PHG is diagnosed by the endoscopic appearance of a mosaic-like pattern of the gastric mucosa; severe PHG has a mosaic-like pattern with superimposed red spots [17].

The usual presentation of PHG bleeding is with anemia, but primary prophylaxis is not recommended. β-Blockers are recommended only in patients with blood loss [18,19]. TIPS is effective in decreasing transfusion dependence in patients who bleed despite β-blocker therapy [20].

GAVE is diagnosed by the endoscopic appearance of red spots without a background mosaic pattern of the mucosa, usually confined to the antrum [21]. In "watermelon stomach," the lesions are linear in arrangement. Red spots distributed throughout the stomach are termed "diffuse gastric vascular ectasia." Mucosal biopsies show dilated mucosal capillaries with ectasia and foci of fibrin thrombi.

GAVE also presents with chronic bleeding. Treatment involves iron replacement and RBC transfusions. Argon plasma coagulation is most often used as treatment. Cryotherapy is another treatment modality. Oral estrogen 35 μg with norethindrone 1 mg daily can be used but side effects of gynecomastia may limit its use. TIPS is not recommended for GAVE because it does not reduce the bleeding risk [20]. GAVE resolves with liver transplantation, but few patients are actually candidates for the procedure because the lesions typically occur in older patients.

Ascites

Case 2

A 59-year-old woman patient presents to your clinic complaining that her clothes are steadily getting tighter, especially around the waist. She also complains of worsening swelling in her feet. She has a history of primary biliary cirrhosis diagnosed 10 years ago for which she has been on ursodiol. She has had no other complications of her disease and has no other medical problems.

On examination, she is afebrile, pulse 68, blood pressure 106/78. Abdominal examination reveals mild distension, positive for shifting dullness on percussion. Abdominal ultrasonography confirms the presence of ascites.

What would you do next?

Introduction

Ascites is an increase in fluid in the abdominal cavity beyond the normal 50–100 mL.

Pathophysiology of Cirrhotic Ascites

The most common cause of ascites in the USA is cirrhosis and is present in about 85% of patients [22]. The remaining 15% of patients have ascites from other causes.

Ascites in cirrhosis results from increased renal retention of sodium and water, and elevated hepatic sinusoidal pressure, which leads to localization of fluid to the peritoneal space.

Vasodilation in the splanchnic and systemic vascular beds leads to effective hypovolemia [23]. This decrease in effective arterial blood volume activates

vasoconstrictive pathways including the renin–angiotensin–aldosterone pathway, sympathetic nervous system, and antidiuretic hormone (ADH). The result is sodium and water retention and an increase in the intra-arterial blood volume. ADH hypersecretion leads to water retention and hyponatremia, a marker for advanced disease [24]. The increased sinusoidal hydrostatic pressure causes movement of fluid out of the sinusoids into the space of Disse. As portal hypertension worsens, the lymphatics become overwhelmed and excess lymph spills into the peritoneal cavity. Over time, the leaky sinusoidal basement membranes become less permeable to albumin with less loss of albumin into the peritoneal cavity. This results in a low albumin and high serum ascitic fluid–albumin gradient (SAAG) [25].

Clinical Features

History

Ascites presents as increasing abdominal girth and may be associated with other clinical features of chronic liver disease.

In patients with ascites, a history of risk factors for liver disease should be obtained. Other important questions are country of origin, family history of liver disease, autoimmune disease, exposure to herbal teas or supplements, and history of obesity.

If a patient with compensated cirrhosis has sudden development of ascites, hepatocellular carcinoma, portal vein thrombosis, hepatic venous outflow obstruction, and worsening renal function are considered.

In a patient with a history of malignancy, peritoneal carcinomatosis is suspected. Tuberculous peritonitis is suspected in patients from endemic countries, or those with AIDS.

Myxedema may present with ascites and, therefore, thyroid function must be evaluated.

Physical Examination

Ascites is demonstrated by shifting dullness. Approximately 1500 mL of fluid are needed in the abdomen for flank dullness to be present [26]. Demonstration of ascites is more difficult in patients with obesity or with gaseous bowel distension. Abdominal ultrasonography is necessary to diagnose small-volume ascites. During the physical exam, other features of chronic liver disease, congestive heart failure, nephrotic syndrome, or malignancy should be noted.

Diagnosis

Ultrasonography, CT, or MRI is used to determine the cause of ascites. However, ascitic fluid analysis is imperative for confirmation of the diagnosis. Paracentesis must be performed when ascites is diagnosed for the first time and whenever a patient with ascites is hospitalized. Paracentesis can be repeated if signs or symptoms of an infection including SBP develop.

Complications of paracentesis are rare and include abdominal wall and retroperitoneal hematomas, and bowel perforations [27]. Measurement of platelet counts and prothrombin time, and prophylactic transfusions of blood products, are not recommended routinely before paracentesis [28].

The site for paracentesis may be guided by ultrasonography, but, if not available, the left lower quadrant is used (right lower quadrant may contain distended cecum or scar tissue from a previous appendectomy). A point lateral to the midpoint between the umbilicus and left anterosuperior iliac spine is usually a safe location. The midline below the umbilicus may also be used provided that the bladder is not distended. Paracenteses must be performed using sterile precautions and a local anesthetic; fluid is sent for a complete and a differential cell count, and albumin. If there is suspicion of SBP, ascitic fluid is cultured.

The SAAG is used to differentiate between causes of ascites. It is calculated by subtracting the ascitic fluid albumin concentration from the serum albumin concentration. A SAAG of 1.1 or greater indicates portal hypertension as the cause of ascites [29]. The SAAG can be used to define the cause of ascites, as shown in Table 14.1 and the characteristics of other causes of ascites are in Table 14.2.

Treatment

New-onset Ascites

Management of non-cirrhotic ascites involves treatment of the underlying disease, and is not discussed here.

Ascites secondary to alcoholic hepatitis is unique in that it occurs secondary to portal hypertension, but may be reversed by abstinence from alcohol [30]. These patients are treated as outlined below but, when they abstain from alcohol, ascites may resolve.

Sodium restriction (90 mmol/day) is a very important part of the treatment and requires rigorous dietary education.

Table 14.1 The serum ascites–albumin gradient (SAAG) used to differentiate the cause of ascites.

High SAAG (≥1.1)	Low SAAG (<1.1)
Cirrhosis	Tuberculous peritonitis
Alcoholic hepatitis	Peritoneal carcinomatosis
Fulminant hepatic failure	Pancreatic ascites
Cardiac failure	Biliary ascites
Budd–Chiari syndrome	Nephrotic syndrome
Sinusoidal obstruction	Bowel infarction
Portal vein thrombosis	Serositis in connective tissue disease

Table 14.2 Characteristics of causes of ascites.

Ascitic fluid test	Abnormality	Disease condition
Bilirubin (mg/dL)	>6	Bile duct or upper small intestinal perforation
Glucose (mg/dL)	<50	Secondary peritonitis
LDH (mU/mL)	≥225	Secondary peritonitis
Amylase	Highly increased	Acute pancreatitis or small intestinal perforation
Triglyceride (mg/dL)	>200	Chylous ascites
Absolute PMN count (cells/mm^3)	>250	Spontaneous bacterial peritonitis
Absolute lymphocyte count	Highly increased	Tuberculous peritonitis

LDH, lactate dehydrogenase; PMN, polymorphonuclear leukocytes.

Oral diuretics are the other component of management. The recommended initial doses of diuretics are furosemide 40 mg/day and spironolactone 100 mg/day. Side effects from the furosemide are hypokalemia, hyponatremia, and dehydration. Spironolactone, used alone, can cause hyperkalemia. The most common reason for discontinuation of spironolactone is, however, painful gynecomastia. If this occurs, spironolactone can be replaced with amiloride at a starting dose of 10 mg/day. Diuretic doses may be increased every 5–6 days as long as the serum creatinine and electrolytes are stable.

To evaluate compliance with salt restriction and response to diuretics, either a random or a 24-h urine sodium is measured; the latter is more accurate.

If ascites is tense, a large-volume paracentesis (LVP) may be performed. Whenever more than 5 L of ascitic fluid are removed, or in a patient without lower limb edema, albumin replacement should be provided intravenously during or immediately after the procedure in a dose of 6–8 g of albumin/L of fluid removed. Albumin administration prevents post-paracentesis circulatory dysfunction, which is associated with worsening renal function, rapid reaccumulation of ascites, and reduced survival [31,32].

Refractory Ascites

This is defined as ascites that is unresponsive to maximal doses of diuretics or recurs rapidly after paracenteses [33]. Refractory ascites may be diuretic resistant or diuretic intractable.

Repeated LVP can be used to treat diuretic-resistant ascites with albumin replacement after each tap. However, survival is not improved [34].

TIPS is used if patients require frequent LVP [35,36]. However, TIPS is associated with an increased risk of hepatic encephalopathy. Sodium restriction and diuretics may need to be continued after TIPS placement, albeit at lower doses. Since the advent of TIPS, peritoneovenous shunts are seldom used.

Complications

Dilutional hyponatremia, associated with worsening of the underlying cirrhosis, results from excess free water retention. Hyponatremia is best treated with fluid restriction to 1000 mL/day. Hypertonic saline administration is required only if hyponatremia is secondary to overdiuresis.

Hepatic hydrothorax results from movement of ascites across the diaphragmatic apertures into the pleural cavity, more often on the right side. Treatment is sodium restriction and diuretics; thoracocentesis is performed for symptomatic hydrothorax. A chest tube should not be placed because persistent leakage of fluid may worsen survival. TIPS is carried out for refractory hepatic hydrothorax.

Prognosis

The mortality rate after onset of ascites is approximately 50% in 2 years [37]. Hyponatremia is an independent

predictor of poor outcome [24,38]. Patients with ascites should be referred for consideration of liver transplantation.

Spontaneous Bacterial Peritonitis

Case 3

A 48-year-old man with a history of cirrhosis secondary to hemochromatosis presents to your clinic with his wife. She complains that he has been confused for the past 2 days. He does have a history of ascites which is treated with furosemide 40 mg/day and spironolactone 100 mg/day. However, he is not very compliant with his salt restriction and hence his ascites has been hard to control completely.

On examination, he is febrile, pulse 82, blood pressure 94/70. Abdominal examination reveals a positive fluid wave and the abdomen is diffusely tender to deep palpation. Asterixis is also present.

A paracentesis is performed and the cell count shows 800 white blood cells with 98% neutrophils. Cultures are pending.

What would you do next?

Introduction

SBP is diagnosed when the absolute polymorphonuclear leukocyte (PMN) count is >250 cells/mm^3 (neutrocytic ascites) with positive bacterial culture (usually a single organism) in the absence of an intra-abdominal source of infection [22]. Culture-negative neutrocytic ascites (CNNA) occurs when ascitic cultures are negative in the presence of neutrocytic ascites. Bacterascites is the term to describe positive ascitic cultures in the absence of neutrocytic ascites.

Pathophysiology

Increased translocation of bowel bacteria into the circulation through the mesenteric lymph nodes results in bacteremia and subsequent colonization of ascitic fluid. When immune defenses are compromised, as in low protein ascites [39], intercurrent infections, and advanced liver disease, the patient develops SBP.

SBP may be associated with bacteremia from pneumonia or urinary tract infections.

Secondary bacterial peritonitis, occurring secondary to intra-abdominal infection, is usually polymicrobial, including anaerobes.

Organisms

The most common organisms causing SBP are *Escherichia coli*, *Klebsiella pneumoniae*, and pneumococci. Other enteric Gram-negative and Gram-positive organisms may be cultured.

Oral selective bowel decontamination can alter the enteric flora and patients may get SBP secondary to Gram-positive organisms, including enterococci [40].

Clinical Features

Patients with SBP may be symptomatic but SBP should be ruled out in any hospitalized patient with ascites, especially with variceal bleeding [41]. Fever is the most common symptom associated with SBP [30]. Also noted are abdominal pain or tenderness, altered mental status, and hepatorenal syndrome.

Diagnosis

The diagnosis of SBP requires demonstration of an absolute neutrophil count >250/mm^3 in ascitic fluid. The optimal method of ascitic fluid culture is inoculation of at least 10 mL of ascitic fluid in blood culture bottles at the bedside immediately after paracentesis.

Rare causes of neutrocytic ascitic fluid include tuberculosis, peritoneal carcinomatosis, and pancreatitis, although these conditions are more likely to have a lymphocytic predominance.

Treatment

Empirical antibiotic therapy for suspected SBP is warranted if a patient has convincing symptoms, or signs of an infection [42], or the ascitic fluid neutrophil count is >250 cells/mm^3 but culture results are pending [42].

Initially, cefotaxime 2 g i.v. every 8 h or a similar third-generation cephalosporin is used [42], with dose adjusted in renal impairment.

Antibiotic coverage for anaerobes, *Pseudomonas* and *Staphylococcus* spp., is not usually needed. If secondary peritonitis is suspected, metronidazole 400 mg i.v. every 8 h or piperacillin–tazobactam 3.375 g i.v. every 6 h is the recommended agent. Antibiotics are tailored according to susceptibility results.

Intravenous albumin at the dose of 1.5 g/kg body weight on day 1 and 1.0 g/kg body weight on day 3 decreases the risk of renal failure and improves survival [43,44].

The duration of treatment of SBP is usually 5 days. The ascitic fluid culture can become sterile after a single dose of cefotaxime in 86% patients. A decrease in ascitic neutrophil count >25% after 48 h demonstrates response to treatment. If the neutrophil count does not decrease, secondary peritonitis is suspected.

Prognosis

Prognosis for patients with SBP may be improved with early detection and antibiotic therapy after an episode of SBP.

Secondary prophylaxis with norfloxacin 400 mg once daily is recommended. Primary prophylaxis is also used in patients without a history of SBP but with low protein ascites (<1.0 g/dL). In patients with variceal hemorrhage, norfloxacin is recommended for 5–7 days.

Hepatorenal Syndrome

Case 4

A 75-year-old woman with a history of cirrhosis secondary to alcohol is admitted with SBP. She has had ascites for 2 years, controlled with diet and diuretics. On admission, her serum creatinine is 1.3 mg/dL. She is treated with intravenous cefuroxime for her SBP. On day 3, her serum creatinine rises to 2.8 mg/dL.

What would you do next?

Introduction

Hepatorenal syndrome (HRS) is a functional renal failure occurring in patients with advanced liver disease [45]. Type 1 HRS with median survival <30 days is rapidly progressive; type 2 HRS is more indolent with a median survival <6 months.

Pathophysiology

The pathophysiology of HRS represents the extreme end of renal vasoconstriction and renal sodium retention. A precipitating event such as SBP results in further systemic and renal vasoconstriction and type 1 HRS can develop. Type 2 HRS develops when this circulatory imbalance continues for a prolonged period, but to a lesser degree.

Clinical Features

- Type 1 HRS is a severe and rapidly progressive renal failure with doubling of serum creatinine to >2.5 mg/dL in <2 weeks [46].
- It almost always follows a precipitating event such as SBP and variceal bleed [47]. About 25% of patients with SBP can develop type 1 HRS.
- Type 2 HRS is a more slowly progressive renal failure; the serum creatinine levels are usually between 1.5 g/dL and 2.5 g/dL.
- Type 2 HRS is usually associated with refractory ascites.
- Patients with type 2 HRS can develop type 1 HRS as well if there is a precipitating event.

Diagnosis

The following are the current diagnostic criteria for HRS:

- Cirrhosis with ascites
- Serum creatinine >1.5 mg/dL
- No improvement in serum creatinine to <1.5 mg/dL after at least 2 days with diuretic withdrawal and volume expansion with albumin (1 g/kg of body weight per day daily)
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, microhematuria (>50 RBCs/high power field), and/or abnormal renal ultrasonography.

HRS always needs to be differentiated from other causes of renal failure such as prerenal ones including overdiuresis, acute tubular necrosis, and rarely obstructive uropathy. Drugs such as aminoglycosides [48], non-steroidal anti-inflammatory drugs [49], and vasodilators such as prazosin and nitrates can all cause renal failure and must be avoided. Intrinsic renal diseases such as glomerulonephritis in patients with hepatitis B or C must be ruled out.

Treatment

The aim of treatment in HRS is correction of (1) the circulatory dysfunction including expanding the intra-arterial volume with albumin and use of splanchnic vasoconstrictors, and (2) the portal hypertension.

Albumin

Albumin expands the central blood volume and increases cardiac output. It is most effective in type 1 HRS but

must also be used in type 2 HRS when therapeutic paracentesis is carried out. It is usually given intravenously as 1 g/kg body weight per day up to 100 g/day.

Vasoconstrictor Agents

Terlipressin is the most widely used splanchnic vasoconstrictor worldwide [49]; however, it is not available in the USA. Oral midodrine (an α-agonist) at a dose of 2.5–10 mg three times a day along with subcutaneous octreotide at a dose of 100 µg/day is the combination most often used in the USA [50]. Norepinephrine has also been shown to be an effective and safe vasoconstrictor [51] but it is not often used.

With vasoconstrictors and albumin, about 60% of type 1 HRS will resolve. If a relapse occurs, the same agents are used.

Transjugular Intrahepatic Portosystemic Stent Shunt

TIPS works by improving renal perfusion and the glomerular filtration rate (GFR), increasing urine sodium and water excretion, and correcting hyponatremia [52]. It thus helps to eliminate the refractory ascites in patients with type 2 HRS. However, it can worsen hepatic encephalopathy. The role of TIPS in type I HRS is less clear.

Liver Transplantation

The ideal treatment for both types of HRS is liver transplantation.

After receipt of a liver transplant in patients with HRS, the GFR may continue to decline for a brief period before it starts to recover. These patients have more complications and higher mortality rates than patients without HRS [45,46].

Hepatic Encephalopathy

Case 5

A 68-year-old man with cirrhosis secondary to hepatitis C presents to your surgery for a routine visit. He feels well and his ascites is well controlled with diuretics. However, he informs you that he has been feeling very tired recently and feels that he is unable to get a good night's rest. He is sleeping a lot during the day. Also, he has noticed that his wife is always upset at him for forgetting about routine chores that he is asked to perform.

On exam, he is afebrile, pulse 59, blood pressure 98/64. Abdomen is soft, non-tender. Asterixis not present.

What would you do next?

Introduction

Hepatic encephalopathy (HE) is the neuropsychiatric manifestation of cirrhosis, which results from a combination of portosystemic shunting and liver dysfunction.

Pathophysiology

Plasma ammonia, which is increased in HE, reaches the brain where it is taken up by astrocytes, resulting in upregulation of astrocytic peripheral-type benzodiazepine receptors (PBRs). PBRs are potent stimulants of neurosteroid production. Neurosteroids are the main modulators of γ-aminobutyric acid (GABA), which cause cortical depression and, thus, hepatic encephalopathy. In fulminant hepatic failure, high levels of ammonia result in accumulation of glutamine in the astrocytes causing them to swell, resulting in cerebral edema.

Clinical Features

HE usually presents as altered mental status or consciousness and is classified as follows:

- Type A, associated with **a**cute liver disease
- Type B, secondary to portosystemic shunts (**b**ypass), without chronic liver disease
- Type C, due to **c**irrhosis.

The classification based on clinical presentation is as shown in Table 14.3.

The West Haven classification, which scores the level of consciousness, personality and intellect, neurologic and EEG abnormalities, is seldom used in clinical practice.

Diagnosis

The diagnosis of HE can be made on history and physical examination alone but may require formal neuropsychiatric testing when mild. Altered sleep patterns and collateral history from the patient's family may provide

Table 14.3 Classification of hepatic encephalopathy.

Type	Characteristics
Episodic	Occurs intermittently
Precipitated	Occurs in the presence of a specific precipitant
Spontaneously	Occurs without a precipitant
Persistent	Affects the patient's daily living and activities

clues to the diagnosis of HE. The cranial nerves are usually spared and sensory functions are intact. However, increased tone, motor slowing, impaired posture, and increased deep tendon reflexes may be seen.

As there is no pathognomonic feature to diagnose HE, other causes of altered sensorium such as neurologic disorders, encephalopathies, and toxin or drug ingestions must be excluded.

The most common precipitants are excess dietary protein, constipation, gastrointestinal bleeding, infection (especially SBP), renal failure, overdiuresis and dehydration, hypokalemia, spontaneous or iatrogenic portosystemic shunts, decompensation of liver disease, hepatocellular carcinoma (HCC), and use of benzodiazepines.

HE after a TIPS procedure is more common in patients over the age of 60 and in those with a prior history of HE [53].

Asterixis, also called "flapping tremor" is present in grades 2 and 3 HE. It is elicited by having the patient fully extend the elbows and dorsiflex the wrists with the fingers spread apart. Asterixis appears as a rapid flexion–extension movement at the wrist and the metacarpophalangeal joints, with flexion being the more rapid component. Other causes of asterixis include uremia, hypercapnia, and drugs such as phenytoin, carbamazepine, and lithium.

Treatment

Chronic HE

1 Treatment of the precipitant depends on the precipitant identified. Hydration and correction of renal insufficiency are a key element of treatment.

2 Reduction in the production and absorption on ammonia.

3 Diet: dietary protein must be limited to 1–1.5 g protein/kg per day. Dairy and vegetable proteins are preferred to animal protein. Branched-chain amino acids impact time to decompensation [54,55] but are not routinely recommended.

4 Non-absorbable disaccharides: include lactulose and lactitol (not approved for use in the USA). These act by acidifying the colonic contents, which causes ionic trapping of ammonia, and reduce ammonia-producing bacteria by a cathartic effect [56]. Lactulose dosage must be titrated to achieve two to four semi-formed bowel movements a day.

5 Antibiotics: include neomycin (4–6 g/day), metronidazole (250 mg three times daily), and rifaximin (200 three times daily). These antibiotics are believed to reduce the burden of ammonia-producing organisms in the gut. However, systemic absorption may occur and produce side effects—neomycin can cause ototoxicity and nephrotoxicity, and metronidazole can cause peripheral neuropathy.

6 L-Ornithine-L-aspartate (LOLA): given orally or parenterally, increases ammonia fixation by the liver. It provides ornithine as a substrate in the urea cycle which is defective in patients with cirrhosis and improves hepatic ammonia clearance [57]. LOLA is not available for use in the USA.

7 Zinc: a cofactor in the urea cycle, it is often deficient in patients with cirrhosis, and is administered as zinc sulfate 600 mg/day.

8 Centrally acting agents: flumazenil, a benzodiazepine receptor antagonist administered intravenously, is short acting and not practical to use.

9 Liver transplantation: this is the definitive treatment for HE.

HE Associated with Fulminant Hepatic Failure

Patients with grade 3 or 4 HE should be in an intensive care unit, sedated, paralyzed, and electively ventilated.

Intracranial pressure (ICP) catheters are used to monitor ICP. However, epidural catheters or subdural bolts carry a risk of hemorrhage as high as 20%.

Blood pressure should be tightly controlled using phenylephrine if low, or sodium nitroprusside or hydralazine if high to maintain a cerebral perfusion pressure >60 mmHg.

Hyperventilation, mannitol boluses (100 mL of 20% mannitol at 10-min intervals) or intravenous furosemide is used to decrease ICP. Mannitol is contraindicated if serum osmolality ≥320 mosmol/L, or with oliguric renal failure. Hypothermia to 32–33 C can also reduce ICP.

Specific therapy for the underlying disease should also be started simultaneously—*N*-acetylcysteine for acetaminophen toxicity, penicillamine for Wilson disease, and corticosteroid therapy for autoimmune hepatitis. Liver transplantation must also be considered urgently in these patients.

Prognosis

HE is a manifestation of both decompensation of chronic liver disease and acute hepatic failure, and is associated with decreased survival [58].

Hepatopulmonary Syndrome: Portopulmonary Hypertension

Case 6

A 55-year-old woman with cirrhosis secondary to hepatitis B complains of worsening dyspnea with exercise. Her cirrhosis has been well compensated so far and in fact she has continued to work full time. Now, she is unable to walk up a single flight of stairs without needing to stop for air.

On exam, she is afebrile, pulse is 76 beats/min, blood pressure 108/80 mmHg. Heart exam is normal including jugular venous pressure. Lungs are clear. Abdomen is soft, non-tender. No pedal edema seen.

Pulse oximetry on room air shows oxygen saturation of 88% at rest.

What would you do next?

Introduction

The pulmonary vascular complications of portal hypertension, hepatopulmonary syndrome (HPS), and portopulmonary hypertension (PPH) significantly impact both survival and quality of life.

Hepatopulmonary Syndrome

Pathophysiology

HPS is primarily an arterial oxygenation defect induced by dilation of the pulmonary precapillary and capillary vessels (15 μm diameter). Pleural and portopulmonary venous anastomoses may rarely be present. Intrapulmonary vascular dilation (IPVD) results in rapid shunting of mixed venous blood into the pulmonary veins, producing a ventilation–perfusion defect, causing hypoxemia. As a result of an attenuation in the hypoxic vasoconstriction response in patients with cirrhosis, vasodilation is unopposed.

In advanced stages of the disease, an alveolar–capillary diffusion limitation to oxygen develops. This, along with increased cardiac output seen in advanced cirrhosis, leads to further worsening of the total oxygenation of blood in the lungs.

Enhanced pulmonary production of NO by increased pulmonary vascular endothelial NO synthase (eNOS) and inducible NO synthase (iNOS in macrophages) causes vasodilation.

Clinical Features

HPS occurs in association with portal hypertension of all causes, as well as in patients with acute [59] and chronic hepatitis [60].

Dyspnea with exertion, or at rest, is the most common symptom. However, dyspnea is fairly common in patients with liver disease because of anemia, ascites, and muscle wasting. The diagnosis of HPS is made by measuring arterial blood gases, echocardiography, and brain–lung perfusion scanning.

Platypnea (worsened dyspnea from the supine to the upright position) is the pathognomonic symptom of HPS. Platypnea results from worsening of the ventilation–perfusion mismatch on standing due to orthodeoxia (decrease in arterial partial pressure of oxygen ≥5% or ≥4 mmHg).

In advanced HPS, digital clubbing and cyanosis of the lips and nail beds occur. Rarely, complications of right-to-left pulmonary communications such as brain abscesses or polycythemia may be seen [61].

Diagnosis

- Oxygenation defect: a Pa_{O_2} <70 mmHg and/or P_A–a_{O_2} ≥15 mmHg in the presence of portal hypertension and in the absence of other factors is diagnostic for HPS.
- Pulmonary vascular dilation:
  - Contrast-enhanced transthoracic echocardiography is a qualitative screening method to demonstrate pulmonary vascular dilation. Agitated saline microbubbles when injected into a peripheral vein normally do not appear in the left heart. Appearance of bubbles in the left heart in less than three cardiac cycles suggests an intracardiac right-to-left communication. Appearance of microbubbles after three to six cardiac cycles confirms IPVD. Transesophageal echocardiography is more sensitive but not used routinely.
  - Perfusion lung scanning: ^{99m}Tc-labeled macroaggregated albumin injected into a peripheral vein is normally trapped in the lung because the particle size is >20 μm. In HPS, particles pass through the dilated vasculature and get retained in the brain. Measurement of

the uptake in the lungs and brain allows quantification of the pulmonary shunting.
- Pulmonary angiography is used only when embolization of macroscopic shunts is planned.

Treatment

There are currently no curative medical or pharmacological therapies for HPS. Liver transplantation is the only curative treatment.

Long-term oxygen therapy is used. Coil embolization of the IPVD is attempted only when a macroscopic IPVD is demonstrated on a chest CT scan.

Prognosis

Median survival for patients not undergoing liver transplantation is about 41 months after diagnosis of HPS [62]. Mortality is usually due to complications of the liver disease. After transplantation, there is complete resolution of HPS in most patients.

Portopulmonary Hypertension

Pathophysiology

Pulmonary arterial hypertension associated with portal hypertension results from pulmonary vasoconstriction. Endothelial and smooth muscle proliferation, *in situ* thrombosis, and plexogenic arteriopathy ultimately result in increased resistance to pulmonary arterial blood flow and pulmonary hypertension. Eventually, right ventricular hypertrophy, tricuspid regurgitation, right atrial dilation, and right heart failure develop. The resulting decrease in cardiac output worsens symptoms.

There has been a variety of proposed mechanisms for the cause of vasoconstriction. Vasoactive substances that escape the liver metabolism due to portosystemic shunting reach the lungs. Neurohormones such as serotonin and endothelin have also been implicated to cause vasoconstriction and mitogenesis. Release of cytokines such as tumor necrosis factor β and growth factors promotes vascular proliferation.

Clinical Features

Dyspnea and fatigue are the most common presenting manifestations. As portopulmonary hypertension (PPH) worsens, symptoms of right heart failure develop including lower extremity edema. In advanced PPH, chest discomfort and syncope may be seen.

Diagnosis

- Transthoracic Doppler echocardiography is the test used to screen for PPH. Echocardiography can estimate only right ventricular systolic pressure. However, right heart catheterization (RHC) is necessary to measure mean pulmonary arterial pressure (MPAP).
- Hemodynamics: RHC is used to measure MPAP, pulmonary vascular resistance, and cardiac output. The hemodynamic response to vasodilators can also be measured to guide treatment. PPH is confirmed in a patient with portal hypertension with an MPAP ≥25 mmHg, and pulmonary capillary wedge pressure <15 mmHg, and pulmonary vascular resistance >240 dyn s/cm^5.

Treatment

- Diuretics may be used when pulmonary hypertension is secondary to volume overload. Hypovolemia, however, can worsen cardiac output and precipitate HRS.
- Oral anticoagulants are not usually recommended in PPH because of risk of variceal bleeding.
- Vasodilators, the mainstay of medical therapy, can reverse the vasoconstriction, but have no effect on the fibrotic and proliferative vascular changes.

Prostacyclin (epoprostenol), a systemic and pulmonary vasodilator, is administered by continuous intravenous infusion. Adverse effects include headaches, nausea, diarrhea, and flushing, and catheter-related infections and thromboses. The interruption of the infusion can be life threatening due to the sudden loss of vasodilation. Sildenafil is an effective pulmonary vasodilator administered orally.

Oral endothelin receptor antagonists such as bosentan are used in selected patients with varying results.

TIPS in PPH may worsen the pulmonary hypertension by increasing right ventricular preload.

Unlike HPS, PPH is not considered an indication for liver transplantation. In fact, moderate-to-severe pulmonary hypertension has been shown to increase perioperative mortality and morbidity [63,64] and is hence a contraindication to liver transplantation. In the immediate post-transplantation period, acute worsening of right heart failure can occur.

Prognosis

Median survival for patients not undergoing liver transplantation is about 6 months after diagnosis.

Take-home points

Varices:

- Varices are dilated veins that develop due to portal hypertension. They can be seen in the esophagus, stomach, rectum, at the umbilicus, and in the retroperitoneum.
- At the GE junction, varices in the lower third of the esophagus are most likely to bleed.
- Hematemesis or melena is the usual presentations and variceal bleeding must be suspected in a patient who presents with either and has features of cirrhosis.
- Portal hypertension is diagnosed by measurement of the hepatic vein pressure gradient.
- Varices are diagnosed by EGD.
- Screening for varices should be done when cirrhosis is diagnosed. If no varices at EGD, repeat EGD in 2–3 years. If small varices at EGD, repeat EGD in 1–2 years. If large varices at EGD, start primary prophylaxis.
- Primary prophylaxis of varices is with non-selective β-blockers or endoscopic variceal ligation.
- Acute variceal bleeding treated with supportive measures, octreotide and vasopressin analogues, and endoscopic therapy in the form of variceal banding. Also, antibiotic prophylaxis to prevent development of SBP is needed.
- If bleeding is recurrent or intractable, a TIPS may be beneficial, but can have complications of right heart failure and hepatic encephalopathy.
- In the stomach, bleeding is most common from varices in the fundus, both isolated and those in continuity with esophageal varices. They should be treated similarly except the endoscopic therapy of choice is injection of cyanoacrylate glue into the varix.
- Portal hypertensive gastropathy may be mild (mosaic pattern of mucosa) or severe (with superimposed red spots). It responds to TIPS.
- GAVE appears as red spots without the mosaic background. It most commonly involves the antrum. It resolves with liver transplantation.

Ascites:

- The most common cause of ascites in the USA is cirrhosis.
- Other causes include congestive heart failure, nephrotic syndrome, peritoneal carcinomatosis, and infections including tuberculosis.
- Ascites is the result of hemodynamic changes in the circulatory system, leading to salt and water retention.
- Ascites can be diagnosed on physical examination and by abdominal imaging, including ultrasonography, CT, and MRI.
- A diagnostic paracentesis must be performed when ascites is diagnosed and whenever a patient with ascites is admitted to the hospital for any reason. Fluid must at least be sent for albumin, protein, cell count with differential, and culture.
- Management of ascites is with dietary restriction of sodium to 90 mmol/day and with diuretics—specifically furosemide and spironolactone.
- If ascites becomes refractory to diuretics, then repeated paracenteses or TIPS is the treatment option.
- Hepatic hydrothorax should be treated similarly. Avoid placement of chest tubes.
- Hyponatremia is an independent predictor of mortality and is treated with restriction of free water.

SBP:

- Defined as ascitic fluid with a neutrophil count >250 cells/mm^3 and a positive bacterial culture.
- Most common causative organisms are Gram-negative enteric flora—*E. coli*, *Klebsiella* sp., and pneumococci.
- In patients on chronic suppressive antibiotics or oral selective bowel decontamination, Gram-positive organisms are more common.
- May present with fever or abdominal pain. SBP must be ruled out in patients who present with hepatorenal syndrome, variceal bleeding, or encephalopathy.
- Treatment is with antibiotics, initially cefotaxime 2 g i.v. every 8 h or equivalent. Duration of treatment is 5 days in uncomplicated cases.
- Intravenous albumin should be given on days 1 and 3 to prevent hepatorenal syndrome.

Hepatorenal syndrome:

- Type 1 HRS is rapidly progressive, usually associated with a precipitating event and has a very poor prognosis.
- Type 2 HRS is more slowly progressive, usually associated with refractory ascites and has a longer survival, but still with a 100% mortality rate without treatment.
- Precipitating events include SBP, variceal bleeds, and other bacterial infections.
- When HRS occurs, all diuretics must be discontinued.
- Volume resuscitation with intravenous albumin must be started.
- Vasoconstrictor agents such as midodrine and octreotide must be started after volume resuscitation.
- TIPS can be performed but liver transplantation is the only cure.

Hepatic encephalopathy:

- Hyperammonemia is the underlying cause.
- Fulminant hepatic failure occurs when hepatic encephalopathy (HE) develops within 8 weeks of the onset of symptoms or 2 weeks of the onset of jaundice.
- HE associated with acute hepatic failure can cause cerebral edema, herniation, and death. It is treated more aggressively with intubation, ICP monitoring, and mannitol.
- Diagnosis is by history, clinical exam, and neuropsychiatric testing.
- Management includes dietary protein restriction, use of lactulose, antibiotics such as neomycin and rifaximin, and ultimately liver transplantation.

Hepatopulmonary syndrome: portopulmonary hypertension:

- Hepatopulmonary syndrome (HPS) is caused by dilatation of the pulmonary capillary and precapillary vessels. Thus, there is rapid shunting of blood throughout the lungs which results in an oxygenation defect.
- Pulmonary arterial hypertension (PPH) is caused by pulmonary vasoconstriction with endothelial and smooth muscle proliferation. It eventually causes right-sided heart failure and decreased cardiac output.
- Both may present with dyspnea with exercise and at rest. Platypnea is characteristic of HPS.
- In HPS, the dilated arterial bed is diagnosed by contrast-enhanced transthoracic echocardiography with agitated saline or perfusion lung scanning.
- In PPH, pulmonary hypertension can be diagnosed by characteristic features on transthoracic echocardiography or by selective right heart catheterization with measurement of pressures.
- HPS is treated only by liver transplantation. It is a criterion for the model for end-stage liver disease (MELD) exception. Supplemental oxygen is usually needed till transplantation.
- PPH can be treated medically with diuretics, vasodilators, and supplemental oxygen. TIPS is contraindicated because it may worsen right heart failure.

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15

CHAPTER 15
Hepatocellular Carcinoma

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Summary
Hepatocellular carcinoma is the third most frequent cause of death from cancer worldwide. This cancer is most common in geographic regions with a high prevalence of chronic hepatitis B virus infection—particularly in Asia and sub-Saharan Africa. However, due to increased incidence of chronic hepatitis C virus infection between 1945 and 1990, the incidence rates of hepatocellular carcinoma have been increasing in Europe and North America since the 1970s. Substantial advances have been made in therapy of hepatocellular carcinoma, notably the recognition that in patients with early stage disease liver transplantation can achieve a 5-year survival rate of over 70%. These results, along with advances in surgical resection, local ablation, and locoregional therapies, have led to an increased emphasis on surveillance of individuals at risk for hepatocellular carcinoma, to allow for early diagnosis and more effective treatment of as many patients as possible. For patients with advanced, unresectable disease, the recent Food and Drug Administration approval of the multi-kinase inhibitor sorafenib, which has been shown to moderately extend patient survival, is a positive harbinger for future advances in therapy.

Case
A 57-year-old man has chronic hepatitis B that was first contracted when he was in the military service 30 years ago. He now has cirrhosis with portal hypertension and thrombocytopenia. The serum bilirubin is 1.2 mg/dL. He is enrolled in a program of surveillance with ultrasonography every 6 months. A new 1.3 cm nodule is found on screening ultrasonography. A contrast CT scan is performed and the nodule shows arterial enhancement and delayed washout. A contrast MRI is performed which confirms the arterial enhancement and venous washout of the lesion. Follow-up imaging is performed by CT every 3–4 months. Eventually, at approximately 15 months after initial detection, the lesion reaches 2.1 cm. The patient is evaluated and listed by the liver transplant program. As he meets the criteria for non-invasive diagnosis of hepatocellular carcinoma, a biopsy of the mass is not considered to be necessary. With his blood group, his wait time for liver transplantation is approximately 8 months. The transplant program elects to treat the tumor with chemoembolization while he awaits transplantation. This is performed three times at 2-month intervals, after which there is no evidence of viable tumor enhancement on contrast imaging. Nine months after diagnosis of hepatocellular carcinoma the patient receives a liver transplant. On careful examination after liver transplantation, the explant shows no evidence of viable tumor.

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Epidemiology

Hepatocellular cancer (HCC) is the fifth most common cancer worldwide and the third most frequent cause of death from cancer [1]. The highest incidence reports of HCC are in Asia and sub-Saharan Africa. According to the International Agency for Research on Cancer, in 2002 worldwide incidence ratios were 15.8 cases/100 000 per year for men and 5.8 cases/100 000 per year for women. The highest incidence regions in Asia and Africa have a high prevalence of chronic hepatitis B virus (HBV) infection as well as significant exposure to dietary fungal

aflatoxins. Combinations of risk factors that are important in the epidemiology of HCC include coinfection of HBV and hepatitis C virus (HCV), alcohol use, and other causes of cirrhosis of the liver such as non-alcoholic fatty liver disease (NAFLD), α_1-antitrypsin deficiency, and hereditary hemochromatosis [2,3]. The risk of HCC increases with age. There is a significant effect of gender on the risk of development of HCC. The worldwide male : female incidence ratio is 2.7 : 1. Additional risk factors include diabetes and tobacco smoking [4]. Geographic, immigration, and social patterns result in significant racial and ethnic variations in the incidence of HCC [5].

Risk Factors

Chronic Hepatitis B

There are 350–400 million individuals with chronic HBV infection worldwide. In low prevalence countries, sexual contact is the predominant mode of transmission, while in high prevalence countries most HBV infections are contracted perinatally or in early childhood. Many individuals with chronic HBV infection develop progressive liver disease and the annual incidence of cirrhosis is 2–10%. HBV DNA levels are the strongest predictor of progression to cirrhosis; in addition, hepatitis B e antigen (HBeAg) positivity, abnormal alanine transaminase (ALT) levels, male sex, and increasing age are associated with an increased risk of cirrhosis [6]. The risk of HCC varies from 2% to 10% per year in patients with cirrhosis, depending on the primary etiology and the presence of additional associated risk factors [7]. Immunization of infants and at risk individuals decreases the prevalence of chronic hepatitis B infection and the incidence of HCC [8].

Chronic Hepatitis C

About 170 million people worldwide are infected with HCV. Those at highest risk for acquiring hepatitis C are recipients of contaminated blood transfusions, those subject to unsanitary health practices with contaminated needles, and intravenous drug users. Chronic hepatitis C is a slowly progressive disease. Persistently high ALT levels, increased stage of liver fibrosis, male gender, concurrent alcohol use, older age, and coinfection with hepatitis B or HIV are significant predictors for development of HCC. After surgical resection the presence of active hepatitis and hepatitis C are risk factors for tumor recurrence. Prior treatment of hepatitis C with interferon or combination interferon and ribavirin, with achievement of a sustained viral response, is protective against the initial development of HCC or recurrence after surgical resection. However, patients with HCV and cirrhosis remain at risk for HCC even after sustained virological response to therapy and should remain in surveillance programs indefinitely [9,10].

Dietary Aflatoxin Exposure

Aflatoxins are a group of mycotoxins produced by the fungi *Aspergillus flavus* and *A. parasiticus*. *Aspergillus* species are widespread in nature, occurring in soil and decaying vegetation, in conditions of high moisture and temperature. There are different types of aflatoxins with aflatoxin B1 being the most carcinogenic. Aflatoxins are metabolized in the liver by the cytochrome P-450 and glutathione *S*-transferase enzyme systems. Aflatoxin B1 is a procarcinogen that is converted in the liver to a mutagenic metabolite. Contamination of foodstuffs with aflatoxins predisposes to mutations in the *p53* gene, an event that contributes to the pathogenesis of HCC. The carcinogenic effect of aflatoxin is increased by infection with chronic hepatitis B and C [4].

Pathogenesis of HCC

HCC occurs in multiple genetic and environmental contexts, and oncogene activation and tumor-suppressor inactivation play key roles in carcinogenesis of HCC. In cirrhotic livers macro-regenerative nodules with foci of hepatocyte dysplasia have been identified as precancerous lesions. Multiple mechanisms appear to contribute to hepatitis B-induced hepatic carcinogenesis. Although the sequence of persistent hepatitis with regenerative hepatocellular turnover, premature senescence of the liver, abrogation of the ability of the liver to regenerate its normal architecture, and the eventual development of cirrhosis is presumed to play a major role in HBV-induced carcinogenesis, a significant percentage of HBV-induced HCCs occur in the absence of liver cirrhosis. This suggests that there are additional carcinogenic mechanisms that can drive carcinogenesis in patients with chronic HBV infection in the absence of cirrhosis. Hepatitis B is a small DNA virus that integrates into the

host genome in almost all patients with longstanding chronic hepatitis B. HBV DNA integration is thought to lead to carcinogenesis through a number of pathogenic pathways, including [11]:

1 Generalized genomic instability which leads to focal deletions and translocations

2 The creation of novel oncogenic virus-host fusion proteins

3 HBV-induced modulation of gene transcription through placement of viral enhancer sequences adjacent to host genes

4 Oncogenic effects of HBV proteins such as the X and pre-S proteins.

In patients with chronic HCV infection, persistent liver damage results in repeated cycles of liver injury and regeneration, which in turn result in premature cellular senescence of the liver and the development of genetic aberrations. Although most senescent cells undergo a critical shortening of chromosomal end telomeres, and consequently undergo telomeric crisis and cell death, a proportion of these cells reactivate telomerase activity and become immortalized. Within the context of a highly genotoxic environment with increased reactive oxygen species and inflammatory cytokines, additional genetic and epigenetic aberrations then occur that lead to the initiation of cancer within these immortalized cell clones. Subsequent secondary changes in the tumor microenvironment contribute to the neoangiogenesis, invasion, and metastases that are typical in HCC [12].

Clinical Features

Most patients with HCC are asymptomatic early in the disease. Early stage disease is usually identified during surveillance of patients at risk for HCC. HCC may result in decompensation of cirrhosis by vascular invasion of the portal vein or its branches, worsening portal hypertension and resulting in ascites and variceal bleeding. Tumor infiltration of the hepatic sinusoids also worsens hepatic function, resulting in hyperbilirubinemia, coagulopathy, and encephalopathy. The development of spontaneous bacterial peritonitis (SBP) may be the first sign of HCC, therefore patients diagnosed with SPB should be screened for HCC. Patients with advanced HCC may present with an abdominal mass, obstructive jaundice due to pressure effects on the central bile ducts, an acute abdomen due to intratumoral hemorrhage or intraperitoneal rupture, fever of unknown origin, metastatic disease or constitutional symptoms. Paraneoplastic phenomena associated with HCC include hypercalcemia, hypoglycemia, thrombophlebitis migrans, erythrocytosis, and diarrhea. Laboratory features associated with HCC include changes of advanced liver disease such as elevated bilirubin, alkaline phosphatase, and transaminases with prolongation of the prothrombin time and low albumin levels. α-Fetoprotein (AFP) levels are elevated in up to 75% of cases of advanced disease, but only approximately 30% of cases of early HCC. An AFP value >400 ng/mL has a 95–98% specificity for HCC [13].

Surveillance and Screening Tests for HCC

Patients at risk for HCC should be enrolled in a surveillance program for early detection of HCC. These include individuals with cirrhosis of any cause as well as those with longstanding chronic hepatitis B without cirrhosis. Currently, surveillance is recommended for individuals with chronic hepatitis B who are Asian born, beginning at age 40 for men and 50 for women. African-born individuals are at higher risk of developing HCC early in adulthood and should be enrolled in surveillance programs, starting at age 20. Individuals with chronic hepatitis B and a family history of HCC, high HBV DNA levels, or active inflammation are also at higher risk of developing HCC [14]. At-risk individuals should be screened at 6-monthly intervals with abdominal ultrasonography and serum α-fetoprotein measurements. Other serum tumor markers include the des-gamma-carboxyprothrombin (DCP) and the AFP-L3 isoform. These latter markers have not shown superior performance over the serum α-fetoprotein, but may be useful when used in combination with ultrasonography and AFP [15]. The AFP-L3 may be of particular use in patients with chronic hepatitis C who often have non-specific elevation of the total AFP in the range 10–200 ng/mL [16].

Diagnosis and Staging of HCC

The Barcelona Clinic Liver Cancer (BCLC) staging system is endorsed by the American Association for the

Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver. HCCs are classified into five stages based on the extent of the primary lesion, performance status, presence of constitutional symptoms, vascular invasion, and extrahepatic spread [17]. Once a new nodule is found by screening ultrasonography in a cirrhotic liver, further cross-sectional liver imaging with computed tomography (CT) or magnetic resonance imaging (MRI) can confirm the diagnosis and histologic confirmation from a biopsy is only occasionally required. Current AASLD guidelines for non-invasive diagnosis of HCC state that a new mass >2 cm in size found during regular surveillance of a patient with known hepatitis B, or cirrhosis of other etiology, is HCC if it shows the typical imaging features of arterial enhancement and portal venous phase washout on contrast CT, MRI, or contrast ultrasonography.

If the lesion is between 1 and 2 cm in size, then typical imaging features should be shown on two dynamic contrast studies, e.g., both CT and MRI, in order to confirm the diagnosis. Lesions <1 cm in size have only a 50% chance of being an HCC and should be followed by imaging every 3–6 months. If there is no growth of the lesion over 2 years, one can then revert to routine surveillance. Lesions with atypical imaging features should be biopsied if the results will substantially influence clinical management. The risks of biopsy include bleeding, a small but significant risk of tumor seeding, which occurs in perhaps 0.5% of cases, and a more substantial risk of a false-negative result that may be up to 10% for attempted biopsies of small lesions [14,18]. As the current United Network for Organ Sharing (UNOS) guidelines grant additional model for end-stage liver disease (MELD) points only to individuals with tumors >2 cm in size, in individuals who are candidates for liver transplantation, many centers will closely observe growing nodules in the liver by repeated imaging until they reach the 2-cm size cut-off; by that time, most HCCs show typical imaging features.

Treatment

Surgical Therapies

Surgical Resection

Patients with early stage HCC should be evaluated for surgical resection. Ideal candidates are patients with a solitary lesion <5 cm, no evidence of vascular invasion, no evidence of clinically significant portal hypertension, and well-preserved liver function. A serum bilirubin >1 mg/dL, wedged hepatic venous pressure gradient >10 mmHg, platelet count <100 000/fL, or the presence of esophageal varices are considered to be contraindications for resection. Patients who are good candidates for resection should be Child–Pugh class A or have a MELD score <8 [19]. As the neoplastic potential of the non-resected cirrhotic liver remains unchanged, intrahepatic recurrence of HCC frequently occurs after an apparently curative resection; recurrence rates are up to 50% at 3 years and 75% at 5 years after resection.

Orthotopic Liver Transplantation

Orthotopic liver transplantation (OLT) is the optimal therapy for patients with early stage HCC who have severe liver dysfunction and are not candidates for surgical resection. OLT offers several advantages over partial hepatectomy; it can be employed for patients with all stages of liver disease and it addresses the cancer, the neoplastic potential of the surrounding liver, and the chronic liver disease itself. The best outcomes are achieved in patients without extrahepatic metastases who have a single tumor <5 cm in maximal diameter or two or three lesions, the largest not more than 3 cm in maximal diameter (the Milan criteria) [20]. The most important limitation of OLT is an increasing donor organ shortage. Current policies of the UNOS, which coordinates organ donation in the USA, assign additional MELD points to patients with HCC listed for OLT with a goal of achieving the same rate at which patients with non-malignant liver diseases drop off the waiting list. In addition, the long waiting period for a donor organ often allows a small tumor to become larger or even metastatic. Hence, to prevent tumor growth and metastasis while patients are awaiting OLT, many transplant centers treat these lesions using local or locoregional therapy before OLT.

Non-surgical Therapies

For patients who do not meet the criteria for surgical resection or OLT, local ablation techniques such as radiofrequency ablation and percutaneous ethanol injection are used for treatment of early stage HCC with two to four lesions that are up to 4 cm in size; patients with intermediate stage disease with bilateral multinodular

disease are treated with transarterial chemoembolization (TACE) or transarterial radioembolization (TARE) if feasible. For patients with advanced HCC the only treatment currently shown to have efficacy and improve survival in a large randomized controlled trial is the multi-kinase inhibitor sorafenib.

Percutaneous Alcohol Injection

Percutaneous alcohol injection (PEI) is an option for small, localized HCC. It is a relatively simple and inexpensive technique that can be used with caution in patients with advanced cirrhosis. The most suitable lesions for treatment are <4 cm in size and most experts recommend PEI for treatment of no more than three nodules. The injection of absolute alcohol destroys tumor cells by cellular dehydration, coagulation necrosis, and vascular thrombosis followed by ischemia. The extent of necrosis achieved by a single injection depends on the tumor size. A small lesion may require only one treatment whereas larger lesions may require several treatments. Injection is performed under CT or ultrasound guidance. PEI can be repeated if recurrence occurs. Potential complications of PEI include abdominal pain due to leakage of alcohol into the peritoneal cavity and low-grade fever with tumor necrosis. Contraindications include massive ascites, coagulopathy, and obstructive jaundice.

Radiofrequency Ablation

Radiofrequency ablation (RFA) destroys cancer tissues by thermal energy generated with an alternating electric current generator that operates in the radiofrequency range 200–1200 kHz. A needle electrode is percutaneously guided into the center of the tumor. Some electrodes designed to achieve more uniform treatment of a tumor nodule have smaller metal tines that are deployed radially into the tumor once the probe reaches the tumor surface. RFA is not effective for lesions adjacent to large veins in the liver and can also cause thermal injury if applied too close to large bile ducts. Concerns have been raised about an increased risk of needle track seeding due to the relatively large size of the probes used for RFA; these concerns have been mostly alleviated by technical improvements such as the practice of cauterizing the treatment track during probe removal to prevent the dissemination of tumor cells. Studies have demonstrated superiority of RFA over PEI when both are applied to similar sized lesions. Table 15.1 shows a comparison of the pros and cons of PEI and RFA.

Table 15.1 Pros and cons of percutaneous alcohol injection and radiofrequency ablation.

	Ethanol injection	Radiofrequency ablation
Number of sessions	Multiple	Single
Treatment margin	Less distinct	More distinct
Effective near large vessels	Yes	No
Injury to adjacent structures	Lower	Higher
Risk of bleeding	Lower	Higher
Risk of seeding	Lower	Higher
Overall efficacy	High	Higher

Transcatheter Arterial Chemoembolization

TACE uses angiography to selectively embolize the arterial supply of HCC. Access is via the common femoral artery, and doxorubicin or cisplatin, sometimes given in combination with mitomycin C, in a suspension with gelfoam beads is injected into the feeding artery of the tumor. TACE causes selective ischemia and traps the chemotherapy agent(s) within the tumor, allowing high-dose chemotherapeutic effects on the HCC. TACE takes advantage of the vascular pathophysiology of HCCs, which derive 95% of their blood supply from hepatic artery branches, whereas the adjacent benign liver derives 70–80% of its blood supply from the portal vein. Consequently, perfusion and toxicity to the benign liver tissue are minimized.

Most patients receiving TACE should be hospitalized for observation because of the high frequency of tumor lysis syndrome, resulting in fever and abdominal pain. Potential complications of TACE include contrast allergy, contrast nephropathy, bleeding, pseudoaneurysm formation, and hepatic abscess. Advanced Child class C cirrhosis is a relative contraindication for TACE because of the high risk of fatal complications such as liver failure. Portal vein obstruction is also a contraindication because

additional occlusion of the hepatic artery branches with TACE results in complete ischemia of the treated liver segments. Other contraindications include hepatic encephalopathy, biliary obstruction, and the presence of a transjugular intrahepatic portosystemic shunt (TIPS). TACE is often used as a bridging therapy to liver transplantation because it avoids the potential risk of needle track seeding associated with RFA or PEI. The efficacy of TACE for treatment of intermediate stage HCC has been confirmed in randomized controlled trials [21,22].

Transcatheter Arterial Radioembolization

TARE is similar to TACE in that radiolabeled particles are infused into the hepatic artery and flow into the vascular bed of the HCC, with sparing of normal liver tissue. TARE is available in two variants—yttrium-90 (^{90}Y)-impregnated glass microspheres (TheraSphere, MDS Nordion, Ottawa, ON, Canada) and resin–based ^{90}Y microspheres (SirSphere, Sirtex Medical Inc., Wilmington, MA). Most commonly, patients are considered for ^{90}Y therapy only if they are not candidates for surgical resection or percutaneous ablation; however, increasing experience is being obtained in the use of ^{90}Y microsphere therapy for tumor downstaging or prevention of tumor progression before liver transplantation. TheraSpheres are approved by the US Food and Drug Administration (FDA) under a humanitarian device exemption. ^{90}Y is a β-emitting radioisotope with a half-live of 63 h, a mean tissue penetrance of 2.5 mm, and a maximum radius of action of 1 cm (±2.5 mm). The microspheres have a mean diameter of 25 μm (±10 μm). Each milligram contains between 22 000 and 73 000 microspheres and can deliver up to 150 Gy [23,24]. Before radioembolization, staging hepatic angiography is performed to define the vascular anatomy. If there are hepatic arterial branches identified during the staging angiogram that would lead to extrahepatic deposition of the microspheres (most commonly the right gastric or gastroduodenal arteries), these are occluded using standard angiographic techniques. A technetium-99m (^{99m}Tc)-macroaggregated albumin study is then performed to calculate the proportion of infused radiation that would be shunted to the lungs.

The use of ^{90}Y radioembolization is contraindicated in patients whose ^{99m}Tc-labeled hepatic arterial perfusion scintigraphy shows shunting of blood to the gastrointestinal tract that cannot be corrected by angiographic techniques, and patients who show significant shunting of blood to the lungs that could result in a delivery of >16.5 mCi of radiation to the lungs. Radiation pneumonitis has been seen in patients with shunting, which has resulted in doses to the lungs >30 Gy in a single treatment. The arteriovenous shunting occurs within the tumors, and the patients most likely to have high lung shunts are those with large tumor volumes or hepatic venous tumor thrombus. ^{90}Y radioembolization is also contraindicated in patients in whom hepatic artery catheterization shows vascular abnormalities, patients with bleeding diatheses, and patients with allergy to contrast dye. ^{90}Y radioembolization is not recommended for treatment of patients with renal insufficiency, pulmonary insufficiency, and/or severe liver dysfunction. Some authors suggest that patients should have a serum bilirubin ≤2.0 mg/dL and creatinine ≤2.0 mg/dL at the time of ^{90}Y radioembolization. Radioembolization is contraindicated in pregnancy. As a result of the absence of vascular occlusion with ^{90}Y microsphere therapy, patients with portal vein thrombosis remain candidates for this therapy.

Complications of radioembolization include worsening hepatic dysfunction, cholecystitis, gastric or duodenal ulcers, allergic reactions, fatigue, and abdominal pain. TheraSpheres have high specific activity and hence a relatively small mass of beads is infused into the tumor vasculature which does not occlude hepatic arterial flow. The post-embolization syndrome typical of TACE is therefore significantly less common after TARE. In addition, TACE can be applied after TARE, whereas TARE can generally not be used after TACE because of the vascular occlusion produced by TACE. TheraSphere administration has been shown to be effective for downstaging HCCs to resection or RFA, and as a bridge to OLT [24]. Table 15.2 shows a comparison of the pros and cons of TACE and TARE.

Systemic Therapy

As a result of the inherent ability of the liver to detoxify drugs and the need to limit dosing in patients with chronic liver disease and portal hypertension with splenomegaly, because of their propensity to develop cytopenias, HCCs have been difficult to treat effectively with conventional chemotherapy. The results of a phase III study of a multitargeted kinase inhibitor, sorafenib, have revealed a significant survival benefit in patients

Table 15.2 Pros and cons of transarterial chemoembolization and transarterial radioembolization.

	Transarterial chemoembolization	Transarterial radioembolization
Availability	Widely available	Few treatment centers
Strength of evidence	Randomized trials	Case series
Portal vein thrombosis	Contraindicated	Applicable
Tumor lysis syndrome	Frequent	Infrequent
Number of treatments	Multiple	Two treatments per lobe maximum
Sequence	After TARE	Before TACE

with Child–Pugh class A cirrhosis and advanced unresectable HCC. Sorafenib affects tumor cell angiogenesis and proliferation by inhibition of the Raf kinase and vascular endothelial growth factor receptor. The primary endpoint, overall survival, was improved in the sorafenib group when compared with placebo (7.9 versus 10.7 months) [25]. Treatment with sorafenib is relatively well tolerated. In routine clinical practice, the most significant side effects are fatigue, diarrhea, hypertension, and hand–foot skin reaction.

Conclusion

HCCs are highly lethal tumors that usually occur in the setting of chronic liver disease and cirrhosis. The most important risk factor worldwide is chronic hepatitis B virus infection; immunization against this virus is therefore capable of preventing the development of HCC. Most patients are diagnosed with HCC at an advanced stage when they are no longer candidates for potentially curative treatment. This underscores the importance of establishing effective surveillance programs to allow early diagnosis and effective therapy. Early stage HCC is amenable to therapy with surgical resection or OLT. Patients with early stage HCC who are not surgical candidates can be treated with RFA or PEI. Patients with intermediate stage disease are candidates for TACE or TARE.

Take-home points

- Individuals with cirrhosis of any cause or chronic hepatitis B virus infection without cirrhosis (age >20 if African born, age >40 if male and Asian born, and age > 50 if female and Asian born) should be enrolled in a surveillance program for hepatocellular carcinoma (HCC).
- Current surveillance recommendations are for patients to have a liver ultrasonography and α-fetoprotein measurement every 6 months.
- Liver transplantation is the most effective therapy for HCC, but, for the largest number of patients to benefit, individuals at risk of HCC should be in a surveillance program, which enhances their chances for detection of a new HCC at an early stage at which liver transplantation is feasible.
- Individuals who are not candidates for liver transplantation should be considered for surgical resection if they do not have cirrhosis or have cirrhosis without clinically significant portal hypertension. Those who are not surgical candidates should be considered for local ablation with radiofrequency ablation or percutaneous ethanol injection if they have early stage disease. Individuals with intermediate stage disease are candidates for transarterial chemoembolization or radioembolization. Chemoembolization has been rigorously evaluated in randomized controlled studies. Radioembolization has not been compared in a randomized study with chemoembolization, but has the advantage of fewer embolic side effects and can be used for patients with portal vein thrombosis.
- Patients with advanced HCC are candidates for treatment with the multitargeting kinase inhibitor sorafenib. Major side effects of sorafenib include fatigue, diarrhea, hypertension, and hand–foot reaction.

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CHAPTER 16
Pregnancy and Liver Disease

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Summary

Serious liver disease in pregnancy is rare, although 3–5% of pregnancies will be complicated by abnormal liver tests. The differential diagnosis of abnormal liver tests in pregnancy is wide, encompassing the usual range of liver disorders as well as some that are unique to pregnancy. These heterogeneous diseases differ in etiology, symptomatology, laboratory findings, and outcomes. Hyperemesis gravidarum occurs in the first trimester and is characterized by intractable nausea and vomiting, leading to dehydration and electrolyte derangement. Intrahepatic cholestasis of pregnancy causes intense pruritus and can lead to fetal demise, although maternal outcomes are excellent; ursodeoxycholic acid improves pruritus and fetal outcome. The pre-eclampsia-associated liver diseases are pre-eclampsia/eclampsia and the **h**emolysis, **e**levated **l**iver tests, and **l**ow **p**latelet count (HELLP) syndrome; this can be life threatening to mother and fetus if complications occur. Immediate delivery is the only definitive therapy; corticosteroids are usually given to promote fetal lung maturity. Acute fatty liver of pregnancy is a sudden catastrophic illness of microvesicular fat accumulation in the liver that occurs in the third trimester; frank liver failure with coagulopathy and encephalopathy is imminent, prompting the need for rapid diagnosis and delivery.

Case: Presentation and Findings

A 32-year-old G2P1 woman at 24 weeks' gestation presented with 2 weeks of severe pruritus. Her last pregnancy was notable for mild pruritus with abnormal liver chemistries, and an ultrasound done at that time demonstrated freely mobile gall stones without gall-bladder wall thickening or pericholecystic fluid. The pruritus had resolved after delivery. She described current symptoms of pruritus present continuously, but with nocturnal exacerbation preventing sleep. All surfaces were affected, especially the palms of the hands and soles of the feet. She denied fever, nausea, jaundice, or abdominal pain.

Her examination was notable for a gravid uterus and a few excoriations on the arms. AST was 177 IU/L, ALT 355 IU/L, and total bilirubin 2.1 mg/dL; complete blood count (CBC), electrolyte panel, and renal function were normal.

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Definition and Epidemiology

There are two distinct categories of liver disease in pregnancy: liver diseases that are unique to the pregnant state and those that are coincident to pregnancy. Abnormal liver tests occur in only 3–5% of pregnancies. There are many potential causes, but most liver dysfunction in pregnancy is the result of one of the five liver diseases unique to pregnancy [1]. Pregnancy in a patient with underlying chronic liver disease is uncommon but possible, and any liver disease can occur coincidentally in a pregnant woman. Although this chapter focuses on liver diseases unique to pregnancy, other causes of hepatic dysfunction must be excluded, including viral hepatitis, gall stones, and hepatic venous outflow obstruction (Table 16.1).

Familiarity with normal hepatic parameters in pregnancy is imperative for assessment of the pregnant woman with an abnormal liver profile. Aspartate transaminase (AST) and alanine transaminase (ALT) values

Table 16.1 Diagnostic categories and differential diagnosis of liver disease in pregnancy.

Coincidental to pregnancy	Underlying chronic liver disease	Diseases unique to pregnancy
Viral hepatitis	Chronic hepatitis B or C	Hyperemesis gravidarum
Gall stones	Autoimmune hepatitis	Intrahepatic cholestasis of pregnancy
Drugs	Primary sclerosing cholangitis	Pre-eclampsia
Sepsis	Wilson disease	HELLP syndrome
Budd–Chiari syndrome	Primary biliary cholangitis (rare)	Acute fatty liver of pregnancy
	Cirrhosis (uncommon)	

HELLP (hemolysis, elevated liver tests, and low platelet count) syndrome.

are normal during pregnancy but may be elevated during or immediately after delivery as a result of vigorous uterine contractions. Alkaline phosphatase (ALP) is elevated in pregnancy from placental and bone sources; the liver fraction should be normal. Albumin levels steadily drop throughout pregnancy as a result of the increase in plasma volume. Total and direct bilirubin levels should be normal or decreased, again related to increased plasma volume and hemodilution.

The five liver diseases unique to the pregnant state are the focus of this chapter. Hyperemesis gravidarum (HG), occurring in 0.3% of pregnancies, is intractable nausea and vomiting leading to severe dehydration in the first trimester. It may be associated with liver profile abnormalities. Intrahepatic cholestasis of pregnancy (ICP) is characterized by severe pruritus in the setting of elevated bile acid levels. It appears in the second half of pregnancy and resolves after delivery. In the USA, it occurs in 0.3–5.6% of pregnancies, with jaundice occurring in 20% of cases [2]. It has a striking geographic variability with the highest incidence in Chile and Sweden, especially in the winter months.

Pre-eclampsia is the triad of hypertension, edema, and proteinuria in the third trimester. It occurs in 5–10% of pregnancies and is the most common cause of hepatic tenderness and liver profile abnormalities in pregnancy. Severe pre-eclampsia is complicated 2–12% of the time by **h**emolysis, **e**levated **l**iver tests, and **l**ow **p**latelet count (LP), referred to as the HELLP syndrome. Acute fatty liver of pregnancy (AFLP) is the most severe and rarest of the pregnancy-related liver diseases; it is a sudden catastrophic illness in which microvesicular fatty infiltration results in hepatic failure. The incidence of AFLP is 1/7000–1/16 000 pregnancies.

The pregnancy-associated liver diseases are all complications of pregnancy itself, each with a characteristic timing in relation to the trimesters of pregnancy. HG occurs in the first trimester, ICP in the second half of pregnancy, and the other three in the third trimester. They fall into two main categories depending on their association with or without pre-eclampsia. The pre-eclampsia-associated liver diseases are pre-eclampsia itself, the HELLP syndrome, and AFLP. HG and ICP have no relationship to pre-eclampsia.

Pathophysiology

Hyperemesis Gravidarum

The etiology of HG remains enigmatic. Immunologic, hormonal, and psychologic factors associated with pregnancy may play an etiologic role, although the exact interactions are unknown. Risk factors include hyperthyroidism, psychiatric illness, molar pregnancy, pre-existing diabetes, multiple gestations, female fetus, and a history of nausea induced by motion, medications, migraines, or odors [3]. Geographic variation has been noted, with the highest prevalence of HG occurring in women born in India or Sri Lanka and the lowest in women born in western Europe [4].

Intrahepatic Cholestasis of Pregnancy

ICP is a disorder of intense pruritus and elevated serum bile acid levels, which occurs in the second and third trimesters of pregnancy. It is associated with abnormal biliary transport across the canalicular membrane. The etiology is likely heterogeneous with hormonal, genetic, and exogenous factors exerting different influences on the hepatocyte and/or canalicular membrane. The temporal relationship to hormone levels in the third trimester, the increased incidence in twin pregnancies, and the precipitation by exogenous progesterone in the third trimester suggest that ICP is strongly influenced by estrogen

and/or progesterone. ICP may be more common with assisted reproduction, when exogenous hormones are administered. Sex hormones have known cholestatic effects, including inhibition of the bile salt export pump. Impaired sulfation and abnormalities in progesterone metabolism have been found in ICP.

The recognition of familial cases and the high incidence in certain ethnic groups have long suggested a genetic predisposition to ICP. Pedigree analysis of family members of a child with progressive familial intrahepatic cholestasis has identified a mutation in the *MDR3* (*ABCB4*) gene associated with ICP. *MDR3* is the transporter for phospholipids across the canalicular membrane and mutations may result in loss of function with raised bile acids as a secondary effect. At least 10 different *MDR3* mutations have been identified in ICP and *MDR3* mutations may account for 15% cases of ICP [5–7].

Exogenous factors may also play an etiologic role. ICP recurs in only 45–70% of pregnancies and there is a clear seasonal variability, occurring more commonly in the winter months. Recurrence in subsequent pregnancies may be more or less severe than the initial episode. It has striking geographic variation and dietary factors such as selenium deficiency have been implicated in some studies from Chile [8].

Bile acid synthesis appears to be reduced in ICP, probably due to bile secretory failure and retention of bile acid in hepatocytes, resulting in their increase in urine and serum. Maternal fasting bile acid levels in ICP are higher than in a normal pregnancy and exceed 10 μmol/L. Normally, fetal levels of bile acid are higher than maternal levels and must be transported across the placental membrane to the maternal circulation; high maternal levels of bile acid in ICP correlate with fetal morbidity and mortality [9]. Abnormal placental bile acid transport from fetal to maternal circulation, increased maternal bile acid levels, and immaturity of fetal transport systems may all contribute to elevated fetal bile acid levels in ICP.

The HELLP Syndrome

The HELLP syndrome is a microangiopathic hemolytic anemia associated with vascular endothelial injury, fibrin deposition in blood vessels, and platelet activation with platelet consumption. Small to diffuse areas of hemorrhage and necrosis occur in the liver, involving zone 1 or the whole lobule [10]. Large hematomas, capsular tears, and intraperitoneal bleeding can occur, sometimes with catastrophic results. The precipitating injury is not known. The HELLP syndrome may be a complication of pre-eclampsia, because it occurs in 0.1–0.2% of all pregnancies and 10–20% of women with severe pre-eclampsia. However, up to 20% of women with the HELLP syndrome do not have hypertension or proteinuria, and 30% present post partum. HELLP has some overlap with AFLP and fatty acid oxidation (FAO) defects but this is less well established than for AFLP. Studies of families with known FAO deficiencies have shown a high incidence of HELLP syndrome but babies of mothers with HELLP syndrome do not have a proven increased risk of the FAO deficiencies. Women with heterozygosity for factor V Leiden are at increased risk of HELLP syndrome, although other hypercoagulable conditions have not been implicated [11]. Toll-like receptor 4 (TLR-4) gene variants in association with elevated interleukin-6 levels are sevenfold more common in women with pre-eclampsia and HELLP syndrome, suggesting involvement of the maternal immune system in the etiology.

Acute Fatty Liver of Pregnancy

AFLP is a sudden catastrophic illness of microvesicular fat infiltration in the liver. It occurs in about 5/100 000 pregnancies, and may be more common in twin pregnancies and when the mother is underweight [12–14]. Abnormal fatty acid oxidation appears to be the cause in at least some cases of AFLP [15]. Defects in the β-oxidation of fatty acids in hepatic mitochondria are implicated in the pathogenesis of AFLP. Long-chain 3-hydroxyacyl CoA dehydrogenase deficiency (LCHAD), an inherited defect in the mitochondrial β-oxidation of fatty acids, has been found in a majority of women with AFLP. The *G1548C* mutation of LCHAD is most strongly associated. Of 24 babies with defects in FAO, 62% of their mothers had maternal liver disease, either AFLP or HELLP syndrome. Further study showed that, in 83 pregnancies in families with known FAO deficiencies, 24 pregnancies were complicated by maternal liver disease (AFLP in 20 cases), all with the *G1528C* mutation of LCHAD. A separate study showed an 18-fold increase in incidence of maternal liver disease, both HELLP syndrome and AFLP, in the mothers of 50 infants with FAO defects [16].

When babies of mothers with AFLP are screened for FAO defects, approximately 20% have LCHAD deficiency. It is hypothesized that maternal heterozygosity

for LCHAD deficiency reduces the maternal capacity to oxidize long-chain fatty acids in both the liver and the placenta. This, together with the metabolic stress of pregnancy and fetal homozygosity for LCHAD deficiency, causes accumulation in the maternal circulation of hepatotoxic LCHAD metabolites. External factors, such as carnitine deficiency or other dietary factors, may exacerbate this situation. There are reports of maternal liver disease associated with defects of other enzymes involved in FAO but the role of these other enzymes in causing AFLP remains controversial.

Clinical Features

Hyperemesis Gravidarum

HG is intractable, with dehydrating vomiting, typically starting at 4–10 weeks' gestation, and occurring most often in young mothers during their first pregnancy. Symptoms peak around 9 weeks and plateau near the middle of the second trimester. Laboratory tests often display the sequela of protracted vomiting: hypokalemia, contraction alkalosis, and hemoconcentration. Liver test abnormalities are present in half of hospitalized patients; the elevation parallels the severity of vomiting. Transaminases may rise 20-fold elevation and jaundice may occasionally occur. Bilirubin levels rarely exceed 4 mg/dL.

Intrahepatic Cholestasis of Pregnancy

The onset of pruritus around 25–32 weeks' gestation in a patient in whom there are no other signs of liver disease is strongly suggestive of ICP. Occasionally the pruritus occurs earlier than 25 weeks but 80% of cases have pruritus after 30 weeks. The pruritus affects all parts of the body, especially the palms and soles of the feet, is worse at night, and may be of sufficient severity to cause suicidal ideation. Excoriations are usually obvious and occasionally the cholestasis is complicated by diarrhea or steatorrhea. Jaundice occurs in 10–25% of patients and usually follows the pruritus by 2–4 weeks. Jaundice without pruritus is rare and should prompt additional evaluation. Fetal complications in ICP include placental insufficiency, premature labor, and sudden fetal death, probably due to elevated fetal levels of bile acids.

Variable levels of transaminase elevations are seen in ICP, from mild increase to >1000 IU/L; bilirubin is usually <5 mg/dL. ALP is less helpful in pregnancy because of placental contribution, but is usually elevated. Mildly elevated levels of γ-glutamyl transpeptidase (GGT) can be found in <30% cases but GGT can be normal. The most specific and sensitive marker of ICP is serum bile acid levels, which are always elevated at >10 μmol/L in this condition, can be 100 times above normal, and may correlate with fetal risk. Subclinical steatorrhea may be present.

Pre-eclampsia

Pre-eclampsia is the most common cause of hepatic tenderness with abnormal liver tests in the pregnant woman. Patients with severe pre-eclampsia may present with right upper abdominal pain, jaundice, and a tender, normal-size liver. Transaminases are variably elevated from mild to 10–20 times the upper limit of normal; bilirubin is usually <5 mg/dL. Liver involvement always indicates severe pre-eclampsia with the potential for significant perinatal morbidity and mortality.

The HELLP Syndrome

Most patients (71%) present between 27 and 36 weeks' gestation, but occasionally presentation will be earlier in the second trimester. The HELLP syndrome presents in the postpartum period in 20–30% of cases and may occur even in the absence of antepartum pre-eclampsia. HELLP is more common in white, multiparous, and older women but can occur in any parity and age. The most common presentations of the HELLP syndrome include epigastric/right upper quadrant pain (65–90%), nausea and vomiting (35–50%), a "flu-like" illness (90%), or headache (30%). Other common features include edema and weight gain (60%), right upper quadrant tenderness (80%), hypertension (80%), and proteinuria (86%) [13]. Jaundice is uncommon (5%). Rarely the patient may be asymptomatic.

Transaminase elevation is variable from mild to 10- to 20-fold and bilirubin is usually <5 mg/dL. Hemolysis and thrombocytopenia are present by definition; prothrombin time (PT), activated partial thromboplastin time (APTT), and fibrinogen levels are usually normal without increase in fibrin-split products but in severe cases disseminated intravascular coagulation (DIC) is present. Computed tomography (CT) of the liver may show subcapsular hematomas, intraparenchymal hemorrhage or infarction, or hepatic rupture; these abnormalities

correlate with thrombocytopenia of <20 000 but not with liver dysfunction.

The HELLP syndrome is associated with significant maternal morbidity. Complications include hepatic hemorrhage and infarction, DIC, acute renal failure, abruptio placentae, retinal detachment, and pulmonary edema. Fetal mortality ranges from 7% to 20%, usually related to prematurity; fetal complications include prematurity (70%), intrauterine growth restriction, and abruptio placentae.

Acute Fatty Liver of Pregnancy

AFLP occurs almost exclusively in the third trimester from 28 weeks to 40 weeks, rarely in the late second trimester. Unlike HELLP, 40–50% patients with AFLP are nulliparous, with an increased incidence in twin pregnancies. The disease is always present before delivery, but diagnosis may not occur until the postpartum period. The presentation of AFLP can vary from asymptomatic to fulminant liver failure. The typical patient has 1–2 weeks of anorexia, nausea and vomiting, headache, and right upper quadrant pain [17]. Examination may reveal jaundice, hypertension, edema, ascites, a small liver, and hepatic encephalopathy. Intrauterine fetal death can occur. About 50% of patients with AFLP have preeclampsia and there is some overlap with the HELLP syndrome [18].

The AST is usually in the range 300–500 IU/L, but may vary from near normal to 1000 IU/L; bilirubin is usually <5 mg/dL but may be higher in severe or complicated disease. ALP is usually moderately elevated. Other typical abnormalities are normochromic, normocytic anemia, leukocytosis, normal–low platelets, abnormal PT, APTT, and fibrinogen with or without DIC (75%), metabolic acidosis, renal dysfunction (often progressing to oliguric renal failure), hypoglycemia, high ammonia, and biochemical pancreatitis. Extrahepatic manifestations include central diabetes insipidus and infection.

Diagnosis

Case: Diagnosis

Hepatobiliary ultrasonography showed mobile stones in the gall bladder without ductal dilation or signs of cholecystitis. The benign findings on ultrasonography precluded the need for further abdominal imaging. The characteristic clinical picture suggested intrahepatic cholestasis of pregnancy, and treatment was started while awaiting results of additional laboratory testing. Serum bile acid level was 100 µmol/L, confirming the diagnosis.

Hyperemesis Gravidarum

The diagnosis of HG is clinical: severe intractable vomiting necessitating intravenous hydration. A characteristic laboratory profile may support, but does not confirm, the diagnosis. The presence of elevated liver tests in conjunction with intractable vomiting occurs only with HG, as uncomplicated vomiting in pregnancy does not cause liver dysfunction. Other causes of transaminitis, such as viral hepatitis, must be excluded. Liver biopsy is needed only to exclude more serious disease; the hepatic histologic appearance is generally normal or shows bland cholestasis.

Intrahepatic Cholestasis of Pregnancy

Intense pruritus in conjunction with elevated serum bile acids characterizes ICP. The presence of classic clinical features in the absence of other liver diseases is strongly suggestive of ICP, especially if pruritus was present in previous pregnancies and disappeared after delivery. Diagnosis in the first pregnancy is usually presumptive and made on clinical grounds alone as serum bile acid levels are difficult to obtain. Rapid postpartum resolution may confirm the diagnosis in the absence of laboratory support.

The distinguishing laboratory abnormality in ICP is an elevation in serum total bile acid level but this test may not be readily available. Total bilirubin may be elevated, usually remaining <6 mg/dL. ALP and serum transaminases can be high, although placental origin of ALP must be considered. Hepatic synthetic function remains normal. If jaundice is present, an ultrasound scan should be obtained to exclude obstruction; the bile ducts are of normal caliber in ICP. Liver biopsy is needed only to exclude more serious liver disease; in ICP the liver has near-normal appearance with mild cholestasis and minimal or no hepatocellular necrosis. The differential diagnosis of cholestasis in pregnancy is wide and includes viral hepatitis and gall stones; however, pregnancy is a cholestatic and pruritogenic state and may therefore unmask underlying chronic liver disease such as primary sclerosing cholangitis or hepatitis C.

Table 16.2 Diagnostic criteria for the HELLP (hemolysis, elevated liver tests, and low platelet count) syndrome.

H Hemolysis	EL Elevated liver tests	LP Low platelets
Abnormal blood smear	AST >70 IU/L	<50 000 (class 1)
LDH >600 IU/L		50–99 000 (class 2)
↑ indirect bilirubin		100–149 000 (class 3)

AST, aspartate transaminase; LDH, lactate dehydrogenase.

The HELLP Syndrome

The diagnosis of HELLP syndrome (Table 16.2) must be quickly established because the maternal and fetal complications are severe. The most stringent diagnosis requires the presence of all three criteria. The most widely accepted criteria for the syndrome are:

- hemolysis with an abnormal blood smear, elevated lactate dehydrogenase (LDH >600 IU/L), and increase in indirect bilirubin
- AST >70 IU/L
- platelet count <100 000.

Patients with the HELLP syndrome may be further stratified according to platelet count with severe disease indicated by a platelet count <50 000, moderate when the platelet count is 50 000–99 000, and mild disease when the platelet count is 100 000–150 000.

Unfortunately the diagnostic criteria used are variable and inconsistent. Occasionally the HELLP syndrome must be distinguished from other conditions, especially AFLP with which it has significant overlap in some cases, or from the rare conditions of thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, or antiphospholipid syndrome. Cross-sectional imaging of the abdomen is used to exclude the complications of hepatic infarction, hematoma, or rupture in women with abdominal pain or hypotension, but is not required to make a diagnosis of HELLP.

Acute Fatty Liver of Pregnancy

The diagnosis of AFLP is usually presumptive, based on compatible clinical and laboratory features. The definitive diagnosis is histologic, but biopsy is not always feasible given the need for expeditious therapy and the presence of coagulopathy. Histology shows microvesicular fatty infiltration occurring predominantly in zone 3, with lobular disarray, mild portal inflammation, and cholestasis. A peripheral ring of fat droplets surrounding central nuclei gives the cytoplasm a foamy appearance. Occasionally the histologic picture cannot be differentiated from viral hepatitis or pre-eclampsia. The differential diagnosis of acute liver failure in the third trimester includes AFLP, HELLP, and fulminant viral hepatitis. In comparison to those with HELLP syndrome, patients with AFLP are more likely to have overt liver failure with coagulopathy, hypoglycemia, encephalopathy, DIC, and renal failure (Table 16.3).

Table 16.3 Diagnostic differences between acute fatty liver of pregnancy (AFLP) and the HELLP (hemolysis, elevated liver tests, and low platelet count) syndrome.

	AFLP	HELLP
Parity	Nulliparous, twins	Multiparous, older
Jaundice	Common	Uncommon
Mean bilirubin (mg/dL)	8	2
Encephalopathy	Present	Absent
Platelets	Low–normal	Low
PT	Prolonged	Normal
APTT	Prolonged	Normal
Fibrinogen	Low	Normal–increased
Glucose	Low	Normal
Creatinine	High	High
Ammonia	High	Normal
CT scan	Fatty infiltration	Hemorrhage

APTT, activated partial thromboplastin time; PT, prothrombin time.

Therapeutics

Case: Therapeutics

The patient was started on ursodeoxycholic acid 900 mg/day. Although the pruritus did not completely resolve, improvement was soon noted. Careful monitoring did not reveal signs of fetal distress and the pregnancy was allowed to continue to 37 weeks, when a healthy baby was delivered. Pruritus resolved immediately after delivery and follow-up lab results revealed a normal hepatic function panel.

Hyperemesis Gravidarum

Hospitalization is necessary for hydration and parenteral nutrition; otherwise therapy is symptomatic with antiemetics. Pharmacologic interventions may mitigate symptoms but overall results have been disappointing. Pyridoxine improves nausea but not vomiting. Antihistamines (H_1-receptor antagonists) are effective, with an acceptable safety profile [19]. Metoclopramide, promethazine, droperidol with diphenhydramine, and prochlorperazine benefit some patients. Corticosteroids are used occasionally although the mechanism of action is not understood and controlled trials yield conflicting results. Corticosteroid use in the first trimester may increase the risk of cleft palate and later in pregnancy may be associated with premature rupture of membranes. When possible, avoidance of environmental triggers such as strong odors, flickering lights, and sudden or jerking movement is suggested. Powdered ginger is superior to placebo in controlling nausea, but the lack of standard preparations of pharmacologic quality limit this intervention [20].

Intrahepatic Cholestasis of Pregnancy

Management of ICP is twofold: symptomatic therapy for the mother and close monitoring and early delivery for the fetus. Pruritus and liver dysfunction resolve immediately after delivery with no maternal mortality, although some patients are severely distressed, even suicidal, with the pruritus. Withdrawal of exogenous progesterone may cause remission of pruritus before delivery. Women with significant cholestasis may develop deficiency of the fat-soluble vitamins, requiring replacement. Mild steatorrhea can also occur.

Ursodeoxycholic acid, generally in doses of 10–15 mg/kg, is the treatment of choice for ICP. In several, small, randomized trials, ursodeoxycholic acid produced relief of pruritus with improvement in liver tests and no adverse maternal or fetal effects; fetal outcome was improved with less prematurity. High-dose ursodeoxycholic acid (1.5–2.0 g/day) reduces abnormal maternal and fetal bile acid levels and is completely safe for the fetus. Ursodeoxycholic acid is more effective in reducing pruritus, transaminases, and bile acid levels than cholestyramine, with fewer preterm deliveries and side effects [21]. Dexamethasone (12 mg/day for 7 days) has the advantage of promoting fetal lung maturity but was less effective than ursodeoxycholic acid in reducing pruritus and transaminase levels [22]. *S*-Adenosyl-L-methionine (SAMe) is less effective than ursodeoxycholic acid but may have an additive effect [23].

The main risk in ICP is to the fetus, necessitating referral to a high-risk obstetrician. Fetal complications include placental insufficiency, prematurity, meconium-stained amniotic fluid, and intrauterine demise. Most fetal deaths occur in the last month of pregnancy. Monitoring for chronic placental insufficiency is essential but will not prevent all fetal deaths from acute anoxia which can be prevented only by delivery as soon the fetal lungs are mature; 60% of babies are delivered before term. Fetal distress occurs in 20–40% with occasional perinatal death; an early onset in the second trimester and severe biochemical abnormalities are risk factors. A recent Swedish population study of >45 000 pregnancies with 693 cases of ICP (1.3%) showed that fetal complications correlate with maternal bile acid levels and with premature delivery, asphyxial events, and meconium staining occurring only in the 19% of cases with maternal bile levels >40 μmol/L [9]. Early delivery is recommended based on the patient's symptoms, degree of cholestasis, and fetal lung maturity.

Pre-eclampsia

No specific therapy is needed for the hepatic involvement of pre-eclampsia and its only significance is as an indicator of severe disease, with the need for immediate delivery to avoid eclampsia, hepatic rupture, or necrosis.

The HELLP Syndrome

Although recognized for over 50 years, management of the HELLP syndrome remains difficult. The first priority is hospitalization with antepartum stabilization of the mother, including treatment of hypertension, DIC, and initiation of seizure prophylaxis with magnesium sulfate. Transfer to a tertiary referral center with high-risk obstetric care should be performed if possible.

Delivery is the only definitive therapy and, for patients with true HELLP syndrome, there is progressive and often sudden deterioration in maternal condition. Immediate delivery is indicated if the patient is beyond 34 weeks and there are signs of fetal distress, or if the mother has multiorgan dysfunction, DIC, renal failure, or abruptio placentae. Many deliveries will ultimately occur via cesarean section, although well-established labor should be allowed to proceed in the absence of obstetric compli-

cations or DIC. Half the patients will require blood or blood products to correct hypovolemia, anemia, or coagulopathy. DIC is a contraindication for epidural anesthesia. Prophylactic antibiotics are recommended.

The optimal management when the patient is remote from term is unknown. Corticosteroids are commonly used, although their benefit is controversial [24, 25]. Early small trials suggested improved outcomes, but two recent, large, randomized controlled trials did not support this except for women with severe HELLP syndrome [24, 26]. The main benefit of corticosteroid therapy is to improve fetal lung maturity but it also improves the maternal platelet count. Despite weak evidence, some experts advocate giving dexamethasone to all patients [26], and recent work suggests that steroids reduce the inflammatory component of HELLP syndrome [27]. The diagnosis of HELLP syndrome is a harbinger that the fetal and maternal risks of continuing pregnancy outweigh the benefits, and most cases of conservative therapy will result in rapid deterioration with a high risk of fetal loss.

Most patients have rapid, early resolution of HELLP syndrome after delivery with normalization of platelets by 5 days. However, some women have persistent thrombocytopenia, hemolysis, and progressive elevation of bilirubin and creatinine. Persistent laboratory abnormalities for >72 h with no improvement is usually taken as an indication for specific therapy. Many different treatment modalities have been used—plasmapheresis, plasma volume expansion, antithrombotic agents, steroids, plasma exchange with fresh frozen plasma, dialysis—without supporting data from clinical trials. Heparin therapy increases bleeding complications and is not recommended. In about 25% of patients, HELLP syndrome will develop in the postpartum period and therapy is the same as ante partum.

Serious maternal complications are common, including DIC (15–20%), abruptio placentae (9–16%), eclampsia (9%), pulmonary edema (8%), severe ascites (8%), acute renal failure (3–8%), subcapsular hematoma (1.5%), hepatic failure (1–2%), acute respiratory distress syndrome (1%), or wound hematomas. Presence of abruption exacerbates many of the other complications. Maternal mortality rates range from 1% to 25% and are worse than for patients who have severe pre-eclampsia without HELLP. Indications to proceed with liver transplantation are very limited—hepatic rupture, persistent bleeding from a hematoma, or liver failure from extensive necrosis. Once delivered, most babies do well but overall there is a reported 11% prenatal mortality rate due to prematurity, dysmaturity from placental insufficiency, or the consequences of severe maternal complications.

Hepatic hemorrhage without rupture is generally managed conservatively but patients need close hemodynamic monitoring in an intensive care unit. Immediate availability of resuscitation and diagnostic aids is essential, including availability of large-volume transfusion of blood and blood products, diagnostic cross-sectional imaging, and immediate intervention for rupture or rapid expansion of a hematoma. Potential routes of exogenous trauma must be avoided such as abdominal palpation, seizure activity, emesis, and unnecessary transportation.

Liver rupture is a rare, life-threatening complication of HELLP, usually preceded by an intraparenchymal hemorrhage progressing to a contained subcapsular hematoma in the right lobe in patients with severe thrombocytopenia. Survival depends on rapid, aggressive, supportive care and immediate laparotomy. The best surgical management is controversial; most successful is evacuation of the hematoma with pressure packing and drainage, followed by consideration of hepatic artery embolization or ligation, partial hepatectomy, or oversewing of the laceration. In the rare hemodynamically stable patient with contained hepatic rupture, or a rapidly enlarging hematoma, angiographic embolization may be considered. Maternal mortality rate from hepatic rupture remains very high at 50% and perinatal mortality rates are 10–60%, mostly from placental rupture, intrauterine asphyxia, or prematurity. Of the selected women who undergo liver transplantation for HELLP syndrome, the 1-year survival rate is about 80% [28].

Acute Fatty Liver of Pregnancy

Early recognition and clinical diagnosis of AFLP are essential for both maternal and fetal survival. Delivery of the fetus is the definitive therapy, and there are no reports of recovery before delivery. Immediate hospital admission allows maternal stabilization, fetal monitoring, and confirmation of diagnosis. Supportive care, usually in an intensive care setting, allows for hydration, glucose infusion, and transfusion of blood products. Delivery usually occurs by cesarean section but the necessity for this has

not been tested in randomized trials. The type of delivery should be based on obstetric assessment of the likelihood of a vaginal delivery in <24 h. Rapid controlled vaginal delivery with fetal monitoring is probably safer if the cervix is favorable, the fetus is stable and in a good position, and delivery occurs later in gestation. Vaginal delivery may reduce complications of intra-abdominal bleeding and infection. Maintaining an international normalized ratio (INR) <1.5 and platelet count >50 000 during and after delivery is recommended, as is the use of prophylactic antibiotics. With correction of the coagulopathy, epidural anesthesia is probably the best choice because it will allow better ongoing assessment of maternal level of consciousness.

Improvement in transaminases and encephalopathy should occur within 48–72 h of delivery, but intensive supportive care is needed to manage the many complications of liver failure until recovery is well established. Patients who are critically ill at the time of presentation, develop complications (encephalopathy, hypoglycemia, coagulopathy), or continue to deteriorate despite emergency delivery, should be transferred to a liver transplant center.

Most patients improve in 1–4 weeks post partum. Plasmapheresis has been used in some patients although its benefit is unproven. Corticosteroids are ineffective and may exacerbate infection. Although liver function will start to improve within 3 days of delivery in most patients, the disease then enters a cholestatic phase with rising bilirubin and ALP. Full recovery without residual chronic liver disease is the rule, although the time frame varies from days to months. With advances in supportive management, the maternal mortality rate in AFLP is now 10–18% and fetal mortality rate 9–23%. Infectious and bleeding complications remain the most life threatening. Liver transplantation has a very limited role because of the great potential for recovery with delivery, but should be considered in patients whose clinical course continues to deteriorate with advancing fulminant hepatic failure and no signs of hepatic regeneration.

Prognosis

Hyperemesis Gravidarum

The recurrence rate of HG in subsequent pregnancies is 15–20%. Maternal and infant outcomes in HG are usually excellent, but poor maternal weight gain is associated with adverse infant outcome. HG resolves on delivery of the infant, but the disease exerts a significant psychosocial toll [29]. Depression, anxiety, job loss, and fear of future pregnancy are common.

Intrahepatic Cholestasis of Pregnancy

ICP resolves with fetal delivery, but may recur in 45–70% of subsequent pregnancies. Some women with ICP also develop pruritus with oral contraceptives. Rare familial cases of apparent ICP have persisted post partum, with progression to subsequent fibrosis and cirrhosis, but these cases may represent chronic cholestatic liver disease from the onset. A large Finnish population study with >10 000 patients showed that patients who have had ICP subsequently develop more gall stones and cholecystitis, more non-alcoholic pancreatitis, more hepatitis C, and non-alcoholic cirrhosis [30]. Therefore, in some patients, ICP may be an indicator of more serious subsequent liver disease. Exposure to exogenous estrogens, usually oral contraceptives, usually does not cause cholestasis, but patients should be counseled about this possibility.

Fetal outcome is poorer than maternal outcome in ICP. Premature delivery occurs in 40–100% of cases and fetal demise ranges from 1% to 5%. Fetal demise usually occurs in the last month of pregnancy and its cause is unknown, although fetal risk appears to correlate with maternal serum bile acid levels [9]. Early delivery appears to improve fetal outcome.

The HELLP Syndrome

The chance of the HELLP syndrome recurring in a subsequent pregnancy is low (2–6%), but subsequent pregnancies carry a high risk of related complications from pre-eclampsia, prematurity, intrauterine growth retardation, and abruptio placentae to perinatal mortality.

Acute Fatty Liver of Pregnancy

Many women do not become pregnant again after AFLP, either by choice as a result of the devastating effects of the illness or by necessity due to hysterectomy to control postpartum bleeding. All babies of mothers with AFLP are tested for defects of FAO because presymptomatic diagnosis and appropriate early management will reduce morbidity and mortality in these children For mothers with previous AFLP, liver tests, glucose, carnitine, and plasma acylcarnitine profile may help identify the

obligate carrier to allow closer fetal and maternal monitoring. Future options may involve genetic testing for the carrier state. For mothers without identifiable abnormalities of FAO, AFLP does not tend to recur in subsequent pregnancies although rare cases have been reported.

Special Circumstances

Cirrhosis and Portal Hypertension

Once liver disease has progressed to cirrhosis, most women are anovulatory and infertile from dysfunction of the hypothalamic–pituitary axis. When pregnancy does occur in a woman with cirrhosis, the predominant concern relates to maternal portal hypertension. At least 25% of women with portal hypertension will have a variceal bleed during pregnancy, and this number rises to 70% if varices are known to be present before pregnancy. Variceal bleeding is most likely to occur in the third trimester, when the maternal blood volume is greatest and the uterine size increases the intra-abdominal pressure. Maternal mortality from variceal bleeding is significant, ranging from 20% to 50%. Active bleeding is managed as in the non-pregnant patient, with octreotide and endoscopic band ligation or sclerotherapy.

Women of childbearing potential with cirrhosis and/or portal hypertension should be counseled about the risk of variceal bleeding. Ideally, staging of portal hypertension is performed before pregnancy, allowing the woman to weigh her risks. If significant varices are found, obliterative therapy before pregnancy is ideal. Other options include shunting (surgical or intrahepatic) or liver transplantation in appropriate individuals. In women with known portal hypertension, endoscopy should be performed early in the second trimester. Primary prophylaxis with β-blockers should be offered if large varices are found. Endoscopic band ligation may be undertaken, but the need for repeated procedures in a pregnant patient is suboptimal.

Liver Transplant Recipient

The restoration of fertility is a benefit of liver transplantation and transplant recipients should be encouraged to consider pregnancy if desired. The National Transplant Pregnancy Registry, a voluntary registry of pregnancy in US transplant recipients, has data on 219 pregnancies in 130 liver transplant recipients. Similar registries exist in Europe and the UK.

Although transplant recipients have good pregnancy outcomes, their pregnancies are considered high risk and referral to a high-risk obstetric program is essential. In liver transplant recipients, the mean gestational age of infants is 37 weeks, with a mean birthweight of 2700 g. Approximately 20% of pregnancies are complicated by pre-eclampsia, which is likely a result of baseline calcineurin-inhibitor-induced hypertension. Approximately a third of women have hypertension during pregnancy and gestational diabetes occurs in over 10%.

Graft function and immunosuppressive drug levels should be monitored closely during pregnancy, at least once a month through week 32, every 2 weeks through week 36, and weekly thereafter. Graft function is not impaired in pregnancy and rejection is rare if normal immunosuppression is maintained.

It is recommended that women wait at least a year after transplantation before attempting to become pregnant. After the first year, most transplant recipients have fully recovered from surgery, are on maintenance immunosuppression, and have completed prophylaxis for opportunistic infections. Corticosteroids, tacrolimus, and cyclosporine have been used successfully in transplant recipients without documented risk to the fetus; mycophenolate is a pregnancy category D drug and should be stopped before conception if possible. There are few known sirolimus exposures in pregnancy but so far no adverse events have been reported. All immunosuppressive medications are detectable in breast milk, but to date there are no adverse events attributable to breastfeeding after transplantation. The long-term outcomes of children born to transplant recipients do not appear to differ from those for the general population.

Take-home points

- Liver diseases coincident to pregnancy must be excluded in the evaluation of the pregnant woman with jaundice or an abnormal liver profile.
- The liver diseases unique to pregnancy are hyperemesis gravidarum, intrahepatic cholestasis of pregnancy, pre-eclampsia/eclampsia, HELLP syndrome, and acute fatty liver of pregnancy.
- Liver diseases in pregnancy may be divided into pre-eclampsia related (pre-eclampsia, HELLP syndrome, AFLP) and those unrelated to pre-eclampsia (HG and ICP).

- Liver abnormalities exist in 50% of patients hospitalized for hyperemesis gravidarum; care is supportive and maternal and fetal outcomes are good.
- ICP is a condition of severe pruritus and elevated serum bile acids. Fetal risk in ICP is mitigated by use of ursodeoxycholic acid and early delivery.
- Maternal outcome in the HELLP syndrome is usually good unless complications occur, but fetal outcome can be poor. Delivery should be expedited.
- Corticosteroid use in the HELLP syndrome may improve fetal and maternal outcomes.
- AFLP can result in overt hepatic failure, with coagulopathy and encephalopathy. Delivery is the definitive therapy and should not be delayed.
- Pregnancy in a woman with cirrhosis is rare; when it occurs, the most common complication is variceal bleeding.
- Liver transplant recipients of childbearing age may become pregnant without undue risk to the fetus or graft.

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17

CHAPTER 17

Biliary Atresia and Cystic Fibrosis: Transitioning Care from Pediatrics to Internal Medicine

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Summary

Advances in the management of infants and children with liver disease are leading to an increasing number of patients surviving into adulthood. Significant improvements have been made in the medical management of the complex, multisystem presentation of cystic fibrosis and in the non-transplant surgical options in biliary atresia. These patients are moving out of pediatric centers. This chapter is designed to give the non-pediatrician an overview of these diseases and their clinical course, and to highlight the issues in caring for adults with biliary atresia and cystic fibrosis liver disease.

Biliary Atresia

Case

A 20-year-old woman with a history of biliary atresia status after a hepatoportoenterostomy at 2 months of age is transitioned to an adult facility for continued management of her liver disease. She is receiving ursodeoxycholic acid. She reports having two episodes of cholangitis, both within the last 5 years. Her chief complaint at this visit is fatigue. Her examination revealed no cyanosis, normal cardiac examination, splenomegaly, spider nevi, and digital clubbing. She was afebrile. Blood testing revealed a platelet count of $53 \times 10^3/mm^3$ and white blood cell count (WBC) count of $2.6 \times 10^3/mm^3$. Her γ-glutamyltransferase (GGT) was elevated at 225 IU/L, alanine transaminase (ALT) 95 IU/L, total bilirubin 2.3 mg/dL with a direct fraction of 1.2 mg/dL, albumin 3.2 g/dL, and prothrombin time 15.2 s. An abdominal ultrasound scan revealed a nodular liver and splenomegaly. Her pulse oximetry reading was 94% in an upright position in room air.

She would like to understand her current clinical status and wonders about her prognosis over the ensuing years.

Pathophysiology/Definition

Biliary atresia is an inflammatory process that results in obliteration and fibrosis of the extrahepatic biliary tract and presents in the first few weeks of infancy with jaundice. Progression of disease, with involvement of the intrahepatic bile ducts, rapidly and predictably leads to cirrhosis and complications of end-stage liver disease before 2 years of age.

Early management of biliary atresia includes surgical construction of a hepatoportoenterostomy (HPE, also known as the Kasai procedure). This procedure entails resection of the fibrotic biliary remnant and construction of a Roux-en-Y loop of intestine that is anastomosed to the resected hilar portion of the liver. Ideally, HPE should

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be performed before 60 days of age. Restitution of bile flow is the major goal of this procedure, and occurs in approximately 50% of children.

HPE is considered by most to be a treatment, not a cure, for biliary atresia. It is well established that HPE extends transplant-free survival. Despite successful HPE and restoration of bile flow, 70–80% of children require liver transplantation before adulthood and biliary atresia continues to be the most common indication for liver transplantation in children. However, with improvement in surgical technique and postoperative care, a percentage of patients are now reaching adulthood before transplantation.

Epidemiology

Although use of HPE as treatment for biliary atresia was first introduced in 1959, the widespread use of this procedure as first-line surgical management did not occur until the 1970s. As such, large studies of patients surviving into adulthood are limited. Survival with the native liver in the first decade of life is reported in the USA and Europe to be between 28% and 43% [1–3]. The Japanese Biliary Atresia Registry reports a 10-year transplant-free survival rate of 53% [4].

The calculated survival rate (with failure defined as death or transplantation) at 20 years was 21% in the USA; however, long-term outcome and complications were not described in this series [1]. The two largest clinical reports of long-term survivors with biliary atresia with a native liver come from Sendai, Japan, and Paris, France. They similarly report survival for more than 20 years in 131 of 594 (22%) patients [5,6]. Long-term survival was significantly greater in individuals where the biliary atresia affected only the common bile duct (type I or so-called correctable biliary atresia) [6]. Given a prevalence of 1:15 000 for biliary atresia, it is estimated that there may be as many as 4000 adults with biliary atresia in the USA.

Clinical Characteristics of Adults with Biliary Atresia

Up to two-thirds of patients have evidence of chronic biliary disease with transient or persistent cholestasis and variable elevations in GGT [5,7,8]; 80% of patients are reported to have organomegaly on physical examination [5]. A subset of patients who survive into adulthood with their native liver has no biochemical evidence of ongoing liver disease. However, biopsies in patients without evidence of portal hypertension, hypersplenism, and/or who have normal biochemical parameters may still show evidence of fibrosis and cirrhosis. The long-term implications of these histologic changes have not been examined as most reported biopsy results were obtained within 8 years of HPE [9].

In the two largest reported series of adult patients, clinical events related to portal hypertension occurred before the age of 20 and not during adulthood. As such, interventions such as ligation or sclerosis of esophageal varices, therapy with non-selective β blockers, partial splenic embolization, splenectomy, and shunt surgery were performed before 20 years of age in the vast majority of patients [5,6]. Standard approaches to the management of portal hypertension are presumed to be reasonable for these patients because they have become adults.

Intrapulmonic shunting has been observed in adult patients with biliary atresia and portal hypertension [5,10]. Hepatopulmonary syndrome (HPS) should be included in the differential diagnosis in patients presenting with dyspnea or physical exam findings such as digital clubbing, spider nevi, or cyanosis. Patients undergoing evaluation for liver transplantation should also be screened. Upright transcutaneous oxygen saturation measurement is a relatively simple screening method. Values <97% should prompt further investigation. The diagnostic criteria for HPS require confirmation of hypoxemia with arterial blood gas levels ($Pa_{O_2} < 80$ mmHg or 10.6 kPa and/or $P_{A–a_{O_2}} \geq 15$ mmHg or 2 kPa) and evidence of shunting with contrast-enhanced echocardiography [11]. Portopulmonary hypertension (PPHTN) has also been described in case reports of patients with biliary atresia and portal hypertension [12,13]. Patients with new-onset dyspnea, syncope, and murmur, and those undergoing evaluation for liver transplantation, should be screened for PPHTN with echocardiography. Confirmation of the diagnosis is made with cardiac catheterization. Diagnosis of and differentiation between HPS and PPHTN, along with appropriate grading of severity of pulmonary disease, are critical in order to determine if medical management or transplantation is a treatment option [11,14].

One of the most common postoperative complications after HPE is cholangitis, with recurrent episodes likely leading to the need for transplantation among affected

children. Multiple theories as to the pathogenesis of cholangitis after HPE have been presented including direct infection via colonization in the Roux limb, bacterial translocation via the lymphatics, and hematogenous infection via the portal vein [15]. Widely accepted diagnostic criteria for cholangitis include fever, rise in conjugated bilirubin, and abdominal pain. Peripheral leukocytosis, elevated transaminase levels, alkaline phosphatase, and C-reactive protein, and positive blood culture provide further supportive evidence for the diagnosis, although blood cultures are often negative in patients who are clinically felt to have cholangitis. Liver biopsy and/or culture is currently not routinely used to make the diagnosis. Cholangitis episodes clearly occur during adulthood as well: 35 of 131 (27%) long-term survivors had at least one episode after the age of 20 [5,16]. Antibiotic treatment of cholangitis should be chosen for broad-spectrum coverage of enteric organisms. Diagnostic imaging (CT, MRI, hepatobiliary scintigraphy) used to determine underlying risk factors for infection in one series reports the presence of fibrosis, dilated intrahepatic ducts, and intrahepatic stones in 70% of patients who developed cholangitis. Surgical intervention for mechanical obstruction of the Roux loop has been described with mixed short-term results [15,16].

Overall, intrahepatic bile duct abnormalities (dilation, cyst formation) and lithiasis develop in about 10–15% of patients and present with jaundice, cholangitis, or as an incidental finding. Yearly screening with ultrasonography or CT has been proposed for long-term survivors after HPE, especially for detection and treatment of intrahepatic stones [7]. Antibiotic prophylaxis may be considered in adults who have undergone HPE and have recurrent cholangitis with ductal abnormalities.

Interestingly there are no reports of cholangiocarcinoma in these adult patients. Hepatocellular carcinoma (HCC) has been reported in younger patients with biliary atresia, but not in the reported cohort of long-term survivors. In spite of this, routine monitoring for HCC would be appropriate, although one needs to be aware of the entity of hepatic pseudotumor, which can mimic HCC [19].

Most long-term survivors are able to attend school or hold gainful employment. Validated quality-of-life measurements performed in 55 long-term survivors in Japan and the UK showed very small differences compared with the normative data [20]. Other reported symptoms impacting quality of life include easy fatigability, pruritus, and abdominal pain [10].

Thirty pregnancies have been reported in 22 patients with biliary atresia who have survived with their native liver [17]. Patients with a history of late cholangitis or portal hypertension were more likely to have worsening liver disease during pregnancy or in the postpartum period. Although portal hypertension and cirrhosis are not contraindications to pregnancy, the increased risk of variceal hemorrhage during pregnancy, malnutrition, postpartum hemorrhage secondary to thrombocytopenia, or synthetic dysfunction, and the need to discontinue or replace potentially teratogenic medications, require careful management by the gastroenterologist and obstetrician with experience in high-risk pregnancies [18].

Transplantation

Evolution to end-stage liver disease continues to occur with advancing age and 12 of 131 patients underwent liver transplantation after the age of 20 [5,6]. Complications of portal hypertension alone are not necessarily an indication for transplantation—more typically advancing cholestasis with features of decompensated end-stage liver disease leads to consideration for transplantation. In pediatric series, the 10-year survival rate in patients with biliary atresia undergoing liver transplantation after HPE is 80–90%. The largest adult series demonstrated in patients undergoing living-related donor transplant reveals a 5-year survival rate of 90% [21].

Cystic Fibrosis

Summary

An 18-year-old man with cystic fibrosis is referred to your office as part of his transition from a pediatric- to an internal medicine-based practice. His pulmonary disease is moderate (FEV_1 65% predicted). He has pancreatic exocrine insufficiency and diabetes mellitus. His medications include pancreatic enzyme supplementation, dornase, albuterol, and insulin. His physical examination revealed barrel chest deformity, normal cardiac exam, his liver is not palpable, his spleen can be felt 3 cm below the costal margin, there is no ascites or peripheral edema, although there is digital clubbing. He was referred after his pulmonologist noted an ALT of 55 IU/dL with a normal bilirubin and GGT on routine testing.

The pulmonologist and the patient have several specific questions:

1. What are the implications of the abnormal ALT and the enlarged spleen, relative to prognosis, further follow-up, and/or surveillance investigations?
2. Would you recommend any pharmacologic therapy?
3. What is the likelihood for the need for liver transplantation?

Pathophysiology/Definition

Cystic fibrosis (CF) is an autosomal recessive disorder characterized by abnormal transport of electrolytes by the cystic fibrosis transmembrane conductance regulator (CFTR). The ubiquitous nature of the transporter leads to multisystem involvement, including chronic lung disease, pancreatic insufficiency, and hepatobiliary manifestations. CFTR is located on the apical membrane of cholangiocytes. Abnormal CFTR is hypothesized to impair bile flow leading to obstruction and subsequent injury.

Epidemiology

The pathognomonic hepatobiliary manifestation of CF, referred to as cystic fibrosis liver disease (CFLD), is focal biliary cirrhosis. Ten percent of patients with focal biliary cirrhosis will progress to multilobular cirrhosis [22]. Improvements in medical management and survival in the last 30 years have led to a dramatic increase in the number of adult patients with cystic fibrosis. Adults with CF represent more than 40% of patients in the Cystic Fibrosis Foundation Patient Registry [23,24]. Prolonged survival, as well as increased awareness of hepatobiliary involvement, has led to greater recognition of CFLD. However, the clinically silent course of CFLD requires active screening for disease. The hepatobiliary manifestations of CF are:

- Micro-gall bladder
- Cholelithiasis
- Bile duct stricture
- Hepatolithiasis
- Focal biliary cirrhosis
- Multilobular cirrhosis
- Steatosis
- Congestive hepatopathy
- Cholangiocarcinoma.

Figure 17.1 evaluates hepatobiliary disease in CF.

CFLD most commonly presents in the first decade of life, in boys, in patients with a history of meconium ileus in infancy, and in those with a pancreatic insufficiency phenotype [25,26]. Most adults with CFLD have a benign course with slowly progressive disease [27,28]. It is not clear that improved survival into adulthood translates into an increased incidence of CFLD. However, complications of end-stage liver disease and portal hypertension will impact clinical course.

Diagnosis

Current consensus recommendations suggest examination of liver and spleen size at every clinic visit and yearly biochemical screening with a hepatic panel, GGT, and bilirubin. Abnormal values (>1.5 times the upper limit of normal) should prompt repeat laboratory testing in 3–6 months. Persistent elevation for >6 months or high elevation (more than five times the upper limit of normal) should prompt further evaluation [24]. Significant liver disease can be seen in patients with relatively normal liver biochemistries, highlighting the importance of a careful physical examination in patients with CF.

Ultrasonography of the liver and gall bladder is the imaging modality of highest yield in diagnosis of the hepatobiliary manifestations of CF. Commonly seen findings on ultrasonography include parenchymal heterogeneity, nodularity, and evidence of portal hypertension, sometimes preceding biochemical abnormality [29]. Liver biopsy is not routinely recommended for a diagnosis of CFLD because of the patchy distribution of disease.

Differential Diagnosis

Biochemical evidence of hepatitis and/or hepatomegaly in CF patients may also reflect steatosis associated with malnutrition [30], hyperexpansion of lung volumes, or cor pulmonale with hepatic congestion. Cholestasis is a worrisome and late finding in CFLD. Cholestasis may alternately represent cholelithiasis [31] and, rarely, bile duct stricture [32], hepatolithiasis, and cholangiocarcinoma [33]. Patients with CFLD are not considered high risk for HCC. Screening in this population is not currently recommended [34]. Evaluation should include a review of medication and toxin effect as well as screening for common viral hepatitides.

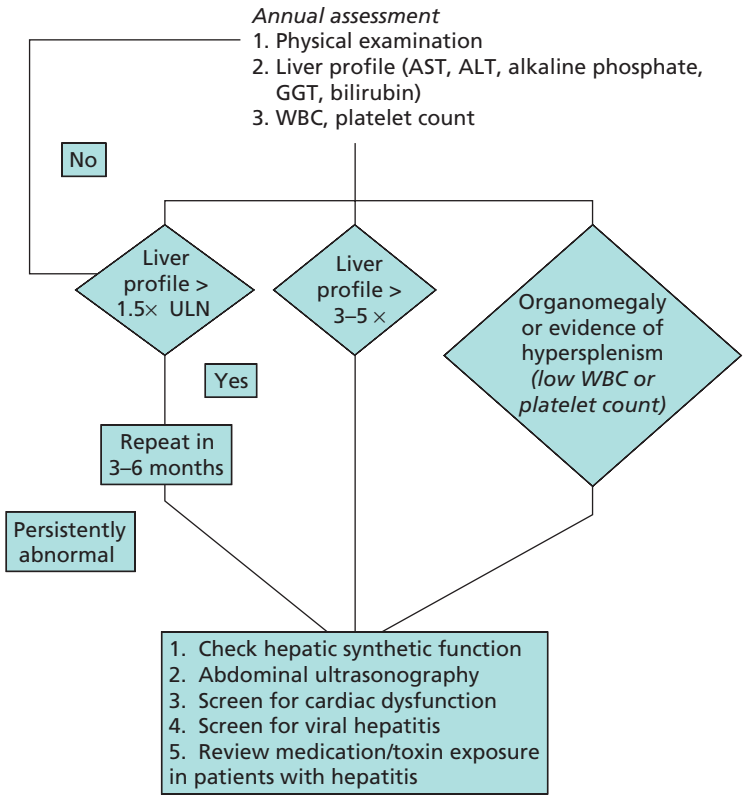

Figure 17.1 Evaluation for hepatobiliary disease in cystic fibrosis. ALT, alanine transaminase; AST, aspartate transaminase; GGT, γ-glutamyltransferase; ULN, upper limit of normal; WBC, white blood cell count.

Extrahepatic considerations

Adequate nutrition is an ongoing challenge in patients with CF. Resting energy expenditure is increased. Fat malabsorption and fat-soluble vitamin deficiency are magnified in patients with both pancreatic insufficiency and liver disease [30]. Supplementation with vitamin K is critical in accurately assessing hepatocellular function.

Bone health is a concern in any patient with CF as a result of pancreatic exocrine and endocrine insufficiency, physical inactivity, delayed puberty, and a chronic inflammatory state. Patients with CF liver disease and cholestasis have the additional burden of fat malabsorption and vitamin D deficiency. Patients with end-stage disease potentially have decreased activity of the 25-hydroxylase enzyme, resulting in high parathyroid hormone levels and increased osteoclast activity. In addition, consideration of bone health should be given to patients evaluated for liver transplantation, given the likelihood of glucocorticoid exposure and the subsequent effect on bone health in these patients [35].

Glucose intolerance and diabetes progressively increase in incidence in adolescence and adulthood in the general CF patient population. Approximately 15% of patients over 35 years of age receive insulin therapy [24]. CFLD has also been reported to increase the risk of developing CF-related diabetes [36].

Therapeutics

Therapy with ursodeoxycholic acid (15–20 mg/kg per day) is widely accepted for patients with CFLD and improves biochemical parameters, nutritional status, and hepatic excretory function [23,27,37]. Definitive evidence that it alters the natural history of the liver disease is not available, but, given its presumed low toxicity, empirical use is common. Potential significant adverse events in adults with primary sclerosing cholangitis treated with higher doses necessitate careful assessment of the risk benefit ratio of this medication and avoidance of higher dosing regimens [38].

Treatment of end-stage liver disease and portal hypertension should be considered in the broader context of the multisystem involvement in CF. For patients with portal hypertension, standard surveillance for varices and treatment with endoscopic therapy should be under-

taken. Procedures should be planned with an anesthesiologist with optimal clearance of respiratory secretion both pre- and postoperatively. The efficacy of β blockade in patients with CFLD and varices has not been formally examined because of the potential adverse effects of airway reactivity and impaired response to hypoglycemia of patients treated for diabetes. Indications for splenectomy and partial splenic embolization have not been clearly delineated and require further evaluation [39–41]. Both transjugular intrahepatic portosystemic shunt and surgical portosystemic shunt have been used as reasonable measures to treat portal hypertension or as a bridge to transplantation [42,43].

Optimum timing for transplantation is a topic of debate with much of the available data based on studies of children. Theoretical risks of deterioration in pulmonary function and exacerbation of infections with immunosuppression do not play a predominant role in post-transplantation outcome [44].

Important considerations include hepatocellular dysfunction, sequelae of portal hypertension, nutritional status, and extent of lung disease. The ideal candidate considered for isolated liver transplantation should have a forced expiratory volume in 1 s (FEV_1) of >40–50% of expected and maximized nutritional status. The risk of morbidity and mortality arises primarily from liver failure and manifests as synthetic dysfunction, encephalopathy, or intractable ascites. Historically, scoring systems devised to guide the need for transplantation were weighted toward variceal bleeding and ascites [45]. However, in a series of 18 adult patients with CF and *preserved* hepatocellular function, endoscopic management of varices and portosystemic shunting resulted in no difference in the long-term survival compared with control patients with CF but no liver disease [46]. Candidacy for transplantation therefore has to be evaluated in the context that CF is a multisystem disease and that liver disease may not be the primary determinant of outcome for the patient.

Published data on an exclusively adult population with CF who have undergone liver transplantation report 1- and 5-year actuarial survival rates of 100% and 69%, but with less dramatic improvement in lung function and nutritional status than in pediatric series. Renal insufficiency and failure (secondary to a combination of CF-related diabetes, repeated antibiotic exposure, and immunosuppression toxicity) can occur and progression of lung and heart disease-impacted outcomes [47]. Combined liver/lung transplantation has been described in case series of limited numbers. Advanced disease in multiple organ systems and longer waiting times in this population lead to increased incidence of pre- and postoperative complications [48,49].

Take-home points

Biliary atresia

- Improvements in surgical technique and medical management have resulted in patients with biliary atresia surviving into adulthood after HPE.
- Frequent monitoring with biochemical testing and physical exam is required to assess progression of disease.
- Standard approaches to the management of portal hypertension are reasonable for these adult patients.
- Regular surveillance for hepatopulmonary disorders is indicated.
- Cholangitis is the most common complication in patients post-HPE and should be suspected in patients with fever, abdominal pain, and rise in conjugated bilirubin.
- Yearly imaging of the liver should be considered to screen for intrahepatic bile duct abnormalities and lithiasis
- Routine monitoring for HCC should be undertaken.
- Transplantation should be considered in patients with advancing cholestasis, decompensated liver disease, or refractory cholangitis.

Cystic fibrosis

- Cystic fibrosis is a multisystem disease with pulmonary, pancreatic, and hepatobiliary manifestations.
- Focal lobular cirrhosis is the pathognomonic hepatobiliary complication, with a minority of patients developing multilobular cirrhosis.
- Diagnosis is made by annual screening with physical exam, biochemical tests, and ultrasonography.
- The majority of patients with CF liver disease have a benign clinical course.
- Ursodeoxycholic acid therapy should be considered in all patients with CFLD.
- Consideration for liver transplantation should take into account the multiorgan involvement in CF.
- Liver transplantation should be considered in the context of evidence of true synthetic liver failure (i.e., coagulopathy unresponsive to parenteral vitamin K), intractable ascites, or severe mechanical pulmonary compromise secondary to organomegaly and/or ascites.

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PART 5
Diseases of the Liver

18

CHAPTER 18

Acute Viral Hepatitis: Hepatitis A, Hepatitis E, and Other Viruses

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Summary
Viral infections by hepatotropic and non-hepatotropic viruses are a frequent cause of acute hepatitis. Hepatitis A and E (HAV and HAE) are enterically-transmitted viral infections and are prevalent worldwide. The clinical spectrum ranges from asymptomatic infection to acute liver failure. Diagnosis of hepatitis A relies on serum anti-HAV IgM, while that of hepatitis E requires heightened clinical suspicion and serologic or molecular confirmation. Prognosis is excellent with spontaneous resolution in most cases. Mortality of HEV is greater than that of HAV, especially in pregnant patients, who have a mortality of 25–30%. No specific antiviral treatment is available for HAV or HEV. Effective immunoprophylaxis for hepatitis A is widely accessible, while a safe and effective recombinant HEV vaccine has recently been tested in volunteers. Non-hepatotropic viruses such as herpesviruses, adenoviruses, enteroviruses, and parvovirus B-19, among others, can cause acute hepatitis and have significant consequences in immunocompromised individuals.

Case
A healthy 20-year-old white woman presented to an acute care clinic 3 weeks after vacationing in Mexico, with a 5-day history of malaise, fatigue, low-grade fever, headache, nausea, anorexia, and dark urine. On physical examination she was afebrile, jaundiced, and had tender hepatomegaly. There were no signs of chronic liver disease and her neurologic exam was normal. Laboratory tests revealed normal complete blood count, blood urea nitrogen and creatinine; alanine transaminase (ALT) 3500 i.u./L, aspartate transaminase (AST) 3200 i.u./L, total bilirubin 6 mg/dL and normal international normalized ratio (INR). Abdominal ultrasound revealed hepatomegaly with normal gall bladder, bile ducts, and spleen.

Practical Gastroenterology and Hepatology: Liver and Biliary Disease, 1st edition. Edited by Nicholas J. Talley, Keith D. Lindor and Hugo E. Vargas.

Hepatitis A

Definition and Epidemiology

Hepatitis A is an acute, enterically-transmitted, self-limited, necroinflammatory viral infection of the liver. Hepatitis A virus (HAV) is a small, non-enveloped, single-stranded RNA virus classified in its own genus (*Hepatovirus*) within the *Picornaviridae* family [1,2].

The epidemiology of hepatitis A varies around the world in close relationship to the overall sanitary conditions of a region. Prevalence is low among industrialized countries compared to developing nations, where the majority of subjects have been infected in early childhood. The prevalence of HAV antibodies in the USA is 10% in children and 37% in adults.

There are 1.5 million cases/year of acute hepatitis A reported worldwide. In the USA approximately 25 000–30 000 cases yearly were reported from 1980 to 1998. A steady decline in the incidence of HAV in the USA, especially among children, has occurred since the

introduction of HAV vaccination in 1995. In 2000 there were 13 397 symptomatic cases reported to the Centers for Disease Control and Prevention (CDC); accounting for under-reporting and asymptomatic cases, there were an estimated 57 000 cases and 143 000 total new infections. In 2006, these figures decreased to 3579, 15 000, and 32 000, respectively, which resulted in a national incidence of 1.2 symptomatic cases per 100 000 population, the lowest ever recorded [3]. In regards to race and ethnicity, in the past, the highest rates were observed in American Indian/Alaska Natives (> 60 cases per 100 000 population before 1995), but have dramatically decreased after the introduction of targeted vaccination strategies. In 2006, the rate of hepatitis A among this group was only 0.5 cases per 100 000 population. Rates among Hispanics remain the highest when compared to non-Hispanics, although they too have improved over the years [3].

Several groups are at higher risk of HAV infection: travelers from non-endemic to endemic areas; military personnel stationed in endemic regions; children, employees, and parents of children attending daycare centers; persons working with non-human primates; clients and employees of institutions for the developmentally disabled; men who have sex with other men (MSM), and intravenous drug users (IVDU). In the USA the most frequently identified epidemiologic risk factor for hepatitis A is international travel (reported by 15% of patients overall), especially to Mexico, Central and South America (72%); followed by sexual or household contact with hepatitis A patients (10%); MSM (9%); suspected food- or water-borne outbreak (7.5%); child/employee in daycare center (4%) and IVDU (2%); the majority of reported cases have no known risk factor (65%) [3].

Table 18.1 Relevant clinical features in hepatitis A and hepatitis E.

	HAV	HEV
Incubation period	~ 30 days	~ 40 days
Transmission	Fecal–oral	Fecal–oral, zoonotic, parenteral, vertical transmission
Person-to-person transmission	Frequent	Infrequent
Dose-dependent severity	No	Yes
Mortality	0.1–2% (increases with age and comorbidity, no effect of pregnancy)	1–4% (up to 30% in pregnancy)
Chronic disease	No	Rarely described in transplant recipients
Prevention	Immune globulin prophylaxis useful. Safe and effective vaccines widely available	Immune globulin ineffective, vaccine in development and under clinical investigation

Pathophysiology (Table 18.1)

HAV is transmitted almost exclusively by the fecal–oral route and is associated with viral shedding in stool during the 3–6-week incubation period. The virus is stable at ambient temperatures and at low pH, enabling it to survive in the environment and be transmitted through contaminated food and drinking water.

Once ingested, HAV reaches the small bowel, traverses the intestinal mucosa, and gains access to the liver through the portal vein. It replicates within the hepatocyte cytoplasm and is excreted back to the intestinal lumen via the biliary tract. Fecal shedding of the virus reaches its maximum shortly before the onset of hepatocellular injury, at which time the subject is most contagious. This is paralleled by extended viremia that follows a similar pattern to fecal shedding, although at a much lower magnitude. Hepatocellular injury ensues, with a marked increase of serum aminotransferase activity. Viral antigen continues to be shed for up to 3 weeks after aminotransferase elevation, although sensitive molecular techniques can detect continued shedding of HAV RNA for many weeks. Fortunately, prolonged viral shedding is rare and has only been documented in infected premature infants. Long term fecal viral shedding does not occur [4].

At present, the mechanisms responsible for hepatocellular injury in HAV infection are poorly understood. The virus does not appear to be cytopathic, suggesting that liver injury is the result of an immunopathologic response to infection in the hepatocyte, rather than to a direct viral effect. The currently accepted hypothesis is that hepatocellular injury is the result of activated HLA-restricted, virus-specific, cytotoxic CD8+ lymphocytes. These cells have been shown to secrete interferon-γ and hence stim-

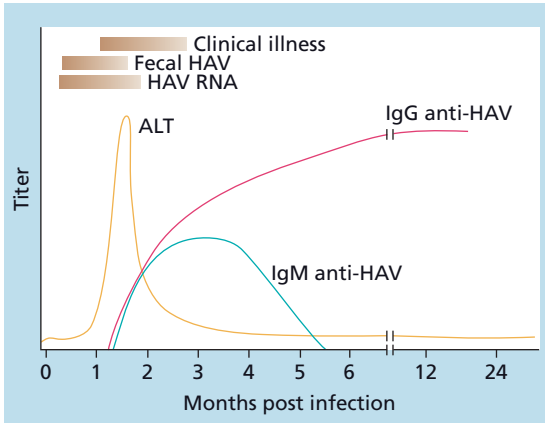

Figure 18.1 Relevant clinical, viral, and serologic events in hepatitis A. (Reproduced from Bacon et al. (eds) *Comprehensive Clinical Hepatology*, 2nd edn, 2006: 208, with permission from Elsevier Mosby.)

ulate the recruitment of additional, non-specific inflammatory cells to the liver [1,4].

The lack of chronic infection in hepatitis A is the result of a robust and effective response from the adaptive immune system to HAV. Neutralizing serum antibodies can be detected concurrently with early evidence of elevation of aminotransferases and liver injury. The early humoral response is largely comprised of IgM antibodies, which serve as the basis of serologic diagnosis (see below), followed by the presence of IgG, which can be detected shortly after symptom onset. Importantly, anti-HAV IgG persists for life and confers protection against reinfection (Figure 18.1). This is the basis for passive and active immunoprophylaxis with immune globulin or vaccination, respectively [4].

Clinical Features (Table 18.1)

The clinical spectrum of HAV ranges from asymptomatic to acute liver failure (ALF), although in most patients morbidity and mortality are minimal. The presence or absence of symptoms is strongly correlated to the age at which infection is acquired, as young children generally do not develop significant symptoms (jaundice < 20%), while 70–80% of older children, adolescents, and adults develop jaundice [1,2].

The clinical presentation of hepatitis A may be indistinguishable from other causes of acute viral hepatitis. After an incubation period of 2–6 weeks, patients may experience non-specific prodromal symptoms, such as fatigue, malaise, low-grade fever, headache, nausea and vomiting, myalgias, arthralgias, anorexia, and weight loss. Hepatic-specific symptoms tend to appear later in the course, and include abdominal pain, dark urine, jaundice, acholia, and pruritus. On exam patients may have tender hepatomegaly, scleral icterus, and jaundice. Occasionally patients will present with cervical lymphadenopathy and mild splenomegaly [1,2].

Other than serologic test for HAV, there are no specific laboratory findings in hepatitis A. Patients generally have significant elevations in serum aminotransferases (500–5000 i.u./L), mild-to-moderate elevations in bilirubin, and occasionally prolonged prothrombin time and decreased serum albumin (frequently associated with ALF). Alkaline phosphatase is generally normal or only minimally elevated. Other laboratory features may include transient neutropenia, atypical lymphocytosis, and non-specific elevations of IgM and total gammaglobulin [1,2].

Complete clinical recovery is the rule and there is no chronic infection or carrier state. The majority of patients recover within the first 8 weeks, and only rarely do laboratory abnormalities persist for up to a year (Figure 18.1) [1,2].

The "classical" clinical pattern of hepatitis A is described above, but other patterns have been described, including a cholestatic form, with jaundice that may persist for up to 10 weeks; a relapsing form, with two or more bouts of acute HAV infection with elevation of serum aminotransferases occurring over a 6–10 week period and rarely an ALF presentation (1 in 10 000 cases) [1,2]. In a recent report from the USA ALF group, 3% of all cases of ALF in adults were due to hepatitis A, with good overall prognosis, as 58% recovered spontaneously, but 29% required liver transplantation and 13% died [5].

Diagnosis

Case continued

Serologic studies for viral hepatitis were remarkable for positive total anti-HAV antibodies, positive anti-HAV IgM and hepatitis B surface antibody, negative hepatitis B surface antigen, hepatitis B core IgG and IgM antigens, and absence of anti-HCV antibodies, as well as normal antinuclear antibodies and anti-smooth muscle antibodies. Diagnosis of hepatitis A was established.

Hepatitis A is clinically indistinguishable from other causes of acute hepatitis; thus, the diagnosis is based on serologic testing. The presence of IgM anti-HAV antibodies establishes the diagnosis with excellent sensitivity and specificity. Anti-HAV IgM can be detected up to 3 months after acute infection. Thereafter, beginning during convalescence and persisting indefinitely, anti-HAV IgG predominates and is associated with lifelong immunity. Thus, anti-HAV IgG serves as a marker of prior HAV infection while anti-HAV IgM serves as a marker of acute or recent infection [2,4].

Liver biopsy is rarely indicated, but when performed, the pathologic features are similar to those encountered in other forms of acute viral hepatitis, including ballooning of hepatocytes, coagulative necrosis, focal necrosis, portal expansion by mononuclear cell infiltrate, periportal inflammation, and hyperplasia of Kupffer cells. In some cases, cholestasis may be prominent and interface hepatitis with or without bridging necrosis is frequently present in more severe cases [1].

Differential Diagnosis

A thorough history and physical exam, together with appropriate laboratory tests, can help differentiate HAV from other causes. Useful tests include hepatitis B, C, and E serologies, antinuclear and anti-smooth muscle antibodies, other viral serologies as appropriate, as well as serum and/or urine drug levels, including acetaminophen and alcohol serum levels. In rare instances, patients may harbor more than one viral infection, such as chronic hepatitis B or C with superimposed acute hepatitis A. Occasionally, imaging studies are indicated to exclude both benign and malignant causes of obstructive jaundice (Table 18.2) [1,2].

Table 18.2 Differential diagnosis of acute hepatitis.

Category	Specific condition
Viral hepatitis	Hepatitis A to E Epstein–Barr virus Cytomegalovirus Other herpes-group virus
Systemic infections	Bacterial infections Tuberculosis
Drugs/toxins	Acetaminofen Amoxycilin with clavulanic acid Isoniazid Sulfonamides Fluconazole, itraconazole Alcohol
Metabolic	Hyperglycemia Hyperthyroidism Wilson disease
Immunologic	Autoimmune hepatitis
Vascular	Ischemic hepatitis ("shock liver") Budd–Chiari syndrome
Pregnancy-related	Cholestasis of pregnancy HELLP syndrome* Acute fatty liver of pregnancy
Pancreatobiliary disease	Acute cholecystitis Acute ascending cholangitis Acute pancreatitis Pancreatic cancer

*HELLP, *h*emolysis, elevated *l*iver enzymes, and *l*ow *p*latelets.

Therapeutics

Case continued

The patient was prescribed acetaminophen as needed for symptom control. She was advised not to drink alcoholic beverages. Her sexual partner was contacted and was immunized with a first dose of HAV vaccine, as he had not been vaccinated in the past.

The patient recovered completely 2 weeks after initial presentation, and at a 3-month follow-up visit with her primary care physician, her liver enzymes had completely normalized.

Because of the self-limited nature of the disease, there is currently no specific antiviral therapy for acute hepatitis A. Treatment is generally symptomatic and in the rare cases of ALF management is mainly supportive in an intensive care setting, and only sporadically will patients require liver transplantation. There is generally no need for hospitalization, which is only indicated in the presence of significant comorbidity, inability to maintain oral intake, or when incipient liver failure is detected, especially in the very young and the elderly, as well as in subjects with underlying advanced liver disease or cirrhosis.

In the past, corticosteroids have been used, without clear benefit in patients with the cholestatic pattern. Most patients may benefit from judicious use of acetaminophen or non-steroidal anti-inflammatories for systemic

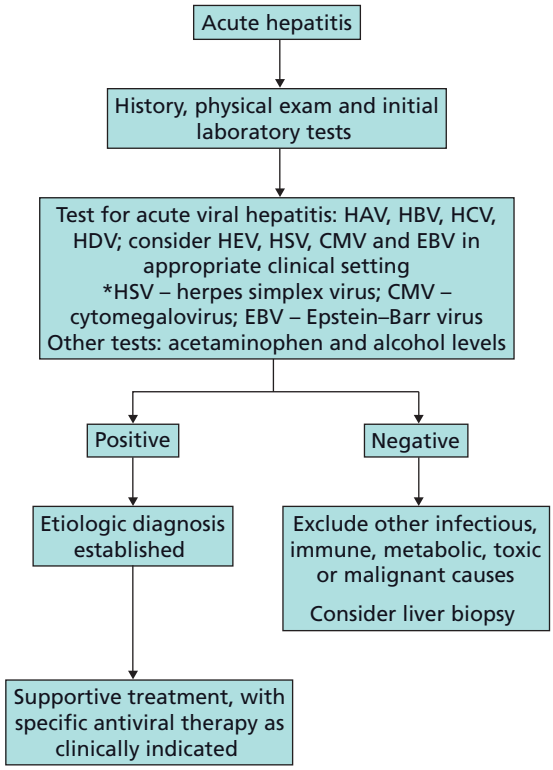

Figure 18.2 Management of acute viral hepatitis. HAV, HBV, HCV, HDV, HEV, hepatitis A–E virus; HSV, herpes simplex virus; CMV, cytomegalovirus; EBV, Epstein–Barr virus.

symptoms. At times, cholestyramine may be of use in patients with severe pruritus. Time honored interventions, such as bed rest or dietary restrictions, are of no significant benefit. Abstinence from alcoholic beverages seems a reasonable recommendation, albeit without proven clinical benefit [1,2] (Figure 18.2).

Prevention

The principal measures to decrease the risk of HAV transmission, especially effective in endemic areas, include adequate sanitation, improvements in environmental hygiene, and safe water supply. Also valuable are hand washing and special training of food handlers.

International travelers to HAV endemic areas should avoid tap water and undercooked or raw food, as well as beverages that could be contaminated with HAV. No special precautions are required for co-workers, classmates, or casual contacts of subjects infected with HAV, as spread of the disease depends on close person-to-person contact. Compliance with universal precautions in health-care settings is sufficient to prevent nosocomial spread of the infection, and no further measures are required [1,2].

Fortunately, there are currently excellent methods of both passive and active immunization to prevent HAV infection. Before the advent of efficacious vaccines, passive immunization through transfer of anti-HAV antibodies from immune globulin was the only available prophylactic measure. A dose of 0.02 mL/kg intramuscularly is 80–90% effective in preventing HAV infection when administered within 2 weeks after initial exposure. Later administration may still be beneficial, as it has been demonstrated to attenuate the severity of hepatitis A. At present, the worldwide availability of safe and effective HAV vaccines has relegated the use of immune globulin to postexposure prophylaxis or for passive pre-exposure immunization in pregnant or lactating women and immunocompromised subjects [1,6]. In the future the use of immune globulin might be further limited, as recent data on the use of HAV vaccine in postexposure prophylaxis have demonstrated similar efficacy to immune globulin, with the advantage that vaccination results in long term immunity [7].

Since the mid-1990s the United States Food and Drug Administration (FDA) has licensed two formalin-inactivated HAV vaccines to be used in people aged 2 years or older, and since September 2005 in infants older than 1 year of age. Both commercially available vaccines (Havrix®, GlaxoSmithKline; Vaqta®, Merck & Co) are highly immunogenic, with neutralizing antibodies present in 94% of subjects 4 weeks after the first dose and almost 100% after the second dose. Immunogenicity decreases in chronic liver disease (seroconversion rate 93%), immunocompromised subjects (88%), the elderly (65%) and transplant recipients (26%) [8].

The recommended vaccination regimen is a two-dose schedule for both vaccines, with the second dose at 6–18 months after the first one. If the second dose is delayed, it can still be given without repeating the initial dose. Both vaccines have pediatric and adult formulations, are generally administered intramuscularly, and are considered interchangeable. They can be administered concomitantly with other vaccines and even with immune

Table 18.3 Summary of current United States Advisory Committee on Immunization Practices recommendations on active and passive immunization for hepatitis A [9,10].

Pre-exposure protection	Postexposure prophylaxis
All children should receive HAV vaccination starting at age 1 year Persons at risk for HAV infection: • Travelers to or workers in countries with high or intermediate endemicity • Men who have sex with men • Users of injection and non-injection illicit drugs • Occupational exposure (persons who work with HAV-infected primates or with HAV in a research laboratory setting) • Persons with clotting-factor disorders • Persons with chronic liver disease	Unvaccinated persons who have been recently exposed to HAV should receive HAV vaccination or immune globulin as soon as possible: • For healthy individuals 12 months–40 years, HAV vaccine is preferred • For persons >40 years, immune globulin is preferred; vaccine may be used if immune globulin is not available • For children <12 months old, immunocompromised subjects, patients with chronic liver disease and persons for whom vaccine is contraindicated, immune globulin should be used

globulin, at a different anatomic site, if immediate protection is required. Recently, a combined HAV and HBV vaccine has been licensed in the USA. It is highly immunogenic against both viruses and the recommended vaccination schedule is 0, 1, and 6 months [6,8].

The current recommendations on immunization to prevent hepatitis A are summarized in Table 18.3.

Prognosis

Prognosis for hepatitis A is excellent; most individuals recover spontaneously without any lasting sequelae. Patients at greater risk for poor outcomes include those at the extremes of age and those with significant comorbidities, especially patients with advanced liver disease or cirrhosis. A third of the reported cases of hepatitis A in the USA in 2006 required hospital admission. Hospitalization rate increased with age, from 22% among children aged younger than 5 years to 52% among persons aged 60 years or older. The overall mortality rate was only 0.3%, but was highest in subjects aged 60 years or older (1.5%) [3].

Hepatitis E

Definition and Epidemiology

Hepatitis E is an acute form of generally self-limited, enterically-transmitted viral hepatitis. The causative agent is hepatitis E virus (HEV), a small, non-enveloped, single-strand RNA virus that is the sole member of the *Hepevirus* genus in the *Hepeviridae* family. There are at least four genotypes, but to date, only one serotype has been identified. HEV is not specific to humans and variants have been found in pigs (swine HEV) [11].

Hepatitis E is endemic in many developing countries within the Indian subcontinent, Central and South-East Asia, Africa, the Middle East, and in parts of Central and South America, where water-borne outbreaks are relatively frequent and the seroprevalence of anti-HEV IgG is high (40–80%) [12]. In these countries, HEV is among the main causative agents of acute hepatitis. In contrast, seroprevalence is lower in industrialized nations (9–34%). In the USA prevalence is up to 17–21% and only sporadic cases are reported, which account for a minority of symptomatic acute hepatitis cases [12–14]. Most of the US cases are seen in travelers to endemic areas and only a handful of domestically acquired infections have been reported [15].

Pathophysiology (Table 18.1)

HEV is mainly an enterically-transmitted pathogen. The documented forms of transmission include water-borne infection (drinking contaminated water), zoonotic food-borne transmission (eating raw or undercooked meat from pigs, boar, and deer), and less commonly, parenteral (blood transfusion) and mother-to-infant transmission. In contrast to HAV, peron-to-person transmission is infrequent [16,17].

After an incubation period of 4–5 weeks, elevated serum aminotransferase levels are detected and generally remain abnormal from 1 to 3 months. Viral shedding in feces can be detected 4 weeks after ingestion and may persist for up to 8 weeks. The initial humoral response (anti-HEV IgM) is detected concomitantly with the rise in aminotransferase levels, only to decline shortly thereafter, although occasionally persisting for up to 5 months after initial infection. Anti-HEV IgG can be detected shortly after the IgM response and confers lifelong immunity (Figure 18.3). Most patients will have detectable anti-HEV IgG 20 months after infection and up to

50% can have detectable antibodies 14 years after clinical presentation [16,17].

The precise mechanisms of viral cell entry as well as hepatocyte injury are poorly understood, but current data suggest that liver injury is immune mediated.

Clinical Features (Table 18.1)

The spectrum of disease in hepatitis E is highly variable and the presentation is similar to hepatitis A.

Adults seem to be at increased risk of symptomatic disease compared to children and adolescents. Common symptoms include jaundice, malaise, anorexia, nausea and vomiting, fever, and pruritus. Frequent clinical findings include jaundice, tender hepatomegaly, and occasionally splenomegaly. Laboratory abnormalities generally include elevated aminotransferase levels, hyperbilirubinemia, and elevated alkaline phosphatase and/or gamma-glutamyltransferase [16,17].

The majority of hepatitis E cases follow a self-limited course, with resolution of jaundice and transaminitis 3 weeks (1–6 weeks) after illness onset. Some patients will develop a more protracted course characterized by significant cholestasis with persistent jaundice and pruritus that will ultimately resolve spontaneously (Figure 18.3) [17]. Noticeably, recent reports have described cases of chronic hepatitis and cirrhosis in solid-organ transplant recipients infected with HEV (detailed below).

Although infrequent, ALF has been well-described in hepatitis E. In some regions it accounts for a majority of viral hepatitis-related ALF, particularly among pregnant women.

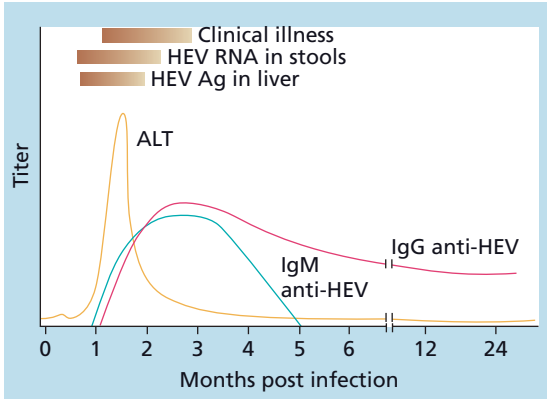

Figure 18.3 Relevant clinical, viral, and serologic events in hepatitis E. (Reproduced from Bacon et al. (eds) *Comprehensive Clinical Hepatology*, 2nd edn, 2006: 211, with permission from Elsevier Mosby.)

Diagnosis

Confirmation of hepatitis E relies on serologic and/or molecular techniques. Acute infection is characterized by the presence of serum anti-HEV IgM antibodies, while past infection is documented on the basis of anti-HEV IgG. No antibody testing is currently commercially available in the USA. Molecular detection of HEV RNA in biologic samples is not routinely available to the clinician, but constitutes an important research tool and recent developments may help make it accessible in the near future [13,17].

Liver biopsy is not a requisite for diagnosing hepatitis E, and there are no pathognomonic findings. Two histopathologic patterns have been described in HEV outbreaks: a cholestatic pattern with prominent bile deposits in canaliculi and hepatocytes (58%) and a more typical hepatocellular pattern with "ballooning", hepatocyte degeneration, and acidophilic body formation (42%) [16].

Differential Diagnosis

The differential diagnosis is listed in Table 18.2.

Therapeutics

No specific antiviral therapy is available for HEV infection and treatment is symptomatic and supportive. Some patients will require hospitalization and occasionally admission to an intensive care unit for management of ALF. Some patients will need liver transplantation. The role of terminating pregnancy in pregnant patients with ALF from HEV infection has not been studied [16].

Prevention

Preventive measures include improving personal hygiene, community-wide sanitation, and availability of clean water sources. Ongoing research in vaccine development led to testing of recombinant HEV vaccine in volunteers. Vaccine efficacy following three doses was 96% and 87% after two doses and no significant adverse events were reported. In the future, HEV vaccination may prevent significant illness in countries where HEV is endemic [18].

Prognosis

Most patients with hepatitis E will have spontaneous resolution of disease and no long term consequence. Although infrequent, ALF has been described in HEV, especially among pregnant patients. The case mortality for hepatitis E is 0.5–4%, which is higher than that for hepatitis A. Mortality in pregnant patients can reach 25–30%. In a recent observational cohort study from India, pregnant women with symptomatic hepatitis E had an increased maternal mortality rate and worse obstetric and fetal outcomes than pregnant women with other causes of acute viral hepatitis [19].

Recent reports have described the presence of chronic hepatitis and even cirrhosis after HEV infection in solid-organ transplant recipients [20–22]. As such, clinicians involved in the care of transplant patients should entertain HEV infection as the cause of otherwise unexplained abnormal liver chemistries.

Other viruses

Other viral agents, commonly causing systemic virosis, may result in liver involvement, and must be considered in the differential diagnosis of acute hepatitis, especially when hepatitis A–E have been excluded. Clinical manifestations range from asymptomatic elevations in aminotransferases to fulminant hepatitis, with more prominent disease in infants and immunocompromised individuals.

Frequent offenders in this category include members from the herpesvirus family, adenoviruses, enteroviruses, and human parvovirus B-19, among others [23].

Herpesvirus Family

Herpesviruses are a family of large enveloped DNA viruses that infect a wide range of hosts. Herpesviruses known to infect humans (Table 18.4) are herpes simplex virus types 1 and 2 (HSV-1, HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), human herpesvirus types 6, 7, and 8 (HHV-6, HHV-7, HHV-8), and Epstein–Barr virus (EBV). Following primary infection, herpesviruses have the ability to produce latent infection for life. Reactivation can lead to recurrent disease or invasive infection and is generally triggered by host immunosuppression. Tissue damage may result from direct viral cellular injury, immune-mediated cytotoxicity, or neoplastic transformation [23,24].

Table 18.4 Main clinical features of herpesvirus hepatitis (modified from [24]).

Virus	Hepatitis severity	Clinical features
HSV	Mild, self-limited	Frequent in primary infection (14%)
	Severe hepatitis/ ALF	At risk: neonates, pregnant women and individuals with cellular immune deficiency 50% present without typical skin lesions Therapy: acyclovir
VZV	Mild, self-limited	May accompany varicella or "chickenpox" (3–25%)
	Severe hepatitis/ ALF	At risk: HSC recipients, hematologic malignancies, HIV/AIDS Classic skin lesions frequently absent Therapy: acyclovir
CMV	Mild, self-limited	Frequent in mononucleosis-type illness
	Moderate	Frequently part of acute viral syndrome in solid-organ transplant recipients
	Graft hepatitis	May affect 5% of high-risk liver transplant recipients Must differentiate from acute rejection Prophylaxis available Therapy: ganciclovir
EBV	Mild, self-limited	Very frequent in mononucleosis (90%)
	Severe hepatitis/ ALF	At risk: primary EBV infection in patients with Duncan disease

HSV, herpes simplex virus; VZV, varicella-zoster virus; CMV, cytomegalovirus; EBV, Epstein–Barr virus; ALF, acute liver failure, HIV, human immune deficiency virus; AIDS, acquired immune deficiency syndrome; HSC, hematopoietic stem cell.

Herpes Simplex Virus

HSV infection is common and may result in a wide variety of clinical presentations, including mucocutaneous, neurologic, and visceral involvement. HSV hepatitis may occur in neonates (resulting in a high mortality rate), pregnant women, immunocompromised persons, and immunocompetent adults. In a review of the Mayo Clinic experience with ALF from 1974 to 1982, two of 34 cases were secondary to HSV [23].

HSV hepatitis during pregnancy is generally seen as a manifestation of primary infection and may result in

ALF. Mucocutaneous lesions are absent in half the patients, and up to 25% of cases are diagnosed only at autopsy. HSV is an uncommon cause of liver disease in immunocompetent adults, but 14% of healthy individuals with acute genital herpes have mild asymptomatic transaminitis. In immunocompromised hosts, HSV hepatitis may be the result of primary or, rarely, recurrent infection. Clinical features include fever, nausea and vomiting, abdominal pain, leukopenia, thrombocytopenia, and markedly elevated aminotransferases. Serologic diagnosis is unreliable; hence liver biopsy is necessary to establish the diagnosis. Typical findings include hemorrhagic or coagulative necrosis of hepatocytes, limited mononuclear cell infiltrate, and intranuclear inclusions (Cowdry type A). Molecular confirmation is recommended. Treatment of choice is high-dose intravenous acyclovir, but valacyclovir or famciclovir may be used as second-line therapies [24,25].

Varicella-Zoster Virus

Primary VZV infection results in varicella (chickenpox), while reactivation results in herpes zoster (shingles). Varicella in children may be accompanied by asymptomatic mild aminotransferase elevation in up to 28% of cases. In immunocompetent adults, primary infection may infrequently result in severe hepatitis and occasionally ALF. Primary VZV infection in immunocompromised individuals can have devastating effects, including ALF-related mortality, which has been frequently described in solid-organ and hematopoietic stem cell transplant (HSCT) recipients, patients with acute leukemia, and individuals with acquired immune deficiency syndrome (AIDS) [24,25].

Diagnosis relies on identification, by immunohistochemical analysis or PCR techniques, of VZV within liver tissue. Viremia may be detected before clinical manifestations of infection are apparent, allowing for early diagnosis and treatment. The antiviral agent of choice is intravenous acyclovir. Prophylaxis in HSCT recipients may delay, but not prevent, disseminated herpes zoster [25].

Cytomegalovirus

CMV infection is frequent among the general population with a seroprevalence of 70–80% among young adults. Infection in the immunocompetent host is generally asymptomatic, but can present as mononucleosis syndrome accompanied by mild elevations in liver enzymes or jaundice, that resolve spontaneously. Diagnosis of CMV hepatitis should be established with a combination of features: appropriate clinical setting, exclusion of other causes, and detection of CMV within liver tissue (viremia *per se* does not confirm the diagnosis) [23,25].

CMV hepatitis is generally a manifestation of disseminated disease in severely immunocompromised patients, and accounts for the most common organ-specific complication of CMV infection after liver transplantation, especially among seronegative recipients (26%). Clinical features include fever, jaundice, and significant elevation of aminotransferases that can lead to liver dysfunction if not promptly treated [25].

Liver biopsy findings include portal mononuclear cell infiltrates, giant multinucleated cells, microscopic granulomas, multifocal necrosis, and biliary stasis. Classic "owl's eye" inclusions can be found within hepatocytes and bile duct epithelial cells [23,25].

Ganciclovir, foscarnet, and cidofovir are the available antiviral agents to treat CMV infection. Treatment may not be indicated in mild cases of CMV hepatitis in otherwise healthy individuals. High-risk liver transplant patients, defined as seronegative recipient of a graft from a CMV seropositive donor, should receive ganciclovir prophylaxis for the first few months after transplantation [24].

Epstein–Barr Virus

EBV infection has a worldwide distribution, with a prevalence of 90% in adult populations. It is generally transmitted through saliva, but parenteral and sexual transmissions have been documented. EBV has special tropism to B and T lymphocytes. Clinically, it is the most common cause of infectious mononucleosis and is the causative agent for a number of hematologic malignancies, including post-transplant lymphoproliferative disease [23,24].

Liver involvement in EBV infection is common, but generally manifests as transient and self-limited transaminitis (80–90%) or hyperbilirubinemia (< 10%) within the course of mononucleosis. Histologic findings include minimal swelling and vacuolization of hepatocytes with lymphocytic and monocytic portal infiltration. Severe cholestasis and liver failure are uncommon in immunocompetent individuals, but have been described in patients with recent organ transplantation or with immunodeficiency from AIDS, X-linked lymphoproliferative

disease (Duncan disease), or chemotherapy. Some authors have described "chronic" hepatitis in the setting of chronic EBV infection [24,25].

No reliable diagnostic criteria for EBV hepatitis are available, but at present diagnosis should be based on the combination of the following parameters: elevated aminotransferases, EBV serology consistent with active infection, typical histology, and demonstration of viral DNA in liver tissue. Antiviral therapy with acyclovir or ganciclovir is warranted in severe cases of EBV hepatitis, especially in immunosuppressed patients [25].

Take-home points

- Hepatitis A (HAV) and hepatitis E (HEV) are enterically-transmitted RNA viruses that share common clinical features.
- Epidemiology of hepatitis A is changing as a consequence of worldwide vaccination efforts.
- Recent outbreaks of HEV in industrialized nations have pointed to the zoonotic nature of this infection.
- Clinical presentation of HAV and HEV are commonly indistinguishable from other causes of acute hepatitis and a broad differential diagnosis must be considered.
- Diagnosis of acute hepatitis A relies on detection of serum anti-HAV IgM, while that of hepatitis E requires heightened clinical suspicion and serologic or molecular confirmation.
- Clinical course of hepatitis A is generally self-limited, with occasional atypical presentations, including cholestatic hepatitis, relapsing hepatitis, and acute liver failure.
- Cases of chronic hepatitis E and cirrhosis in transplant recipients have been recently described.
- Mortality of hepatitis E is greater than that of hepatitis A, especially in pregnant patients who have a case fatality rate of 25–30%.
- Effective immunoprophylaxis for hepatitis A is widely available, while a safe and effective recombinant HEV vaccine has recently completed phase III clinical trials.
- Other viruses such as herpesviruses, adenoviruses, enteroviruses, and parvovirus B-19, among others, can cause acute hepatitis and have significant consequences in immunocompromised individuals.

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19

CHAPTER 19
Hepatitis B and C

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Summary
With the advent of potent antiviral compounds against hepatitis B virus (HBV) with low susceptibility to resistant mutation, the choice of first-line treatment has become quite clear. However, selection of treatment candidates remains less straightforward. As with any clinical circumstance, individual patient management decisions must be based on risks and benefits of treatment. On the one hand, the main benefit to be achieved with therapy is avoidance of long term sequelae (cirrhosis and hepatocellular carcinoma) of HBV infection through durable suppression of the virus. On the other hand, disadvantages associated with antiviral therapy include potential long term safety concerns, emergence of resistant mutants, and financial burden. Available data and clinical experience guide the physician to balance these factors in individual patients.

While the introduction of the new class of direct agents against hepatitis C virus (HCV) is eagerly awaited, clinicians rely on optimal use of the current standard-of-care medications to maximize patient's response. First, recent evidence points to the need for weight-based therapy. This is especially true of ribavirin—there are benefits of increasing ribavirin doses up to 1400 mg/day in genotype 1 patients with a body weight greater than 105 kg. Even for genotype 2 or 3 patients for whom the standard ribavirin dose is 800 mg/day, weight-based dosing similar to that for genotype 1 patients may be more effective. Second, treatment duration may be tailored based on on-treatment response. In genotype 1 patients whose serum HCV RNA is negative at week 4 ["rapid viral response (RVR)"], treatment may be shortened to 24 weeks. If HCV RNA becomes negative at week 12, the standard 48-week duration is applicable, whereas in those whose HCV RNA does not become negative until 24 weeks, prolonging the duration to 72 weeks may increase the response rate by up to 20%. Shortening therapy duration to 12–16 weeks in genotype 2 or 3 patients with RVR is more controversial—it may be considered in patients whose tolerance is poor, especially if ribavirin is dosed according to body weight.

Management of Chronic Hepatitis B

Case

Mrs T is a 64-year-old Vietnamese American woman who was diagnosed with chronic hepatitis B virus (HBV) infection in 1997. She referred herself for evaluation after a brother recently underwent liver transplantation for hepatocellular carcinoma (HCC). She, herself, was feeling well with no symptoms of hepatitis, such as anorexia, fatigue, nausea, or pruritus. She has no past history of jaundice. Her family history is significant for HCC in multiple members of the family, including her mother and three younger siblings. All of them had been HBV positive. Her mother was diagnosed with HCC at age 63. Her physical examination was normal without stigmata of chronic liver disease, hepatosplenomegaly, or evidence of ascites or peripheral fluid retention. Table 19.1 shows Mrs T's laboratory data.

At the beginning, Mrs T's liver tests were essentially normal with intact liver function. There was no evidence of hypersplenism. Subsequently, her serum alanine transaminase (ALT) and HBV DNA gradually increased. In July 2008, given these changes, a decision was made to perform a liver biopsy. The histologic features of the biopsy included mildly active chronic hepatitis B (grade 2 of 4) with early fibrosis (stage 1 of 4). With these data, should Mrs T receive antiviral therapy?

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Table 19.1 Laboratory data for Mrs T.

	July 2006	July 2007	July 2008
Hemoglobin (g/dL)	13.1	13.7	13.1
WBC (per mm^3)	4200	4500	3900
Platelets (per mm^3)	197 000	206 000	182 000
INR	0.9		0.9
AST (U/L)	33	36	44
ALT (U/L)	30	38	48
Albumin (g/dL)	4.3	4.2	4.1
Creatinine (mg/dL)	1.0	1.0	0.8
Total bilirubin (mg/dL)	0.7	0.8	1.0
HBsAg	Positive		
HBeAg	Negative	Negative	Negative
Anti-HBe	Positive	Positive	Positive
HBV DNA (IU/mL)	120 800	317 000	1 306 000

ALT, alanine transaminase; AST, aspartate transaminase; WBC, white blood cells; INR, international normalized ratio.

Natural History

The natural history of chronic HBV infection is commonly divided into four phases: (1) immune tolerance, (2) hepatitis B e antigen (HBeAg)-positive chronic hepatitis, (3) inactive hepatitis B s antigen (HBsAg) carrier, and (4) HBeAg-negative chronic hepatitis.

The immune tolerance phase is the initial phase of infection seen in patients who acquire HBV infection early in life and is characterized by the presence of HBeAg and high levels of serum HBV DNA [1]. Despite active viral replication, evidence of liver disease is often absent, including normal serum aminotransferase levels and minimal or no inflammation on liver histology [2]. The mechanism of immune tolerance is incompletely understood—animal experiments have shown that transplacental transfer of maternal HBeAg may induce specific unresponsiveness of T cells [3,4]. Over time, the host immune system begins to mature, resulting in immune-mediated hepatocellular injury, which constitutes the HBeAg-positive chronic hepatitis [5,6]. Immune response at this stage is insufficient to bring viral replication under control and this phase is characterized by the presence of HBeAg, high levels of serum HBV DNA, elevation of serum aminotransferase levels, active inflammation and often fibrosis on liver histology [7]. Most patients in this phase remain asymptomatic, although some present with a symptomatic flare of hepatitis mimicking acute hepatitis or even with fulminant hepatic failure [8]. In some patients, these flares precede HBeAg seroconversion, namely the disappearance of HBeAg and the development of antibody against HBeAg, which culminates in remission of hepatitis activity [9]. In contrast, patients who fail to seroconvert and remain HBeAg positive continue to be at risk for progressive liver disease, which may result in cirrhosis and hepatic decompensation [10,11], depending on the duration of the chronic hepatitis and frequency and severity of flares [11,12]. In addition, persistent HBeAg positivity in older patients (e.g., >35 years) has been linked with increased risk of HCC [1]. Thus, spontaneous HBeAg seroconversion is an important landmark in the natural history of chronic HBV infection. One of the most important predictors of HBeAg seroconversion is a high aminotransferase level, a surrogate marker for vigorous host immune response.

In most patients, HBeAg seroconversion is accompanied by stabilization of hepatitis, which leads to the inactive carrier phase of the infection [13]. This is characterized by normalization of ALT levels, decreases in HBV DNA to low (<1000 copies/mL) or undetectable levels and, histologically, minimal to mild hepatitis. Most patients remain in this phase for many years, often for life, which is associated with a reduced risk of subsequent complications from HBV infection [14]. In the remaining patients, hepatitis activity may return, as evidenced by resurgence of HBV DNA and increased serum ALT. This reactivation of hepatitis may occur with or more commonly without reversion to HBeAg positivity. The latter circumstance, namely resumption of hepatitis activity with HBeAg negativity and anti-HBe positivity, is termed HBeAg-negative chronic hepatitis B. Classically, this is associated with mutations in the viral genome that enable viral replication without expressing HBeAg [15]. Importantly, these patients with reactivated hepatitis are at risk of progressive liver disease [16]. Because most, if not all, of these patients have gone through the HBeAg-positive chronic hepatitis phase, varying degrees of hepatic fibrosis are already present—some report cirrhosis in up to 40% of these patients [17,18].

The natural history of HBV infection is complex not only because of these multiple phases in which patients may present but also because of differences in the rate at which liver disease progresses. Table 19.2 summarizes determinants of disease progression, ultimately leading

to cirrhosis and/or HCC, in patients with chronic HBV infection. For HBeAg-positive patients, the central factor is the overall duration of hepatitic activity before HBeAg seroconversion. This tends to be seen in patients who remain e-antigen positive beyond 40 years of age, those with mildly and persistently abnormal ALT without seroconverting, and those with genotype C (compared to genotype B) [19,20]. For patients who are HBeAg negative, recent studies have shown that persistent viral replication is a key determinant of long term outcome.

Table 19.2 Predictors of progressive liver disease in chronic hepatitis B.

	HBeAg positive	HBeAg negative
Underlying event	Prolonged interval before e seroconversion	Persistent viral replication
Phase-specific risk factor	Age > 40 Mildly, persistently abnormal ALT Genotype (C > B)	HBV DNA Abnormal ALT Precore/BCP mutation
Overall risk factor	Male Alcohol Co-infection with HCV, HDV, HIV	

ALT, alanine transaminase; BCP, basal core promoter.

The single most important determinant here is serum HBV DNA level [21,22]. Figure 19.1 correlates serum HBV DNA levels and long term outcome. Figure 19.1a correlates serum HBV DNA with the incidence of HCC (%/year). For example, in patients whose HBV DNA is undetectable or low level, the risk of developing HCC is approximately 0.1%/year. This risk increases progressively such that patients whose HBV DNA is greater than 1 million copies/mL, the risk of HCC is greater than 1%/year or approximately 10% over the next 10 years. Figure 19.1b shows a similar correlation between serum HBV DNA levels and the incidence of cirrhosis. Similar to the risk for HCC, patients with undetectable or low level serum HBV DNA have low risk of cirrhosis, whereas patients who have serum DNA greater than 1 million copies/mL may have annual risk of cirrhosis of 2–3%/year or approximately 25% in the ensuing 10 years. In addition to serum HBV DNA levels, abnormal ALT and viral mutations such as precore or basal core promoter mutations have been associated with more advanced liver disease in patients with HBeAg-negative disease [16]. Finally, regardless of the HBeAg status, male patients tend to have more advanced liver disease, as well as those who consume excessive alcohol and those with concomitant infection with HCV, hepatitis D virus (HVD), and human immunodeficiency virus (HIV) [1].

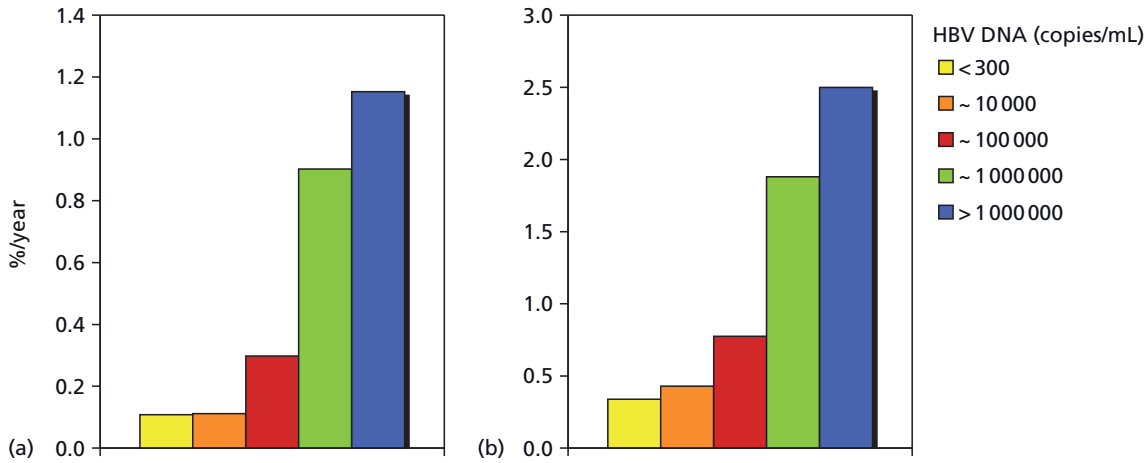

Figure 19.1 Correlation between serum hepatitis B virus DNA and incidence of (a) hepatocellular carcinoma (data from Chen *et al*. [22]) and (b) cirrhosis (data from Iloeje *et al*. [21]).

Table 19.3 Summary of three US recommendations for antiviral therapy.

	AASLD	US algorithm	NIH Consensus Panel
Treatment recommended			
HBeAg positive	ALT > 2 × ULN	ALT elevated HBV DNA > 20 000 IU/mL	Decompensated cirrhosis Cirrhosis or advanced fibrosis and high level viremia Prophylaxis before chemotherapy or immunosuppression Infants born to HBsAg-positive mothers*
HBeAg negative	ALT > 2 × ULN and HBV DNA > 20 000 IU/mL	ALT elevated HBV DNA ≥ 2000 IU/mL	
Treatment may be considered			
HBeAg positive	ALT 1–2 × ULN Biopsy +	ALT normal HBV DNA > 20 000 IU/mL	Immune-active disease without advanced fibrosis or cirrhosis
HBeAg negative	ALT 1–2 × ULN DNA 2000–20 000 IU/mL Biopsy +	ALT normal HBV DNA ≥ 2000 IU/mL Biopsy +	
Treatment not recommended			
HBeAg positive	ALT < ULN	ALT normal HBV DNA < 20 000 IU/mL	Immune-tolerant phase Inactive carrier or low replicative phase Latent HBV infection
HBeAg negative	ALT < ULN	ALT normal HBV DNA < 2000 IU/mL	

*Immunoglobulin and vaccination.
+Moderate/severe inflammation or > septal fibrosis.
AASLD, American Association for the Study of Liver Diseases; NIH, National Institutes for Health; ULN, upper limit of normal; ALT, alanine transaminase.

Indications for Therapy

Table 19.3 compares recommendations put forth by US organizations for the treatment of chronic HBV infection, including the guidelines recommended by the American Association for the Study of Liver Diseases (AASLD) [23], the so-called US algorithm produced by a group of expert hepatologists [24], and the National Institutes of Health (NIH) Consensus Panel [25]. The former two provide specific parameters for indications of treatment based on HBeAg status, ALT activity, and serum HBV DNA levels. The NIH Panel only identified broad categories of patients for antiviral treatment. Insisting on indisputable evidence for clinical benefits, it also made the most conservative recommendation of the three organizations. For example, other than chemotherapy or immunosuppression settings, the Panel restricted antiviral treatment to patients with decompensated cirrhosis or those with advanced fibrosis and cirrhosis and active viral replication. Treatment was left as optional for other patients with immune-active disease, which is the majority of patients the AASLD guideline and US algorithm focused on. These latter two recommended treatment in patients with evidence of liver inflammation (abnormal ALT) and viral replication (high levels of serum HBV DNA). With regard to whom not to treat, there is a fairly good consensus among the three organizations in that patients without evidence of active disease are best observed and monitored.

From Table 19.3, it is evident that the specific cut-off values for ALT and HBV DNA differ between the recommendations made by the AASLD and US algorithm, and that the AASLD version tends to employ narrower criteria to determine treatment candidacy. Which criteria should be adopted in practice remains subjective. This is where the understanding of the natural history of HBV infection is helpful in treatment decisions. In these authors' practice, rather than using one set of criteria to determine treatment indication, an attempt is made to

characterize the patient in light of the phases of infection. In general, patients who are in immune tolerant or inactive carrier phase of the infection are not treated. Patients who have active liver disease, be it HBeAg positive or negative, are prime targets for antiviral therapy. In borderline cases, a liver biopsy is helpful. In HBeAg-positive patients, those with active inflammation and high serum ALT, but without significant fibrosis (stage 0–1 of 4), may be observed for some time (6 months–1 year), as these patients may experience natural HBeAg seroconversion. In other patients, antiviral treatment can be begun right away, including in HBeAg-negative patients with advanced fibrosis and high serum HBV DNA.

Therapeutic Options

Table 19.4 summarizes antiviral agents that have been approved for treatment of chronic HBV infection in the USA. Of the three categories [nucleosides, nucleotides, and interferons (IFNs)], entecavir, tenofovir, and pegylated IFN-α 2a are considered the first-line therapy [26–30]. These agents are considered to be potent and least prone to the development of resistance. Secondary agents include lamivudine, telbivudine, and adefovir [31–33]. Lamivudine and telbivudine have intermediate to high potency against HBV, but they are limited by the propensity to allow resistant mutants. Adefovir is limited by its low potency, intermediate resistance profile, and potential nephrotoxicity. If IFN is to be used, pegylated IFN is preferred because of the convenience of once weekly, as opposed to daily or thrice weekly, injection.

Table 19.4 Available antiviral drugs for hepatitis B virus.

	Nucleosides	Nucleotides	Interferon
Desirable (high potency and low resistance)	Entecavir	Tenofovir	Pegylated interferon
Less desirable (low potency or high resistance)	Lamivudine Telbivudine	Adefovir	Standard interferon

Figure 19.2 compares the potency of these anti-HBV agents as represented by the proportion of patients with undetectable HBV DNA after 1 year of therapy in their respective registration trials. It should be noted that these data are not obtained from face-to-face comparison of these agents and therefore must be regarded as general comparison. Among HBeAg-positive patients, 13–76% of patients in registration trials achieved undetectable HBV DNA after a year of therapy [26,28,29,31,32]. Similarly, among HBeAg-negative patients, undetectable HBV DNA could be achieved in between 63% and 93% of patients [27,28,30,31,33]. The percentage in these latter patients is higher because in general, HBeAg-negative

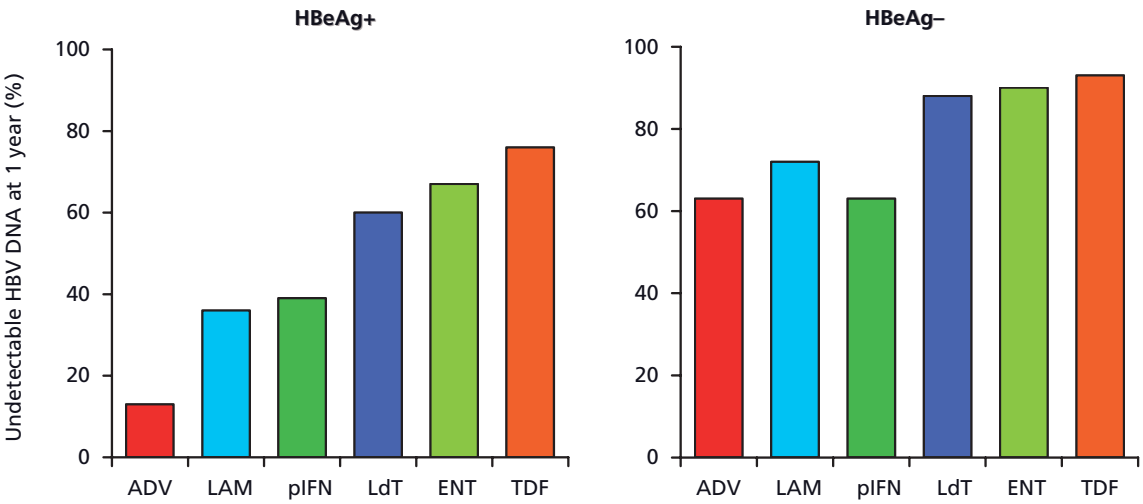

Figure 19.2 Comparison of potency of anti-hepatitis B virus (HBV) agents (data from Chang *et al*. [26]; Lai *et al*. [27,31]; Marcellin *et al*. [28,30]; Lau *et al*. [29]).

patients tend to have low levels of HBV DNA before therapy.

Conclusion

The main decisions to be made by a clinician managing a patient with chronic HBV infection are: (1) when to consider therapy and (2) what agent(s) to use. With the advent of potent antiviral agents with low susceptibility to resistant mutation, these decisions have been made somewhat easier. However, as was discussed above, there is still some disagreement about treatment candidacy. As with medicine in general, individual patient management decisions must be based on risks and benefits of treatment. Figure 19.3 summarizes the factors that are considered in those decisions. On the left-hand side of Figure 19.3 are shown the benefits of antiviral therapy, which are mainly avoidance of long term complications of HBV infection. Data have shown that antiviral therapy can reduce or even eliminate the risk of cirrhosis. Limited data exist that antiviral therapy can also reduce the risk of HCC. On the other hand, premature antiviral therapy may have its downside. There is a potential concern for the safety of long term antiviral therapy. To the degree that HBV infection is not curable and many patients may remain on therapy for decades, the issue of long term safety remains to be determined in an ongoing fashion. It is reassuring, however, that to date, no significant long term safety issues have emerged. More realistically, the potential disadvantages of antiviral therapy are the possibility of antiviral resistance and cost. Although the innate susceptibility to resistant mutation is lower with current first-line agents, patient compliance is a major risk factor for antiviral mutations. Patients who are exposed to intermittent antiviral courses are at higher risk of developing mutations. Non-adherence may be inadvertent, intentional or driven by the cost. These antiviral agents are quite expensive, particularly if prescription coverage is limited. The long term cumulative expense associated with long term antiviral therapy needs to be considered before embarking upon antiviral therapy that may last for decades.

Case continued

Returning to the case of Mrs T, all the above factors were discussed. Although Mrs T does not have advanced fibrosis and therefore is unlikely to face the prospect of developing cirrhosis in the near future, she does have a realistic risk of HCC given her family history. It is well recognized that HBV may cause HCC in the absence of advanced fibrosis.

Mrs T was apprehensive of her cancer risk, particularly given the rising DNA levels. On the other hand, she has a secure health insurance with prescription coverage. She had no other co-morbid conditions that may make safety a predominant issue. Therefore, an antiviral therapy with a high potency and low resistance profile was started. To date, Mrs T has been doing well with normal ALT and now undetectable HBV DNA. She remains on an HCC surveillance program.

Management of Chronic Hepatitis C

Since IFN therapy was introduced for chronic HCV infection in the early 1990s, the results of antiviral therapy for hepatitis C have improved significantly. However, for the past several years, the main armamentarium against hepatitis C has remained unchanged with a pegylated IFN and ribavirin combination. Although new hepatitis C-specific agents are looming on the horizon, as of present, the state-of-art therapy for hepatitis C remains pegylated IFN and ribavirin in the right dose for the right duration. The following case raises several issues that are relevant to this discussion.

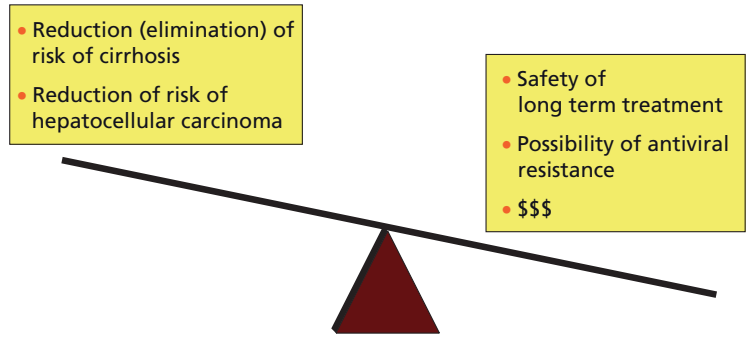

Figure 19.3 Factors to consider in treatment decisions in hepatitis B.

Case

Mr P is a 50-year-old mechanic who was diagnosed with chronic hepatitis C in 1996. He was determined to have genotype 1A virus. He then was treated with standard IFN and ribavirin (doses unknown), the treatment of choice at that time. After 6 months of therapy, his HCV RNA remained detectable and the treatment was discontinued. In 2001, he had a liver biopsy to monitor the progression of his liver disease, which showed minimal activity (grade 1 of 4) and mild fibrosis (stage 2 of 4). He underwent annual follow-ups. As of 2007, he was feeling well with no symptoms of liver disease. On exam, his height was 1.88 m (6′ 2″) and weight 106.6 kg (235 lb) [body mass index (BMI) 30.2]. He was anicteric. He had no cutaneous stigmata of chronic liver disease. In his abdomen, the liver and spleen were not palpable. There was no evidence of ascites or peripheral edema. Table 19.5 summarizes laboratory data.

Although his liver enzymes were noticeably elevated, other biochemical parameters suggest intact liver synthetic function. However, the most alarming element was his platelet count and the splenomegaly, as these suggest advanced fibrosis or cirrhosis causing portal hypertension and hypersplenism. Another biopsy was performed because of these concerns, which showed thick fibrous septa with nodular regeneration as well as abundant macrovesicular steatosis. In a high power view, interface activity as well as steatosis was apparent.

Weight-Based Therapy

Pegylated IFN-α 2b is dosed based on the patient's weight (1.5 μg/kg/week), whereas pegylated IFN-α 2a is recommended to be given at a fixed dose (180 μg/week) [34,35]. However, in the registration trial for the latter, a higher response rate was seen in patients who weighed less than 75 kg (1.9-fold increase in response rate) [36]. With regard to ribavirin dose, an earlier *post-hoc* analysis suggested a near linear relationship between ribavirin exposure (mg ribavirin/kg body weight) and the response rate [37]. The approved ribavirin dose to be used in conjunction with pegylated IFN-α 2b is fixed at 800 mg/day, whereas that for pegylated IFN-α 2a is 1000 mg if body weight is less than 75 kg and 1200 mg if 75 kg or higher for genotype 1 or 4 patients, and 800 mg uniformly for genotype 2 or 3 patients [34,35].

Table 19.5 Laboratory data for Mr P.

Hemoglobin 14.5 g/dL
WBC 5100/mm^3
Platelets 124 000 mm^3
AST 210 IU/mL
ALT 280 IU/mL
Albumin 4.5 g/dL
Total bilirubin 0.8 mg/dL
Ultrasound: diffuse fatty infiltration, mild splenomegaly

ALT, alanine transaminase; AST, aspartate transaminase; WBC, white blood cells.

Figure 19.4 summarizes the results of the WIN-R trial [38]. The trial prospectively compared weight-based ribavirin dosing versus fixed dosing. The weight-based dose for ribavirin was calculated to be 800 mg for patients weighing less than 65 kg, 1000 mg if 65–85 kg, 1200 mg if 85–105 kg, and 1400 mg if greater than 105 kg. On the other hand, in the fixed ribavirin group, ribavirin was given at 800 mg/day. For genotype 1 patients, the fixed and weight-based-dose groups experienced a different pattern of response. In the weight-based group, there was no difference in the response rate by body weight. There was a progressive reduction in the response rate with increasing body weight in the fixed-dose group. For genotype 2 or 3 patients, it was noted that the response rate in general was higher than genotype 1 patients as expected. Again, there was no difference in the response rate in the weight-based-dose group, whereas in the fixed-dose group, the group with lowest body weight had a significantly higher response rate than patients with higher body weight. These data suggest that certainly for genotype 1 patients, weight-based dosing of ribavirin is essential. It also challenges the conventional wisdom that 800 mg of ribavirin is sufficient for all genotype 2 and 3 patients.

A feature that is commonly observed in patients who are heavy is concomitant non-alcoholic fatty liver disease (NAFLD), as was seen in the case of Mr P. Several papers have been published that indicate that steatosis and hepatitis C may be synergistic in producing liver fibrosis [39,40]. For example, in an Italian cohort of 180 patients, those who did not have steatosis had a mean fibrosis stage of 1.2 of 4 [41]. In contrast, patients who had steatosis of grade 3 or 4 had more advanced fibrosis (fibrosis stage 2.7 of 4), whereas those who had a milder degree (grade 1–2) of steatosis had an intermediate result (fibrosis stage of 1.8 of 4). Not only does concomitant NAFLD portend a worse fibrosis, it may also decrease responses to antiviral therapy. In a *post-hoc* analysis of a randomized trial, steatosis was associated with a lower rate of

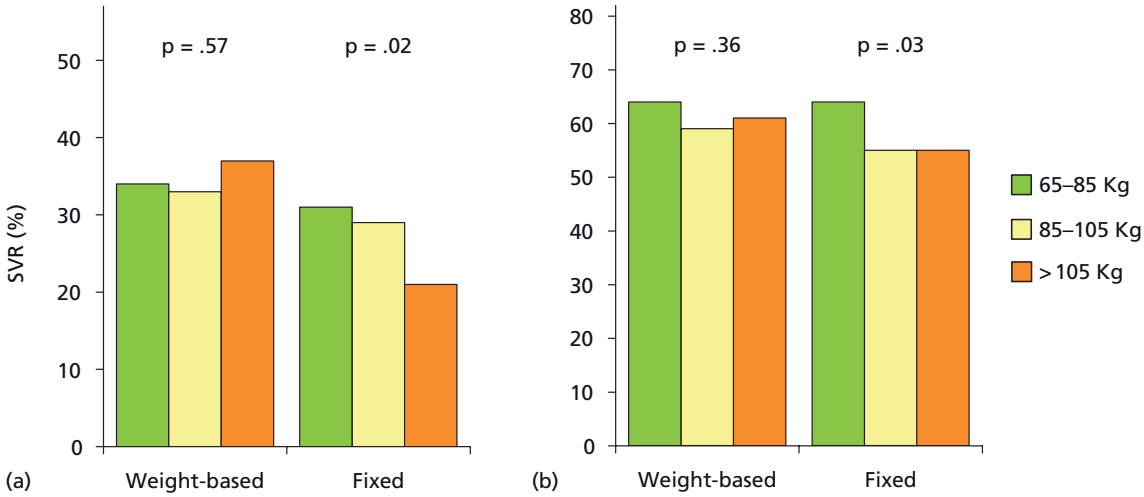

Figure 19.4 Optimal daily ribavirin dosing with pegylated interferon-α 2b 1.5 μg/kg/week for (a) genotype 1 and (b) genotype 2/3 ('WIN-R' trial). Weight-based dose: 800 mg if < 65 kg; 1000 mg if 65–85 kg; 1200 mg if 85–105 kg; 1400 mg if 105 kg. Fixed dose: 800 mg (data from Jacobson *et al*. [38]). SVR, sustained viral response.

sustained viral response (SVR) [42]. Among genotype 1 patients, SVR was achieved in 40% (27 of 67) of patients with steatosis compared to 63% (53 of 85) in those without ($p < 0.01$). Similarly, among patients with genotype 2 or 3 ($n = 66$), all without steatosis ($n = 15$) achieved SVR, whereas all ($n = 6$) of those who failed to reach SVR had steatosis. These data suggest that as hard as it is for NAFLD patients to lose weight, in patients with concomitant HCV infection, weight reduction may have multiple benefits, including slower disease progression and better response on therapy.

Use of On-Treatment Response to Determine Optimal Duration of Therapy

Figure 19.5 illustrates several definitions of on-treatment response. Although the terminology and exact definition have not been officially established, the following concepts are useful in determining the optimal duration of therapy. Rapid viral response (RVR) is commonly defined as disappearance of HCV RNA by 4 weeks of therapy. Early viral response (EVR) has been used since the inception of the pegylated IFN products. Its definition includes undetectable HCV RNA or a 2-log drop compared to the baseline at 12 weeks. EVR can now be divided into two categories. A complete EVR (c-EVR) is disappearance of HCV RNA between 4 and 12 weeks of therapy. A partial EVR (p-EVR) is the loss of HCV RNA between 12 and 24 weeks of therapy after having achieved a 2-log drop of HCV RNA at 12 weeks compared to the baseline. A patient who fails to achieve p-EVR is generally considered a non-responder.

As these definitions involve undetectable HCV RNA, it is critically important that the sensitivity of HCV RNA assays is clearly understood. Most current assays have a lower detection limit than previous polymerase chain reaction (PCR) assays. The current standard for a qualitative HCV RNA test usually has a detection limit of 50 IU/mL. Real-time PCR assays or transcription-mediated amplification (TMA) are more sensitive assays. At Mayo Clinic Rochester, HCV RNA quantitation is performed using the Taqman assay which has a dynamic range between 10 and 50 000 000 IU/mL. Thus, if a less sensitive HCV RNA assay is used, some patients with undetected low level viremia may be misclassified. It is important for an individual clinician to be familiar with the RNA assay being used in his or her laboratory.

Tailored Therapy for Genotype 1 Patients

Figure 19.6 shows the importance of the rapidity with which the HCV RNA titer decreases on therapy. In a

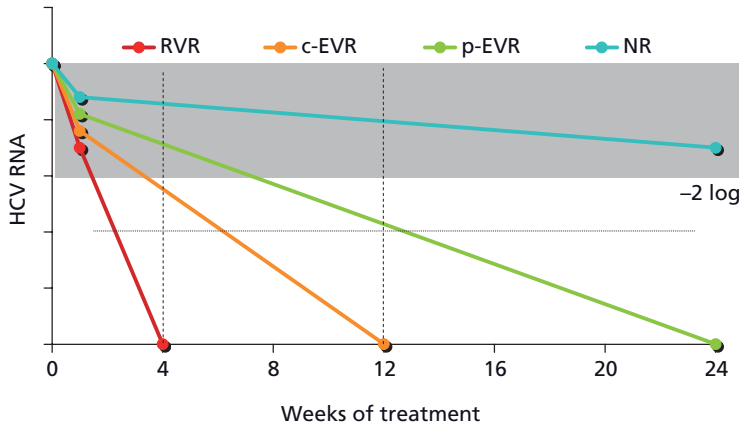

Figure 19.5 Definition of on-treatment responses. RVR, rapid viral response; c-EVR, complete early viral response; p-EVR, partial early viral response; NR, no response.

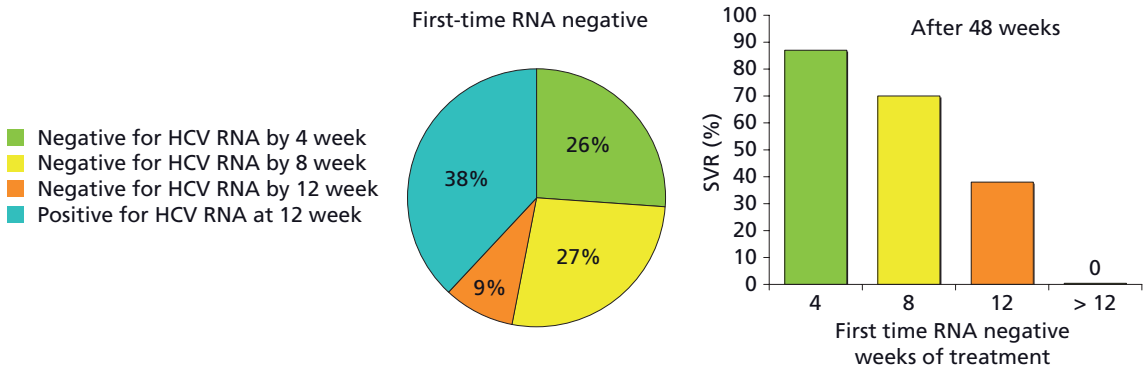

Figure 19.6 Impact of rapid viral response on sustained viral response (SVR) in genotype 1, treatment-naïve patients. Results of 48 weeks of pegylated interferon-α 2b 1.5 µg/kg/week or pegylated interferon-α 2a 180 µg/week + ribavirin 1000 mg/day (<75 kg) or 1200 mg/day (>75 kg) (data from Mangia et al. [43].

study which used weight-based ribavirin (1000 mg/day for patients weighing < 75 kg and 1200 mg/day for those weighing > 75 kg); of 237 patients receiving the standard 48-week-long course of therapy, 26% achieved RVR (negative for HCV RNA by 4 weeks) [43]. An additional 27% were negative for HCV RNA by 8 weeks and another 9% by 12 weeks. The remaining 38% remained HCV RNA positive at week 12. As Figure 19.6 clearly shows, the best response rate was achieved in patients who belonged in the RVR category with an 87% SVR after 48 weeks of therapy. Patients who became HCV RNA negative at 8 weeks had a 70% SVR rate and in those who achieved HCV RNA negativity at 12 weeks, the SVR rate was 38%. In this particular study, if HCV RNA remained positive beyond 12 weeks, none of the patients achieved SVR. In addition to demonstrating the importance of RVR, this study suggested that the duration of therapy in genotype 1 patients may be varied according to their on-treatment response. Among those achieving RVR, therapy for 24 weeks and 48 weeks resulted in SVR rates of 77% versus 87%, respectively ($p = 0.12$), whereas in partial responders, SVR was more common after 72 weeks of therapy (63%) than after 48 weeks (38%), although this difference did not reach significance ($p = 0.07$).

Additional studies have examined utilizing on-treatment responses to determine the optimal treatment duration for genotype 1 patients. In an earlier trial, four

therapeutic arms were compared: (1) 24 weeks of combination therapy of pegylated IFN-α 2a (180 μg once weekly, identical to all other groups) with low-dose ribavirin at 800 mg/day; (2) 24 weeks of therapy with standard-dose ribavirin (1000–1200 mg/day); (3) 48 weeks of low-dose ribavirin; and (4) 48 weeks of standard-dose ribavirin [44]. A *post-hoc* analysis of the study showed that in patients who achieved RVR, the duration and dose of ribavirin did not matter and high rates of SVR (73–91%) could be obtained [45]. On the other hand, in patients who did not achieve RVR, there was progressive increase in the response rate according to the duration of therapy as well as the ribavirin dose. These data confirm the benefit of RVR and suggest that treatment may be shortened in genotype 1 patients who achieve RVR.

These findings were further verified in another prospective study by Ferenci *et al.* [46] in which patients with genotype 1 or 4 who achieved RVR were treated for 24 weeks with pegylated IFN-α 2a in combination with weight-based ribavirin. The overall SVR rate in genotype 1 patients was 79%. Those patients with high viral load at baseline (>800 000 IU/mL) and those with advanced fibrosis (Metavir stages 3 or 4 of 4) had lower response rates (SVR 67% and 75%, respectively).

At other end of the spectrum, accumulating evidence suggests that some patients may do better with longer therapy (i.e., 72 weeks). A German study randomized patients to either 48 or 72 weeks of therapy with pegylated IFN-α 2a at 180 μg/week in conjunction with ribavirin (800 mg/day) [47]. The overall response rate was similar in the two groups (53% with 48 weeks of therapy and 54% with 72 weeks). In a subgroup analysis, while the response rate did not differ between the two groups in patients who cleared their RNA before 12 weeks, patients whose RNA became negative for the first time at 24 weeks (p-EVR) with 72 weeks of therapy had a significantly higher response rate than those with 48 weeks of therapy (29% versus 17%, p = 0.04). In another study from Spain, a total of 510 patients were treated with pegylated IFN-α 2a (180 μg/week) with ribavirin (800 mg) [48]. Patients who did not achieve RVR (i.e., HCV RNA positive at 4 weeks) were randomized to 48 versus 72 weeks of therapy. An SVR was significantly more common in the 72-week group (44%) compared to the 48-week group (28%). The latest study by Pearlman *et al.* randomized patients who achieved p-EVR to 48 versus 72 weeks of therapy [49]. SVR rate was significantly higher (p = 0.03) in patients receiving 72 weeks of treatment (38%) compared to those receiving 48 weeks of treatment (18%). These studies are in agreement that patients who are slow to respond to therapy do benefit from 72 weeks of extended treatment. Patients who do not clear HCV RNA by 24 weeks of therapy are still considered non-responders who are unlikely to respond even with 72 weeks of therapy.

Conclusion

Putting all these data together, these authors generated an algorithm by which patients with genotype 1 hepatitis C are treated at Mayo Clinic. Figure 19.7 summarizes the approach. At the outset of therapy, it is important that appropriate doses of pegylated IFN and ribavirin are

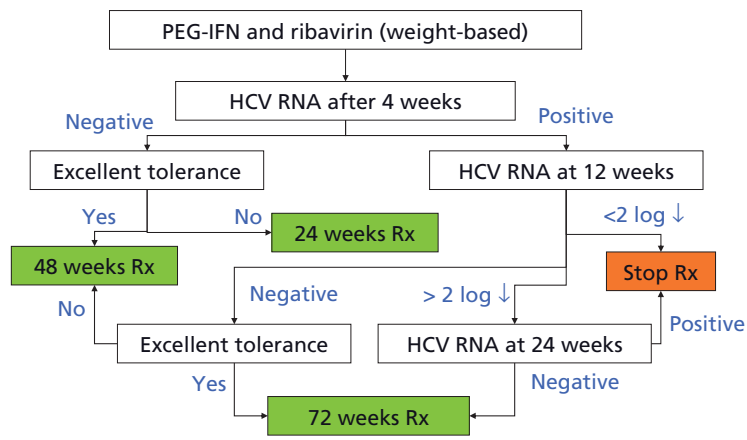

Figure 19.7 Management algorithm for genotype 1 patients (reproduced courtesy of the Mayo Clinic Rochester).

used. Once therapy is begun, serum HCV RNA is tested at 4 weeks. If this is negative, the patient has achieved a rapid viral response (RVR). At that point, if the patient is tolerating therapy well, continuation to 48 weeks of therapy in total would be the standard approach. However, if the patient's tolerance is problematic, it would be reasonable to shorten the duration to 24 weeks and to expect to have a reasonable degree of sustained response. As discussed above, patients who have high viral load at the beginning (e.g., >600 000 IU/mL) or advanced fibrosis (stage 3–4 of 4), standard duration of 48 weeks is preferred. In patients who fail to achieve RVR, the next landmark is HCV RNA level at 12 weeks. If there is less than a 2-log drop in the HCV RNA, the therapy should be stopped because the patient has not achieved early viral response (EVR). If HCV RNA at 12 weeks is negative, the patient may stop the treatment at 48 weeks, unless there is a high risk of relapse (e.g., cirrhosis) for which the treatment may be extended to 72 weeks on a case-by-case basis. On the other hand, for patients who achieve p-EVR, namely a 2-log drop in HCV RNA at 12 weeks and negativity at 24 weeks, our approach would be to continue treatment for 72 weeks. Patients who remain HCV RNA positive at 24 weeks are unlikely to respond to an extended duration of therapy and therefore the therapy is stopped at that point.

Tailored Approach for Genotypes 2 and 3

The current standard approach for patients with genotype 2 or 3 is to use 24 weeks of combination therapy with standard doses of pegylated IFN and 800 mg of ribavirin daily [50]. Recently, several studies have examined whether the treatment duration could be shortened based on on-treatment response. A study by Von Wagner *et al.* took treatment-naïve genotype 2 or 3 patients and instituted pegylated IFN-α 2a at 180 μg/week and weight-based ribavirin (800–1200 mg/day) [51]. Patients who achieved RVR were randomized to receive standard duration of therapy for 24 weeks versus shortened therapy for 16 weeks. Patients who did not achieve RVR received the 24-week standard therapy. The SVR rate was equivalent between patients who were randomized to standard versus shortened duration (80% and 82%, respectively). On the other hand, patients who did not achieve RVR only had an SVR of 36% even with the 24-week therapy. Another randomized trial compared 12 weeks of therapy in patients who achieved RVR versus 24 weeks [52]. This trial utilized pegylated IFN-α 2b at a dose of 1.0 μg/kg plus ribavirin at a dose of 1000–1200 mg (weight based). In patients who achieved RVR, the SVR rate was 85% in the 12-week arm compared to 91% in the 24-week arm (p = NS). In patients who did not achieve RVR, the response rate was 48–64% after 24 weeks.

The largest trial that has been performed on this topic to date included 1469 patients who were treated with IFN-α 2a at 180 μg/week in conjunction with ribavirin 800 mg/day [53]. In Figure 19.8, SVR rate is presented by the RVR status. In patients who achieved RVR, response to therapy was 5–7 percentage points higher with 24 weeks of therapy than 16 weeks. These differences were statistically significant. Moreover, in patients who

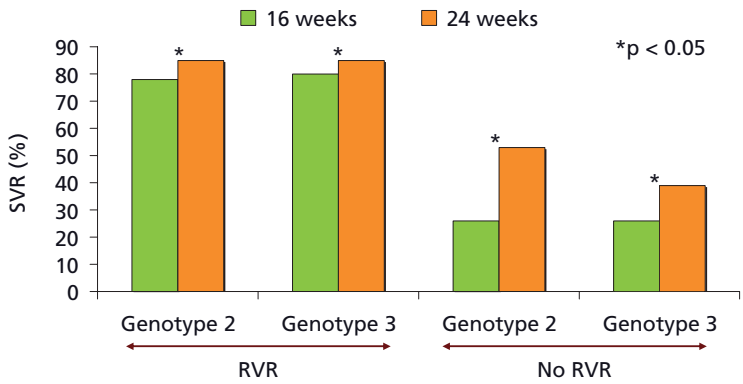

Figure 19.8 Shortened duration therapy for genotype 2/3 patients. Results of a randomized controlled trial comparing 16 and 24 weeks of treatment with pegylated interferon-α 2a (180 μg/week) + ribavirin (800 mg/day) (data from Schiffman *et al.* [53]). RVR, rapid viral response; SVR, sustained viral response.

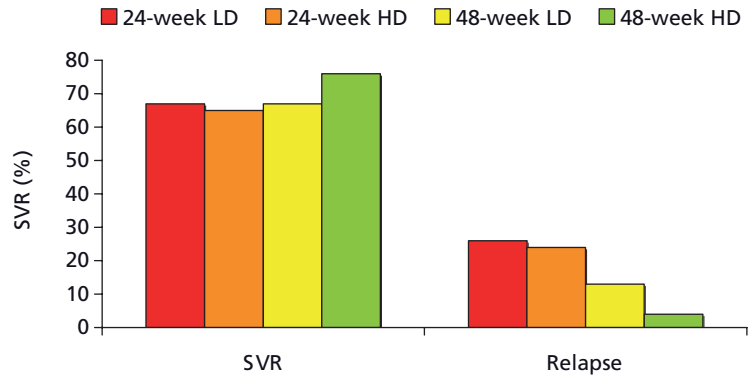

Figure 19.9 Longer duration of therapy for genotype 2/3 patients not achieving a rapid viral response (data from Willems *et al*. [54]). LD, low dose (ribavirin 800 mg/day); HD, high dose (ribavirin 1000–1200 mg/day).

did not achieve RVR, the difference in response rate was even greater in both genotypes 2 and 3. Thus, there is apparent disagreement as to the equivalence of results with shortened duration of therapy for genotype 2 and 3 patients. The largest trial indicates that 24-week therapy is superior. whereas previous smaller trials seem to show that response rates are equivalent in patients who achieve RVR. The difference between these two sets of results may reflect that the last trial used fixed-dose ribavirin at 800 mg, whereas the other trials used weight-based ribavirin. It is possible that for shortened therapy to be successful in genotype 2 and 3 patients, higher doses of ribavirin than the standard 800 mg may be necessary.

Whether there are patients with genotype 2 or 3 who may benefit from longer treatment is less well defined. In a *post-hoc* analysis of a randomized trial that compared low and standard-dose ribavirin given for 24 versus 48 weeks, it appeared that standard-dose therapy of 48 weeks in duration was superior in patients who do not achieve RVR [54]. In Figure 19.9, patients receiving 48 weeks of standard-dose therapy achieved an SVR rate of 76%, with a higher rate of SVR as well as minimal relapse rate. In those patients who did not achieve RVR, it appeared that standard-dose therapy of 48 weeks in duration was superior with higher rate of SVR as well as minimal relapse rate. Although these results must be confirmed in a prospective study, they do suggest that prolonged therapy might be effective in increasing SVR rates in genotype 2 or 3 patients who fail to achieve RVR at week 4.

Summary

Figure 19.10 summarizes these authors' management approach for genotype 2 and 3 patients at Mayo Clinic.

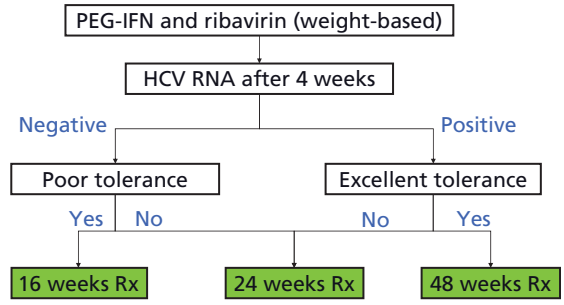

Figure 19.10 Management algorithm for genotype 2/3 patients (reproduced courtesy of the Mayo Clinic Rochester).

Full-dose pegylated IFN and weight-based ribavirin are determined using the same method as for genotype 1 patients. The RVR status is determined at 4 weeks of therapy. If the patient achieves RVR and has poor treatment tolerance, it may be reasonable to truncate the therapy at 16 weeks. For patients who achieve RVR and have good tolerance, a 24-week duration is certainly reasonable. If patients do not achieve RVR, continuation of therapy for 48 weeks may be considered, especially if there is the suggestion of poor response, such as high viral load, genotype 3, and advanced fibrosis. In patients who do not have those risk factors and the tolerance to treatment is suboptimal, treatment is stopped at 24 weeks.

Take-home points

- Patients with chronic hepatitis B virus infection with active liver disease, regardless of their HBeAg status, are treatment candidates.

- Approved first-line treatment agents for chronic hepatitis B include entecavir, tenofovir, and pegylated interferon-α 2a.
- In determining the optimal dosing for pegylated interferon and ribavirin therapy for chronic hepatitis C, patient's body size is an important factor to take into account.
- Assessment of on-treatment response, such as rapid viral response (undetectable HCV RNA at week 4), is useful in tailoring the duration of therapy.

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CHAPTER 20
Bacterial and Other Non-viral Infections of the Liver

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Summary

The liver parenchyma and biliary tree may be involved in infections caused by bacteria, fungi, and parasites. These occur by spread from contiguous organs or hematogenous seeding, or by toxic effects from distant infections and their treatment. The clinical presentations of these infections vary from no symptoms to hepatitis, abscess, granulomas, biliary obstruction, and liver failure. This chapter summarizes the various infections of the liver and biliary tree and their diagnosis and treatment.

Pyogenic Liver Abscess

Microbiology

The most frequently found organisms are *Escherichia coli* and *Klebsiella pneumoniae*, streptococci, and anaerobes [1–3]. *Bacteroides* species is the most common anaerobe [4]. *Streptococcus milleri* is also reported. It is common to grow more than one organism from an abscess aspirate even if blood cultures yield only one pathogen [1]. There has been an increase in resistant bacteria and *Candida* spp., most likely secondary to use of biliary stents and long courses of antibiotics [5].

A unique syndrome of liver abscess secondary to a virulent *K. pneumoniae* has been reported mainly in South-East Asia with dissemination to the eye and central nervous system (CNS) [6,7]. This infection is caused by capsular K1/K2 strains, which have higher resistance to phagocytosis. There is a high prevalence of diabetes in affected patients.

Practical Gastroenterology and Hepatology: Liver and Biliary Disease, 1st edition. Edited by Nicholas J. Talley, Keith D. Lindor and Hugo E. Vargas.

Epidemiology

Pyogenic liver abscess is a serious infection with an incidence of 15/100 000 to 44.9/100 000 patient admissions [1,8]. Earlier series showed higher prevalence in males but more recent series reported equal sex distribution [9]. Most cases occur in the sixth to seventh decades [2,9]. In one series, single and multiple abscesses occurred in 58% and 42%, respectively: 66% in the right lobe, 8% in the left lobe, and 26% in both lobes [10]. Solitary abscesses are usually located in the right lobe whereas multiple abscesses are found in both sides [11].

Pathogenesis

Mechanisms for liver abscess formation include spread of infection from the biliary tract or the abdomen, hematogenous infection, and unclear source or cryptogenic etiology [8]. Biliary and cryptogenic etiologies are more common; up to a third of cases may be cryptogenic [12]. In the pre-antibiotic era, patients tended to be young and the major cause was appendicitis. Patients now tend to be older and are more frequently those with benign or malignant biliary obstruction and extrahepatic malignancies [1,3,12]. Intra-abdominal diseases that may lead to liver abscess include diverticulitis, appendicitis, bowel perforation, and inflammatory bowel disease [9]. Liver

abscess can form after transarterial chemoembolization of hepatocellular carcinoma [2]. Multiple liver abscesses are associated with biliary tract disease such as stones and cholangiocarcinoma [11]. Underlying conditions associated with liver abscess are diabetes mellitus, malignancy, and hypertension [4,8].

Clinical Features

Symptoms can be non-specific, including fever and right upper quadrant (RUQ) abdominal pain, often with serum alkaline phosphatase elevation [1,3,12]. Low albumin, leukocytosis, and increased alanine transaminase levels are common. The classic triad of jaundice, fever, and RUQ pain is uncommon [9]. Intra-abdominal complications include rupture of the abscess into the abdomen, biliary or gastrointestinal tract, and portal or mesenteric vein thrombosis [8]. Mortality has been reported in patients who developed sepsis, liver and multiorgan failure, and mesenteric vein thrombosis [4]. The mortality is higher with multiple liver abscesses [1,9]. Malignancy was found to be an independent risk factor for mortality [2].

Diagnosis

Radiological testing using abdominal computed tomography (CT) and ultrasonography is crucial [1] (Figure 20.1). Half the patients have a positive blood culture and three-quarters have a positive culture of aspirate of the abscess. A chest radiograph may show atelectasis, pleural effusion, or elevated right diaphragm [8,9,11].

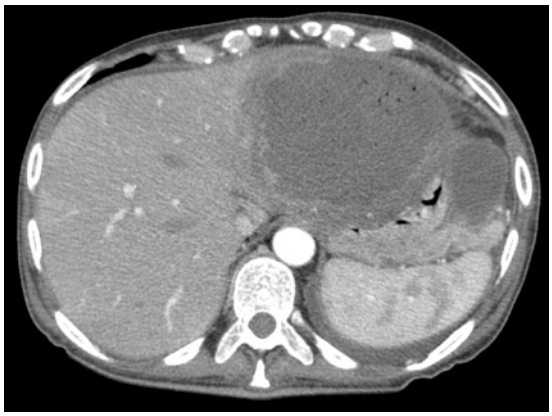

Figure 20.1 CT scan showing pyogenic liver abscess in left lobe.

Treatment

In general, antibiotics and abscess drainage are indicated. Duration of antibiotic treatment is not established, but some have administered intravenous antibiotics for 6 weeks or longer [2]. Choice of antibiotics is determined by culture and susceptibility results, and includes third-generation cephalosporins, cefoxitin, ticarcillin–clavulanate, piperacillin–tazobactam, ampicillin–sulbactam, ciprofloxacin, levofloxacin, imipenem, and meropenem. Metronidazole is usually added to cover possible amebic abscess. Ultrasound-guided needle aspiration is useful as a diagnostic and therapeutic measure [2]. A drain is left until purulent fluid stops draining. Drainage of multiloculated or multiple abscesses is more complicated and sometimes only the large abscess cavity can be drained [1]. Surgery may be necessary, especially with multiloculated abscesses, those that involve the left lobe of the liver, or those accompanied by intra-abdominal disease [12]. When significant necrosis of the liver occurs, segmental hepatectomy is indicated [11].

Pylephlebitis

Septic thrombophlebitis of the portal vein or of one of its tributaries is a complication of intra-abdominal infection, and may be associated with solitary or multiple liver abscesses. In the pre-antibiotic era, it was relatively common in young individuals who had acute appendicitis. It is now a rare condition that still carries high morbidity and mortality mostly due to delay in diagnosis, and thus should be considered in the right clinical setting. The most common condition associated with pylephlebitis is diverticulitis; others are malignancy, cholecystitis, abdominal and pelvic infection, pancreatitis, and hypercoagulable states [13]. Presenting symptoms may include fever, chills, abdominal pain, and distension [14].

In a review of 19 cases, 10 developed liver abscesses (8 multiple, 2 solitary) and 2 developed pulmonary embolism; the mortality rate was 32% [15]. Diagnosis was achieved by ultrasonography and CT. Bacteria involved are Gram negatives, streptococci, and anaerobes, and empiric antibiotics should cover these organisms. Anticoagulation may be considered, but its indication is still under debate.

Amebic Liver Abscess

Microbiology

Entameba histolytica has two forms. The tetranucleated cyst is the form that is ingested and the motile trophozoite is formed in the terminal ileum or colon. *E. histolytica* can be differentiated from *E. dispar* and *E. moshkovskii*, which are not pathogenic, by molecular techniques [16].

Epidemiology

Amebiasis is endemic in temperate and tropical climates such as India, Egypt, and South Africa [17]. There are 40 000–100 000 deaths from *E. histolytica* every year. In the USA, cases of amebiasis are diagnosed in immigrants and travelers to endemic countries. Infection usually results from ingestion of contaminated food or water [16]. There has been a significant increase in transmission among gay men. A report from the USA described only two of 34 000 HIV-positive individuals with invasive *E. histolytica* disease [18]. Reports from Japan, Taiwan, Korea, and Australia documented significant increases in incidence in gay men [19]. The increased incidence is most likely due to anal–oral sex practices and the higher prevalence of this parasite in the Asia–Pacific countries [19].

Pathogenesis

The trophozoites attach to and then invade the colonic epithelium into the submucosa, causing "flask-shaped ulcers" via various proteolytic enzymes and inflammatory cells; this results in diarrhea and destruction of tissue in the bowel [16]. It is believed that the trophozoites reach the liver through the portal circulation, thereby initiating the formation of an abscess.

Clinical Features

Infection with *E. histolytica* may be asymptomatic, but an estimated 4–10% of patients with asymptomatic infection will develop invasive disease each year [16]. A liver abscess is the most common extraintestinal manifestation. Patients may present with or without amebic colitis, and the exposure may have occurred months or even years before presentation with liver abscess. Symptoms and signs include diarrhea (possibly bloody), abdominal pain with RUQ tenderness, hepatomegaly, fever, cough, weight loss, increased alkaline phosphatase, and leukocytosis. Usually there is a solitary abscess in the right hepatic lobe; less common is a left lobe abscess [17]. Bacterial superinfection and sepsis may occur and would require antibiotics against gut organisms and staphylococci. Spread to neighboring structures may cause infection of the diaphragm, subdiaphragmatic area, pleura, lungs, and pericardium, causing fistulas and purulent collections [17].

Diagnosis

In the proper clinical presentation with compatible radiology, the finding of erythrocyte-containing trophozoites is diagnostic of *E. histolytica* infection [16,20]. Trophozoites may be found at the edge of the liver abscess, but usually not in the central necrotic portion (Figure 20.2). Ultrasonography and CT demonstrate a mass lesion. Serology is positive in the presence of *E. histolytica* but not in the presence of *E. dispar*. The indirect hemagglutination test (IHA) is almost 100% positive in hepatic amebiasis [17]. In areas with a low prevalence of *E. histolytica* infection, a positive titer supports the diagnosis of an acute infection; in areas with high prevalence, a positive titer may mean previous infection rather than active current infection [21]. A fecal antigen-based ELISA (enzyme-linked immunosorbent assay) for *E. histolytica* is now available for diagnosis and has very good sensitivity and specificity [20]. A PCR (polymerase chain reaction) test is currently used as a research tool but is not available for routine clinical diagnosis.

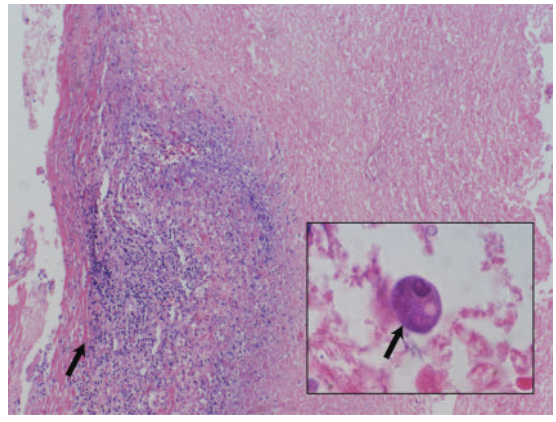

Figure 20.2 Amebic liver abscess. The wall of the abscess is on the left with adjacent purulent inflammation. The center, although necrotic, is largely acellular. The inset shows *E. histolytica*. H & E, ×200 and ×1000.

Distinguishing between a pyogenic and an amebic liver abscess may be difficult. In a review of 577 cases of liver abscess, predictive factors for pyogenic liver abscess included age >50, multiple abscesses, pulmonary findings, and an IHA titer <256 IU [21].

Treatment

Metronidazole is the cornerstone of treatment. Chloroquine, which is active against trophozoites, is added in cases with a very large abscess or multiple abscesses. Surgical drainage is rarely indicated, other than in complicated cases. Treatment with luminal agents, which include iodoquinol, paromomycin, and diloxanide, is necessary to eliminate intestinal *E. histolytica* and prevent relapse.

Acute Cholangitis

Microbiology

The usual organisms involved are *E. coli*, and *Klebsiella* and *Enterobacter* spp.; staphylococci and streptococci are uncommon [22]. Rarely, anaerobes such as *Bacteroides* spp. and clostridia may be present [23]; they are found more frequently in severe cases or in those who have undergone previous biliary and enteric surgery. Biliary stents may be colonized with hospital organisms that could cause infection.

Pathogenesis

Cholangitis results from biliary obstruction. Most cases occur in elderly people and are usually associated with cholelithiasis. When biliary obstruction occurs, it is believed that bacteria ascend the choledochus from the duodenum, or possibly from the gut through the portal circulation, colonize the bile, and cause infection. Increased pressure in the biliary tract may open the hepatocellular junctions and allow bacteria and toxins to infiltrate the general circulation [22].

Aside from cholelithiasis, other etiologies include biliary strictures, malignancy, choledochal cysts, choledochocele, and intrabiliary parasites [23]. Sometimes the cause is an occluded biliary stent [22].

Clinical Features

The median age of patients is 50–60 years. Patients may present with mild symptoms or with an acute, life-threatening illness. The Charcot triad (jaundice, fever/chills, and RUQ abdominal pain) occurs in 50–100%; the Reynold pentad (the Charcot triad plus hypotension and altered mental status) is much less common (<14%) [23].

Some diseases present with recurrent cholangitis, including Oriental recurrent cholangitis, AIDS cholangiopathy, and primary sclerosing cholangitis.

Oriental recurrent cholangitis is a disease of the Far East, usually affecting younger individuals. The intrahepatic bile ducts form strictures, dilations, and biliary stones. The etiology remains unknown but one possible explanation is biliary worms, specifically *Clonorchis*, *Ascaris*, and *Fasciola* spp. Patients are offered biliary procedures to dilate strictures, extract biliary stones, and place biliary stents, and sometimes segmental resection of the liver.

AIDS cholangiopathy was first described in 1986, affecting those with a CD4 count <100. With the advent of potent antiretroviral agents, it is now rarely seen. It causes sclerosing cholangitis, mainly of the large intrahepatic bile ducts and papillary stenosis [24]. *Cryptosporidium parvum*, *Microsporidium* spp., *Cyclospora cayetanensis*, and *Mycobacterium avium* complex have been implicated in the etiology of this disease, but treatment of these infections does not affect it.

Primary sclerosing cholangitis is a chronic disease that causes inflammation and fibrosis of the intra- and extrahepatic bile ducts, usually affecting young and middle-aged men. Recurrent cholangitis usually starts after manipulation and surgical exploration of the biliary tract. Biliary strictures and formation of biliary stones and sludge are found. Ultimately liver failure occurs and liver transplantation may be the only solution [25].

Diagnosis

Leukocytosis, increased alkaline phosphatase and bilirubin, and mildly elevated liver transaminases are typical. Dilated bile ducts may be seen with ultrasonography and CT. Endoscopic retrograde cholangiopancreatography (ERCP) and magnetic resonance cholangiopancreatography (MRCP) may be necessary.

Treatment

The first goal in management is to stabilize the patient using intravenous fluids and antibiotics. An antibiotic with a high biliary concentration, such as piperacillin, is preferred. Blood cultures and bile cultures, if possible,

Table 20.1 Infections that cause granulomatous hepatitis and their etiologic agents.

Infection	Infectious agent	Infection	Infectious agent
Bacterial		**Fungal**	
Tuberculosis	*Mycobacterium tuberculosis*	Candidiasis	*Candida* spp.
Atypical mycobacteria	*M. avium* complex others	Histoplasmosis	*Histoplasma capsulatum* (Figure 20.3)
BCG infection	*M. bovis* (attenuated vaccine mycobacterium)	Cryptococcosis	*Cryptococcus neoformans*
Leprosy	*M. leprae*	Coccidioidomycosis	*Coccidioides immitis/posadasii*
Listeriosis	*Listeria monocytogenes*		
Tularemia	*Francisella tularensis*	**Viral**	
Bartonellosis	*Bartonella henselae*	CMV infection	CMV
Salmonellosis	*Salmonella* spp.	EBV infection	EBV
Brucellosis	*Brucella* spp.	Hepatitis A	Hepatitis A virus
Yersiniosis	*Yersinia* spp.	Hepatitis B	Hepatitis B virus
Whipple disease	*Trophyrema whipplei*	Hepatitis C	Hepatitis C virus
Psittacosis	*Chlamydia psittaci*	Parasitic	
Melioidosis	*Burkholderia pseudomallei*	Toxoplasmosis	*Toxoplasma gondii*
Nocardiosis	*Nocardia* spp.	Schistosomiasis	*Schistosoma* spp.
Secondary syphilis	*Treponema pallidum*	Visceral leishmaniasis	*Leishmania* spp.
Q-fever	*Coxiella burnetii*	Visceral larva migrans	*Toxocara* spp.

CMV, cytomegalovirus; EBV, Epstein–Barr virus.

should be obtained, and antibiotics adjusted based on culture and sensitivity results. Once the patient is stable, the biliary obstruction is addressed via endoscopic, percutaneous, or surgical approaches.

Granulomatous Hepatitis

Microbiology

Table 20.1 shows infections that cause granulomatous hepatitis (GH). Other etiologies include autoimmune diseases, drugs, sarcoidosis (Figure 20.4), or idiopathic causes. Idiopathic GH is usually treated with steroids, but, before idiopathic GH is assumed, a thorough investigation is needed to rule out other diagnoses.

The frequency of the etiologies of GH varies, depending on the time period in which the study was performed. In earlier studies, hepatitis C virus (HCV) was not listed as a potential etiology. An early series from the Mayo Clinic had many idiopathic (50%) cases [26]; with improvement in diagnostic methods the proportion of GH without a known cause decreased. In a series from Germany [27], an infectious etiology was found in 3.4%; PCR was applied for detection of *Bartonella henselae*, *Listeria monocytogenes*, *Mycobacterium tuberculosis*, *M. avium*, *Yersinia enterocolitica*, *Y. pseudotuberculosis*, cytomegalovirus and Epstein–Barr virus, and *Toxoplasma gondii*.

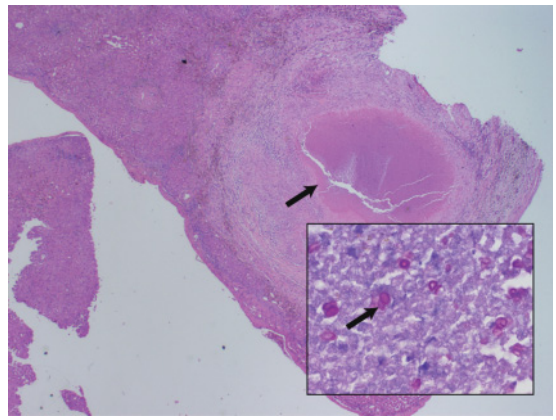

Figure 20.3 Granulomatous hepatitis: this lesion is from an immunocompromised patient with acute leukemia. There is a centrally necrotic, well-defined lesion with a granulomatous rim in hepatic parenchyma. The inset shows fungi with budding and a thin capsule most consistent morphologically with *Histolyticum capsulatum*. Central necrosis is common in infectious granulomas. Hematoxylin and eosin, ×40; periodic acid–Schiff ×400.

There is also substantial variation in distribution of the etiology of GH across countries, as noted in Table 20.2.

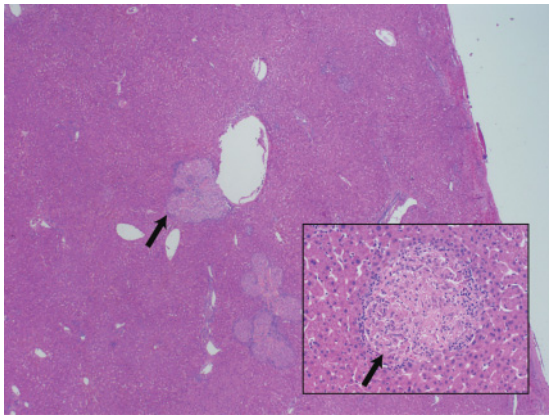

Figure 20.4 Granulomatous hepatitis: non-caseating granuloma from sarcoidosis in liver. In contrast to many infectious granulomas, the granuloma is tightly formed with no necrosis. H & E, ×40 and ×200.

Tuberculosis was listed in every published series, and is still an important etiology of GH.

Diagnosis

Liver biopsy demonstrates granulomas in the parenchyma. These are collections of epithelioid cells, which can include giant cells, surrounded by lymphocytes [32]. The histology of the granuloma and the surrounding tissue is important for a differential diagnosis [29]. As many as 75% of cases present with fever of unknown origin [32].

Table 20.3 shows the diagnostic methods used for bacterial infections; parasitic and fungal infections are detailed below.

Treatment

Treatment for bacterial causes is shown in Table 20.3. Treatment for parasitic and fungal diseases is detailed below.

Table 20.2 Infectious etiology of granulomatous hepatitis in different countries (1990–2006).

Country	USA [26]	Saudi Arabia [28]	Turkey [29]	Scotland [30]	Greece [31]	Germany [27]
Years	1976–1985	1990	1993–1999	1991–2001	1999–2004	1996–2004
Number of cases	88	59	56	63	66	442
Mean age (years)	54.2		30	42	42	
Female : male	45 : 43		30 : 26	47 : 16	51 : 15	
Sarcoidosis (%)	22		20	11.1	7.5	8.37
Autoimmune (%)				**34.5**	**68**	**48.64**
Hodgkin disease (%)			1	6.3		
Drugs (%)	6	3.4	1	7.9	3	2.48
Idiopathic (%)	**50**		19.6	11	6	36
Others (%)	19	1.7		12.7	3	0.013
Infection (%)		**95**	**41**	14.3	12	3.39
Tuberculosis (%)	3	32.2	**19.6**	4.8	1.5	0.67
Brucellosis (%)		6.8	5.3			
Yersiniosis (%)						0.23
Bartonellosis (%)						0.45
Listeriosis (%)						0.67
Typhoid fever (%)		1.7	3.5			
Q-fever (%)						0.23
Cytomegalovirus (%)						0.45
Epstein–Barr virus (%)			1.8			0.90
Hepatitis B virus (%)					3	
Hepatitis C virus (%)			1.8	9.5	4.5	
Schistosomiasis (%)		**54.2**			1.5	
Leishmaniasis (%)					1.5	
Hydatid cyst (%)			8.9			

Table 20.3 Bacterial infections of the liver.

Organism	Usual mode of transmission	Risk factor	Usual signs and symptoms	Liver manifestation	Diagnosis	Treatment
Actinomyces sp.	Endogenous flora	Poor dentition	Oral–cervical disease	Abscess	Anaerobic culture from a sterile site	Penicillin Clindamycin Tetracycline
Bartonella henselae	Inoculation	Cat scratch	Fever, papule/pustule at site of inoculation, lymphadenitis	Microabscess	Serology Blood/tissue culture Tissue/pus PCR Warthin–Starry silver stain of tissue	Azithromycin
BCG infection	Intravesical instillation of BCG vaccine		Fever, cough, weight loss, sepsis	Granulomas	AFB culture of tissue	Isoniazid, rifampin, ethambutol
Borrelia spp.	Tick bite		Stage 1: erythema migrans, constitutional symptoms Stage 2: annular rash, meningitis, encephalitis, neuritis, atrioventricular block Stage 3: arthritis, chronic axonal polyneuropathy	Stage 2: elevated LFTs, jaundice, tender hepatosplenomegaly	Serology PCR of joint fluid	Doxycycline Amoxicillin Ceftriaxone
Brucella spp.	Direct inoculation Ingestion Inhalation	Unpasteurized dairy products, infected animal body fluids	Fever, sweats, anorexia,	Hepatitis, Non-caseating granulomas	Blood or tissue cultures Serology	Doxycycline + rifampin
Ehrlichiosis HME (*Ehrlichia chafeensis*) HGA (*Anaplasma phagocytophila*)	Tick bite		Fever, headache, myalgia, malaise, nausea, anorexia, vomiting, diarrhea	Elevated LFTs, hepatomegaly	HME: morulae in circulating mononuclear cells HGA: morulae in polymorphonuclear cells Serology PCR	Doxycycline
Legionella spp.	Inhalation		Pneumonia, Diarrhea, hyponatremia	Elevated LFTs, hyperbilirubinemia	Detection by immunofluorescence or culture of respiratory specimens, tissue or fluid Antigenuria	Macrolides, quinolones, tetracyclines
Leprosy *(Mycobacterium leprae)*	Inhalation		Skin lesions, hypoesthesia, peripheral neuropathy	Granulomas	Fite acid-fast stain, AFB smear or PCR of tissue	Dapsone + rifampin ± clofazimine

Leptospirosis	Direct or indirect contact with urine or tissues of infected animals	Occupational animal exposure	Biphasic illness (Weil disease): flu-like illness with cough, chest pain, abdominal pain, then defervescence, then second phase with jaundice, muscle pain, renal failure, conjunctival suffusion	Jaundice	Culture of blood or CSF (first phase) or urine (second phase); serology	Severe: penicillin or ceftriaxone, Mild: doxycycline
Listeria monocytogenes	Ingestion of contaminated food	Dairy or poultry products Extremes of age, pregnancy, impaired cell-mediated immunity	Fever, leukocytosis, bacteremia, meningoencephalitis	Hepatitis, abscess, granuloma	Culture of blood, CSF, or other body fluid	Ampicillin
Melioidosis (*Burkholderia pseudomallei*)	Inhalation or inoculation through the skin	Exposure to soil and freshwater in South-East Asia, especially Thailand	Pneumonia, septicemia, tonsillitis	Elevated transaminases, jaundice, abscess, granulomas	Immunohistochemistry; culture	Ceftazidime
Non-tuberculous mycobacteria (*M. avium* complex, *M. kansasii*, *M. genavense*)	Environmental source (ubiquitous in environment)	AIDS, organ transplant, chronic steroids	Fever, weight loss	Elevated alkaline phosphatase, non-caseating granulomas	AFB culture or PCR of blood or bone marrow	Clarithromycin + ethambutol + rifabutin
Q-fever (*Coxiella burnetii*)	Inhalation or ingestion of contaminated raw milk	Direct or indirect contact with infected cattle, sheep, or goats	Fever, flu-like illness with pneumonitis	Acute hepatitis-like illness, isolated elevated LFTs, or FUO with granulomas	Serology, tissue PCR	Tetracycline
Rocky Mountain spotted fever (*Rickettsia rickettsii*)	Tick bite		Fever, headache, rash	Elevated ALT, jaundice, hepatomegaly	Serology	Doxycycline
Salmonella hepatitis	Ingestion	Poultry, eggs Exotic pets, especially reptiles, Travel to endemic area (South-East Asia, Africa) HIV Alcoholism a risk factor for severe disease	Fever, relative bradycardia, left shift, rose spots	Alkaline phosphatase increases much higher than transaminases; hepatomegaly; typhoid nodules (lobular aggregates of Kupffer cells)	Culture of blood, bone marrow or other sterile site, rose spots, stool, intestinal secretions	Fluoroquinolone, ceftriaxone or azithromycin for fluoroquinolone resistant

Table 20.3 *(Continued)*

Organism	Usual mode of transmission	Risk factor	Usual signs and symptoms	Liver manifestation	Diagnosis	Treatment
Syphilis (*Treponema pallidum*)	Congenital Person-to-person (sexual contact or kissing/ touching active lesions)		Primary: chancre (painless, non-tender ulcer) Secondary: rash, condyloma lata, mucous patches, constitutional symptoms, generalized painless lymphadenopathy Tertiary: gummas	Congenital: hepatic gummas; Secondary: hepatitis with disproportionate alkaline phosphatase elevation; Tertiary: gummas	Dark field examination of serous transudate from moist lesions Serology: non-treponemal test (RPR or VDRL) confirmed with treponemal test (FTA-Abs, MHA-TP, syphilis IgG)	Penicillin, ceftriaxone or doxycycline for penicillin allergic
Tuberculosis (*Mycobacterium tuberculosis*)	Airborne—inhalation of droplet nuclei	Homeless, prison inmates, persons from endemic countries, intravenous drug users	Fever, weight loss, abdominal pain, hepatomegaly	Drug-induced hepatitis due to TB drug therapy most common Granulomatous hepatitis (caseating granulomas) Hepatobiliary—nodules or abscesses with bile duct involvement (bile duct epithelial involvement or obstruction by enlarged nodes) Elevated alkaline phosphatase	AFB culture, PCR of liver biopsy	Isoniazid, rifampin, pyrazinamide, ethambutol
Tularemia (*Francisella tularensis*)	Insect bites (ticks or flies), contact with contaminated animal products	Hunting, skinning, dressing, eating infected animals (rabbits, muskrats, beavers, squirrels)	Ulceroglandular: skin lesion (red, painful nodule which necroses to a tender nodule with raised borders) with regional tender lymphadenopathy Pneumonia	Rare liver involvement Modest transaminase elevation, jaundice, abscess	Culture of blood, sputum, pleural fluid, wound Serology, PCR	Streptomycin, gentamicin
Whipple disease *(Trophyrema whipplei)*					Serology, PCR	Ceftriaxone, trimethoprim–sulfamethoxazole, doxycycline

From Johannsson and Stapleton [33], Gordon [34], and Mandell *et al*. [35].
AFB, acid-fast bacillus; AIDS, acquired immune deficiency syndrome; ALT, alanine transaminase; BCG, bacille Calmette–Guérin; CSF, cerebrospinal fluid; FTA-Abs, fluorescent treponemal antibody, absorbed; FUO, fever of unknown origin; HGA, human granulocytic anaplasmosis; HIV, human immunodeficiency virus; HME, human monocytic ehrlichiosis; LFTs, liver function tests; MHA-TP, microhemagglutination test for *Treponema pallidum*; PCR, polymerase chain reaction; RPR, rapid plasma regain; TB, tuberculosis; VDRL, Venereal Disease Research Laboratory.

Bacterial Infections of the Liver

The liver can be involved in a variety of bacterial infections. This could occur as a result of direct liver involvement through bacteremia or by contiguous spread. Alternatively, bacterial toxins could have indirect effects on the liver. Common manifestations of hepatic involvement are cholestasis, jaundice, and elevations of transaminases. Some bacteria present as abscesses and/or granulomas. More uncommon presentations are nodular liver lesions that could appear similar to metastatic lesions. Table 20.3 summarizes the clinical presentation, diagnosis, and treatment of selected bacterial infections.

Protozoa

Systemic protozoan infections that involve the reticuloendothelial cell system can manifest with varying degrees of hepatomegaly and fever. The pathologic changes center on Kupffer cells. *Babesia* spp., not separately discussed, may cause mild hepatomegaly and liver function abnormalities.

Malaria

Epidemiology and organisms

Plasmodium falciparum, *P. vivax*, *P. ovale*, and *P. malariae* initially replicate in the liver after infection by the bite of an anopheline mosquito. The parasites then rupture from hepatocytes into the bloodstream to invade circulating erythrocytes, producing the malaria paroxysm.

The liver is a reservoir for *P. vivax*, and *P. ovale* which shelter there in the form of hypnozoites. Inadequate treatment of this latent phase can lead to recrudescence months to years after the eradication of the hematogenous phase.

Clinical features

Malaria varies from indolent and asymptomatic to multisystem organ failure. The classic presentation is an acute illness characterized by paroxysms of high, spiking, often cyclical, fever of 40°C or more, followed by chills, drenching sweats, rigor, and prostration/fatigue in a traveler or an immigrant from an endemic area. Patients may present with vomiting, abdominal cramps, diarrhea, and hepatosplenomegaly. Hyperbilirubinemia may be mild, due to hemolysis in milder infection, but could be more pronounced with sepsis and organ compromise of severe infection.

A common microscopic finding of severe malaria in any vascular tissue is small-vessel thrombosis and the concentration of malarial pigments, typically seen in Kupffer cells in the liver or macrophages in the spleen.

Diagnosis

Thin and thick blood smears should be examined for the characteristic parasitic forms. Additional methods include immunofluorescence and PCR-based methods for malarial antigens. Rapid stick or card-type tests, based on either the detection of histidine-rich protein 2 (*P. falciparum*) or plasmodial lactate dehydrogenase (all species), can be used when microscopic examination is not available [36].

Treatment

P. falciparum infection requires prompt diagnosis and treatment. These patients can quickly develop sepsis and multiorgan failure. Patients with non-falciparum malaria can usually be treated as outpatients. Mefloquine is used for malaria from most areas; chloroquine can be used for infection from areas with susceptible malaria. Quinine/quinidine is used for severe complicated falciparum malaria [37]. Primaquine is added for eradication of the hepatic parasites of *P. vivax* and *P. ovale*. Pyrimethamine, artemisinin derivatives, and tetracyclines are also used. Information on malaria treatment can be obtained from the Centers for Disease Control (CDC) (Malaria Hotline + 1 770-488-7788). The WHO recommends the use of artemisinin-based combination treatment for infections from areas with endemic resistance.

Leishmaniasis

Epidemiology and organisms

Leishmania species are found worldwide and are transmitted by the bite of sand flies, which typically feed at night. Following inoculation, the organism is phagocytosed by skin macrophages. The subsequent degree of infection is determined by the cell-mediated response of the infected person.

Leishmaniasis may be asymptomatic but frequently causes cutaneous or mucosal infections in the upper aerodigestive tract. Dissemination to the reticuloendothelial system causes visceral leishmaniasis (VL), also known as kala-azar, in both immunocompetent and

immunocompromised individuals. The most common causative organisms are *L. donovani* (eastern India, Bangladesh, and eastern Africa) and *L. infantum/L. chagasi* (southern Europe, North Africa the Middle East, central Asia and South America). *Leishmania* sp. has emerged as a major pathogen in HIV/AIDS patients and an uncommon infection in returning servicemen from Middle Eastern conflicts.

Clinical features

The incubation period is 2–8 months, with variable fever and increasing hypertrophy of the liver, spleen, and lymph nodes. Hepatosplenomegaly may be massive, and peripheral wasting, liver test abnormalities, hypoalbuminemia, hypergammaglobulinemia, and ascites can be seen. Much of VL in South America and southern Europe is associated with HIV infection, in which it usually occurs in patients with a CD4 count <200/mm^3 and was more common in the pre-antiretroviral era. Recurrence after treatment is common, requiring maintenance therapy in immunocompromised individuals.

Diagnosis

Demonstration of the parasite in peripheral blood smears, ascitic fluid, or biopsy of the bone marrow, spleen, or liver establishes the diagnosis. Hepatomegaly is associated with Kupffer cell hyperplasia, with numerous, small, often smudged, amastigotes filling the cell. Culture of the organisms is possible in liquid media but is not widely available. Serology is less helpful, especially in immunocompromised individuals. Newer ELISA and other tests for parasite-specific antigens and PCR-based assays are being developed [38].

Treatment

Sodium stibogluconate, amphotericin B, lipid-associated amphotericin B, miltefosine, paromomycin, pentamidine, and others drugs are used [39].

Toxoplasmosis

Epidemiology and organisms

Caused by the ubiquitous *Toxoplasma gondii*, acute, congenital, ocular, and chronic syndromes of toxoplasmosis occur in both immunocompetent and immunocompromised hosts. Infection occurs through the ingestion of tissue cysts or oocysts. The organism has also been transmitted by transplantation or blood transfusion. After ingestion the organism can disseminate through the blood. Over time, the infection is contained but encysted organisms can persist.

Clinical features

Acute infection in immunocompetent hosts is usually asymptomatic. Some may present with lymphadenopathy and constitutional symptoms, and rarely with hepatosplenomegaly and hepatitis. In the immunocompromised individual any tissue shows a variable inflammatory response characterized by cuffing mixed mononuclear inflammatory infiltrates, visible tachyzoites and cysts, and necrosis with associated phagocytes and neutrophils.

Cysts in chronic infection tend to concentrate in skeletal muscle, myocardium, and the central nervous system. The liver is a less common site for infection, but hepatitis is seen in disseminated infection in immunocompromised hosts. Recrudescence of latent infection in transplant recipients usually occurs within 3 months of transplantation.

Diagnosis

In immunocompetent individuals, serology is helpful. In immunocompromised ones, serology demonstrates those at risk for infection and supports the diagnosis with suggestive pathologic findings. Demonstration of the organism with compatible histologic findings, visualization of cysts in routine sections, and specific immunohistochemical confirmation of the organism are possible. Isolation of parasites in mice or cell culture is possible. PCR methods are available for fluid specimens. [40]

Treatment

Most acute infections in immunocompetent hosts are self-limited. Treatment in immunocompromised hosts is pyrimethamine/sulfadiazine/folinic acid.

Fungi

Fungal infection of the liver is almost always a manifestation of disseminated infection in an immunocompromised host. The liver has the typical granulomatous pattern of infection seen in other organs; focal hepa-

tocellular disease with liver function abnormalities is expected.

The liver biopsy may demonstrate focal granulomatous lesions and, rarely, fungal organisms may be seen [41]. *Histoplasma capsulatum* tends to favor the reticuloendothelial system in the liver with Kupffer cell hyperplasia; organisms can be seen in macrophages. *Candida* spp. cause small microabscesses with central necrosis combined with poorly defined peripheral granulomatous change; hyphae may be seen. The pattern of cryptococcosis, especially in AIDS, can vary widely, ranging from granulomatous and/or necrotic to little tissue reaction with mucinous accumulation from the capsule of *C. neoformans*. *Aspergillus* sp. in immunocompromised hosts is more necrotic than discretely granulomatous, with organisms seen at the edges of necrotic lesions and occasional infarction due to involvement of adjacent vasculature. *Coccidioides* sp. is one of the largest fungi found in tissue and the only one with significant internal structure, caused by its visible endospores; this infection can be seen in disseminated cases in people with a history of exposure in south-western areas of the USA.

Identification of organisms can sometimes be accomplished with hematoxylin and eosin stains or with fungal stains such as GMS (Gomori–Grocott methenamine silver), periodic acid–Schiff (PAS), or mucicarmine stains. Specific diagnosis can be made with culture, serology, or PCR.

Treatment is directed against the etiologic organism using amphotericin, a triazole, or echinocandin, and modification of immunosuppression where possible.

Helminths

Nematodes (roundworms), trematodes (flatworms, flukes), and cestodes (tapeworms) can cause liver disease with a variety of patterns depending on the host response. As many species involve the liver by larval migration from the gastrointestinal tract to the biliary ducts, involvement of the biliary ducts and portal areas is common.

Echinococcosis (Hydatid Disease)

Epidemiology and organisms

Echinococcus granulosus and *E. multilocularis* are found worldwide, associated with raising livestock. Cattle and sheep are intermediate hosts; cats and dogs are definitive hosts for adult worms. Humans acquire infection by ingesting eggs. The egg releases oncospheres which penetrate intestinal mucosa, enter the microcirculation, and migrate to organs, typically the liver, and less likely the lungs or rarely the heart. The oncosphere becomes a cystic metacestode which then forms daughter cysts within the cyst endogenously (*E. granulosus*) or exogenously (*E. multilocularis*) into adjacent tissue.

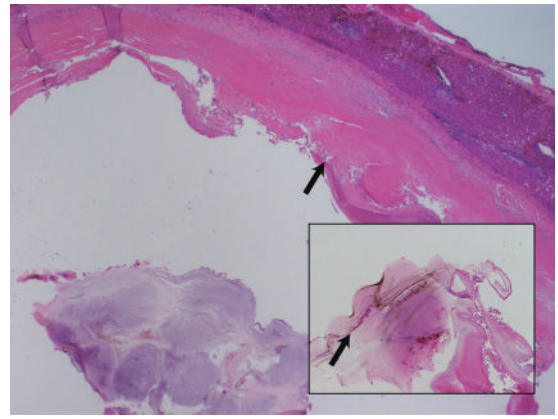

Figure 20.5 Echinococcal cyst: this 48 year old was found to have an "incidental" liver cyst on CT and ultrasonography when being evaluated for gall-bladder disease. This cyst was calcified with a thick fibrous rim. The organisms are no longer present. The unilocularity, thick fibrous rim with calcification, and layered acellular internal debris (inset) suggest the etiology. H & E, ×20 and ×200.

Clinical features

E. granulosus typically forms a unilocular asymptomatic cyst which is usually discovered incidentally on imaging (Figure 20.5). These cysts grow slowly, usually in the right hepatic lobe, may reach a large size (>10 cm), and the wall may calcify. The cyst may present as an obstructing mass (jaundice, tender hepatomegaly, palpable mass) or rupture into adjacent tissue with seeding of new cysts (causing pain, peritonitis, empyema, hemoptysis, and/or pulmonary symptoms, or systemic allergic reactions from the cyst contents, e.g., anaphylaxis) [42].

E. multilocularis causes more invasive, slowly progressive, and often fatal extension into liver parenchyma termed "alveolar hydatid disease." The less common *E. vogeli* and *E. oligarthus* cause polycystic hydatid disease.

Diagnosis

Serology confirms the diagnosis. Sharply circumscribed cysts with regular daughter orbs on imaging are diagnostic, and many calcified cysts can demonstrate the suggestive ring-like calcification. Aspiration of the cyst has been traditionally avoided to decrease the likelihood of rupture, dissemination, or allergic reaction, but has been used recently for diagnosis and sterilization. Protoscolices, hooklets, or brood capsules from the interior of the cyst are diagnostic. The microscopic appearance of an intact cyst wall is pathognomonic.

Treatment

Primary treatment includes excision of the cyst, often with sterilization before surgery to avoid any complication if the cyst ruptures intraoperatively. A calcified cyst is stable and need not be removed [43]. Aspiration and sterilization of the cyst have become more common, combined with albendazole [44].

Trematodes (flukes)

Clonorchis sinensis, *Opisthorchis viverrini*, and *O. felineus* infect the extrahepatic and intrahepatic biliary tract, whereas *Fasciola hepatica* infects the liver parenchyma and biliary ducts [45,46]. Relapsing bacterial cholangitis is associated with biliary tract infection by flukes.

Clonorchis and *Opisthorchis* spp. are acquired from undercooked fish. The adult flukes deposit eggs in biliary ducts. Most infections are asymptomatic. Acute complications relate to biliary obstruction causing fever, hepatomegaly, eosinophilia, and jaundice. Late complications include gall stones (Figure 20.6), secondary bacterial infection, cirrhosis, and cholangiocarcinoma. Diagnosis rests on demonstration of eggs in stool or duodenal aspirate. Praziquantel is the treatment of choice.

Fasciola hepatica is acquired by ingestion of metacercariae associated with freshwater plants (e.g., watercress). It matures in the intestine, migrates though the small bowel into the peritoneal cavity, and then penetrates the liver capsule. Immature flukes reach the liver in 5–6 days and migrate through the liver for 5–6 weeks. Acute symptoms relate to pain from penetration of the peritoneum and hepatic capsule. After flukes establish themselves in biliary ducts, they invade the liver causing a chronic or obstructive phase with inflammation of the biliary tract, eosinophilic microabscesses in hepatic tissue, and occasional wandering larvae, prompting ectopic subcutaneous swellings. Eosinophilia is present in all stages.

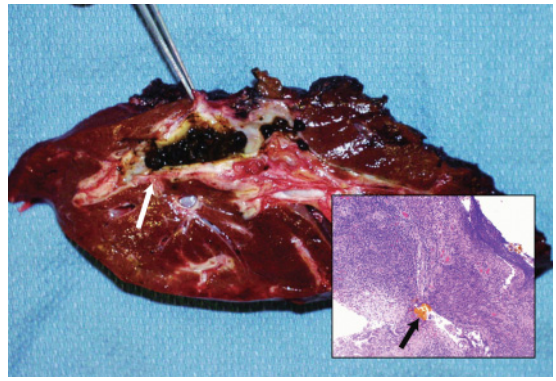

Figure 20.6 Hepatolithiasis: a liver resection from a patient with recurrent pyogenic cholangitis showing multiple stones within large intrahepatic bile ducts. No organisms were present. The inset shows a destroyed biliary ductule with impacted stone material and dense surrounding chronic active inflammation. H & E, ×200.

Fasciolopsis is not associated with biliary carcinoma. Diagnosis is based on finding eggs in stool. Unlike other trematodes, *Fasciola* is not sensitive to albendazole; triclabendazole is the drug of choice. ERCP may be helpful for extraction in cases of biliary obstruction.

Schistosoma spp. are an important cause of portal hypertension worldwide. Unlike other flukes they inhabit blood vessels, typically mesenteric and portal veins. Infecting cercariae, which reside in freshwater, penetrate the skin, migrate through the blood to the lungs and liver, and then through intestinal capillaries to the portal vein. They mature in hepatic portal venules, reproduce, and yield many eggs disseminating to the liver. The intense reaction produced by these eggs leads to the characteristic circumscribed fibrous granuloma, Symmer fibrosis, or "pipestem fibrosis," associated with *S. mansoni* and *S. mekongi* infection, causing portal hypertension (Figure 20.7). Diagnosis is made by serology or demonstration of eggs in feces or biopsy specimens, although eggs are rare in liver biopsies. Praziquantel is effective against all organisms.

Nematodes (roundworms)

Ascaris lumbricoides is the most common human helmintic infection and the largest human nematode. It can complete its entire life cycle in the human host and typically resides in the small intestine. Infection is acquired by ingestion of

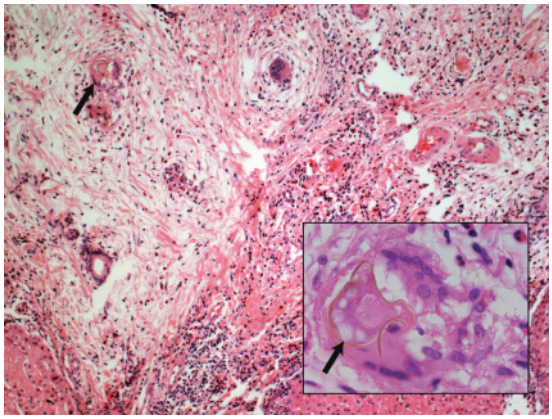

Figure 20.7 Hepatic schistosomiasis: some intact hepatic parenchyma is visible at the extreme bottom of the photograph but most of the liver is unidentifiable, replaced by fibrous tissue with granulomas. The inset demonstrates a granuloma with the remains of pigmented egg and eosinophils in the upper right corner. H & E, ×40, ×400.

eggs from contaminated soil. It causes liver, biliary, or pancreatic disease by direct obstruction of biliary ducts or the ampulla of Vater. Diagnosis is made by demonstration of eggs in stools. ERCP is utilized for extraction of the parasite followed by albendazole or mebendazole.

The dog roundworm, *Toxocara canis*, can cause human infection when eggs are ingested from contaminated soil. The eggs hatch in the small intestine, and then migrate to various organs, causing visceral larva migrans. In the liver, migrating and burrowing larvae cause nodules, characterized by eosinophilic granuloma, which may contain portions of larvae. Diagnosis rests on serology or demonstration of the larvae in tissue. The infection is self-limited. If treatment is necessary, albendazole or mebendazole may be used.

Strongyloides stercoralis rarely invades the liver when filariform larvae in hyperinfection syndrome disseminate through multiple organs.

Capillaria hepatica rarely infects the liver and causes necrotic granulomatous nodules; infection is acquired by ingestion of eggs in contaminated soil.

Take-home points

Diagnosis

- The classic triad of fever, right upper quadrant pain, and jaundice is uncommon in pyogenic liver abscess.
- Three-quarters of patients with granulomatous hepatitis present with fever of unknown origin.
- Previous exposures and travel history will help guide diagnosis of certain infections.
- Diagnostic methods may require testing of blood, stool, body fluid, or tissue specimens by culture, serology, special stains, or molecular methods such as PCR, in addition to radiological imaging.
- Cultures of the blood and abscess aspirate will usually yield the etiologic agents of a pyogenic liver abscess and guide antimicrobial therapy.
- Negative *Entameba histolytica* serology by IHA effectively rules out amebic liver abscess.
- Collaboration of clinicians, pathologists, radiologists, and the laboratory will aid in reaching a diagnosis of infection.
- Ultrasonography and CT are crucial in the diagnosis of liver abscesses.

Treatment

- Antimicrobial therapy and drainage are necessary for most liver abscesses.
- Metronidazole is the treatment for amebic liver abscess. Luminal agents are necessary to treat intestinal amebiasis and prevent relapse.
- The treatment will depend on the etiologic agent identified.

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21

CHAPTER 21
Metabolic Liver Diseases

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Summary
This chapter focuses on hemochromatosis, Wilson disease, and α_1-antitrypsin deficiency. Hemochromatosis is the most commonly inherited metabolic disease. There have been recent observations on the molecular mechanisms of disease and clinical penetrance, and the changes in clinical presentation.

Wilson disease is rare, but it is important to keep in mind because it can present as virtually any liver disease syndrome, and it is treatable. Treatment has evolved and penicillamine is no longer the treatment of choice.

α_1-Antitrypsin deficiency is associated with liver disease in both children and adults, not because of the deficiency but because an abnormal form of the protein accumulates in liver cells. There is no specific treatment for the liver disease.

Case
A 58-year-old woman was found to have a serum ferritin of 1519 ng/mL after an iron abnormality had been noted in her sister. The serum iron was normal at 88 µg/dL and the transferrin saturation was 35%. The patient was obese and had type 2 diabetes. The serum AST (aspartate transaminase) and ALT (alanine transaminase) were normal. MRI of the abdomen showed diffuse fatty infiltration of the liver. Iron-sensitive MR images showed mildly increased R2* values, corresponding to minimally increased levels of liver iron. MR elastography confirmed normal liver stiffness, making significant fibrosis highly unlikely. HFE testing revealed that she was homozygous for the *H63D* mutation. The patient was reassured that she had little or no chance of developing iron-related liver disease. She is focusing on weight reduction and optimization of diabetes treatment.

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Hereditary Hemochromatosis

Pathogenesis

Hereditary hemochromatosis (HH) is most commonly caused by a deficiency or dysfunction of the liver-derived hormone hepcidin [1]. As total body iron increases, hepcidin is released from the liver and binds to the iron transport protein ferroportin, thereby decreasing the rate of iron absorption across the small intestinal epithelium. If the demand for iron increases, hepcidin expression is decreased, allowing accelerated transport of iron from the gut and release of iron from body cells, mainly macrophages. The relationship between hepcidin–ferroportin abnormalities and the HFE protein is not clear. Approximately 95% of HH is associated with mutations in the *HFE* gene: 90% are homozygous for *C282Y* and about 5% are *C282Y*/*H63D* compound heterozygotes [2]. Those with only *H63D* mutations do not develop serious iron overload. "Non-HFE" hemochromatosis has been found to be associated with abnormalities of hepcidin, ferroportin, or other proteins involved in iron metabolism, such as the trans-

ferrin receptor [3]. If ferroportin is not expressed on the cell surface, iron is not released from body cells and this results in a situation where iron overload is associated with a high serum ferritin and a low transferrin saturation.

Clinical Features

Approximately 10% of white people in North America are carriers of a mutation in the *HFE* gene, and about 1 in 200 has HH, making it the most common hereditary disease [4]. However, the clinical expression and penetrance of HH are lower than previously thought, and progression to significant iron overload does not always occur [5]. Moreover, a large population study found that only 28% of males and 1% of females who were homozygous for *C282Y* had disease-related symptoms [6]. Thus, most individuals are asymptomatic at the time of diagnosis and are discovered through laboratory testing. The most common symptom is arthralgia of the metacarpophalangeal (MCP) joints; diabetes is a late complication and has become rare [7]. Conditions that call for iron testing include liver test abnormalities, hepatomegaly, skin hyperpigmentation, and erectile dysfunction. Unfortunately, HH typically causes progressive fibrosis with little or no inflammation, presenting as previously undiscovered cirrhosis or hepatocellular carcinoma.

Transferrin Saturation

Although the transferrin saturation (TS) has long been to used screen for iron overload (>45% for women, >50% for men), new studies have shown that its wide variability within the same individual at different points in time greatly limits its sensitivity and specificity [8]. Moreover, it is non-specifically elevated by a wide range of inflammatory conditions, including other types of liver disease [9]. In a population study of over 100 000 individuals, the positive predictive value of an elevated TS in screening for *C282Y* homozygotes was only 2%, and the sensitivity was only 75% [10]. In other words, the TS misses about 25% of *C282Y* homozygotes in the general population. The test should be used as supplemental information only, realizing its limitations.

Serum Ferritin

The ferritin reflects body iron stores more accurately than the TS, but is also non-specifically elevated by a number of inflammatory conditions. Both the ferritin and the TS have high accuracy for the detection of iron deficiency but lower accuracy for predicting iron overload [1]. Most patients with significant fibrosis due to HH have ferritin levels >1000 ng/mL [11]. In a study of 182 patients with phenotypic HH from 6 tertiary care referral centers, 39 of 89 (44%) with a ferritin >1000 ng/mL had cirrhosis, compared with 1 of 93 with ferritin <1000 ng/mL [12].

Diagnosis

The *HFE* gene test should be performed if there are clinical features suggesting iron overload, or if there is elevation of the transferrin saturation or serum ferritin. It is also indicated for first-degree relatives of those identified as *C282Y* homozygotes [2]. Individuals found to have *C282Y*/*C282Y* or *C282Y*/*H63D* have HH and may need further evaluation to determine the severity of disease and the degree of iron overload. If the ferritin is <1000 ng/mL and the transaminases are normal, they may proceed directly to weekly phlebotomy therapy. If the ferritin is >1000 ng/mL, the patient should have a liver biopsy to determine the tissue iron concentration and the degree of liver fibrosis. Alternatively, in the hands of a dedicated radiologist, MRI can provide highly accurate information regarding tissue iron content [13] and/or the degree of liver fibrosis [14], as in the case history above.

If the *HFE* gene test shows only one copy of *C282Y*, or any non-*C282Y* combination, the individual should be evaluated for other causes of inflammation or liver disease. If an alternative explanation is not found, a liver biopsy may be needed to settle the issue. If a liver biopsy or MRI shows significant tissue iron, and if the ferritin is elevated but the transferrin saturation is normal, the patient may have non-HFE hemochromatosis due to a ferroportin mutation and may still require long-term phlebotomy therapy. The "hepatic iron index" (calculated by dividing the hepatic iron concentration by the patient's age) was previously used to help distinguish HH homozygotes from heterozygotes, but *HFE* gene testing is far more accurate [15].

Treatment

Although iron chelators are available, phlebotomy remains the treatment of choice [16]. A one-unit phlebotomy of 500 mL removes about 250 mg iron. Patients with heavy iron overload have tissue iron concentrations >10 000 μg/g dry weight, occasionally as high as 30 000–

40 000 µg/g dry weight. A trial of phlebotomy can confirm iron overload in borderline cases where a liver biopsy is contraindicated or declined. Most individuals with normal or minimally increased amounts of tissue iron will become iron deficient after six or fewer phlebotomies [15]. If a patient can tolerate 20 phlebotomies (removal of 5 g iron) without becoming iron deficient, iron overload is confirmed [17]. The phlebotomy requirement can be estimated from the hepatic iron concentration [15]. The normal limit for the hepatic iron concentration (HIC) is about 1400 µg/g dry weight. The phlebotomy requirement can be calculated as:

$$\text{Units of blood} = [(\text{HIC} - 1400)/100] \times 3.$$

Phlebotomy of 500 mL is initially performed weekly, with treatment temporarily deferred if the pre-phlebotomy hemoglobin is <10–11 g/dL. The serum ferritin is checked monthly in cases of mild iron overload and every 2–3 months in cases of heavy iron overload. Treatment is continued until the ferritin is in the range 20–50 ng/mL. At that point, treatment is stopped and the ferritin is checked every 2 months to gauge the rate of iron reaccumulation. This will serve as a guide for determining the frequency of maintenance phlebotomy, which usually ends up being three to six times a year for patients with initially heavy iron overload. Some patients may not have significant reaccumulation of iron for several years. Although reversal of liver fibrosis has been documented after iron removal [18], this cannot be assumed, so patients with cirrhosis need to continue cancer surveillance with regular liver imaging.

Deferasirox is an oral iron chelator that has been proven to be effective for patients with secondary iron overload [19]. The results of a clinical study in patients with HH are pending, but the drug appears to be an alternative for the rare patients who cannot tolerate phlebotomy. Adverse effects have included renal insufficiency, cytopenias, and elevated liver enzymes.

Iron removal therapy has beneficial effects on cardiomyopathy, skin hyperpigmentation, and liver inflammation, but improvement in arthropathy or hypogonadism is less likely [16].

Liver transplantation is indicated for patients with HH who develop decompensated cirrhosis or hepatocellular carcinoma [20]. Older studies showed poor post-transplantation survival for patients with HH, but a more recent series suggests that the outcome may be improving with better selection of patients and more aggressive pursuit of iron removal therapy before transplantation [21]. Interestingly, even though the metabolic defect in HH is often presumed to be at the intestinal level, long-term follow-up of transplanted patients thus far has not shown reaccumulation of iron in the liver [20].

Wilson Disease

Pathogenesis

Wilson disease is caused by a mutation in the gene *ATP7B* that encodes a membrane-bound copper transport protein [22]. As a consequence, the movement of copper within hepatocytes is greatly limited, leading to (1) decreased biliary excretion of copper and (2) decreased incorporation of copper into ceruloplasmin. As bile is the only route for getting rid of excess copper, copper accumulates in the liver and causes acute and/or chronic liver damage. Serum ceruloplasmin is decreased, partly because of decreased hepatic production and partly because of accelerated breakdown of the non-copper-containing form of the protein [23]. The accumulation of copper eventually exceeds the liver's capacity and copper is then released and deposited in other organs, including the brain, kidneys, and cornea [22]. Ionic copper promotes the production of reactive oxygen species that damage membranes, particularly the mitochondria [24].

Even though Wilson disease shows a recessive pattern of inheritance, it differs from hemochromatosis in that there are over 300 mutations identified thus far, and most patients are compound heterozygotes with different mutations on the two alleles [22].

Clinical Features

Wilson disease is rare (1 in 30 000), but it needs to be kept in mind when encountering patients with liver disease or certain neurologic symptoms, because it is treatable. It is not limited to young people and has been diagnosed in patients aged >70 years [22]. It can mimic virtually any acute or chronic liver disease syndrome. Most patients who present with acute liver failure already have underlying cirrhosis; they frequently have associated hemolytic anemia and acute renal failure. Many individuals remain asymptomatic in their younger years and present later on with complications of cirrhosis.

There have been occasional reports of hepatocellular carcinoma complicating cirrhosis in Wilson disease [22]. Neurologic manifestations range from subtle symptoms, such as changes in behavior or deterioration in schoolwork, to severe extrapyramidal signs that may include tremor, dysarthria, and spasticity [23]. Hemolytic anemia due to increased blood levels of ionic copper may be the main feature, occurring either as a single acute episode or as a chronic condition [22,23].

Peripheral deposition of copper in the corneas causes the characteristic gold–brown Kayser–Fleischer (KF) rings, most often seen at the upper and lower poles [23]. KF rings may occasionally be seen directly by shining a flashlight from the side, but it usually takes a slit-lamp examination by an experienced observer to visualize them. They are present in over 90% of patients with neurologic symptoms, but only half of patients presenting with liver disease [22]. KF rings are not necessarily specific for Wilson disease, having been found in a variety of cholestatic disorders. If present, they are useful in monitoring the effectiveness of treatment for Wilson disease because they gradually disappear; reappearance indicates non-compliance.

Diagnosis (Figure 21.1)

A summary of diagnostic tests for Wilson disease is presented in Table 21.1. The diagnosis is made if two of the following are present [23]:

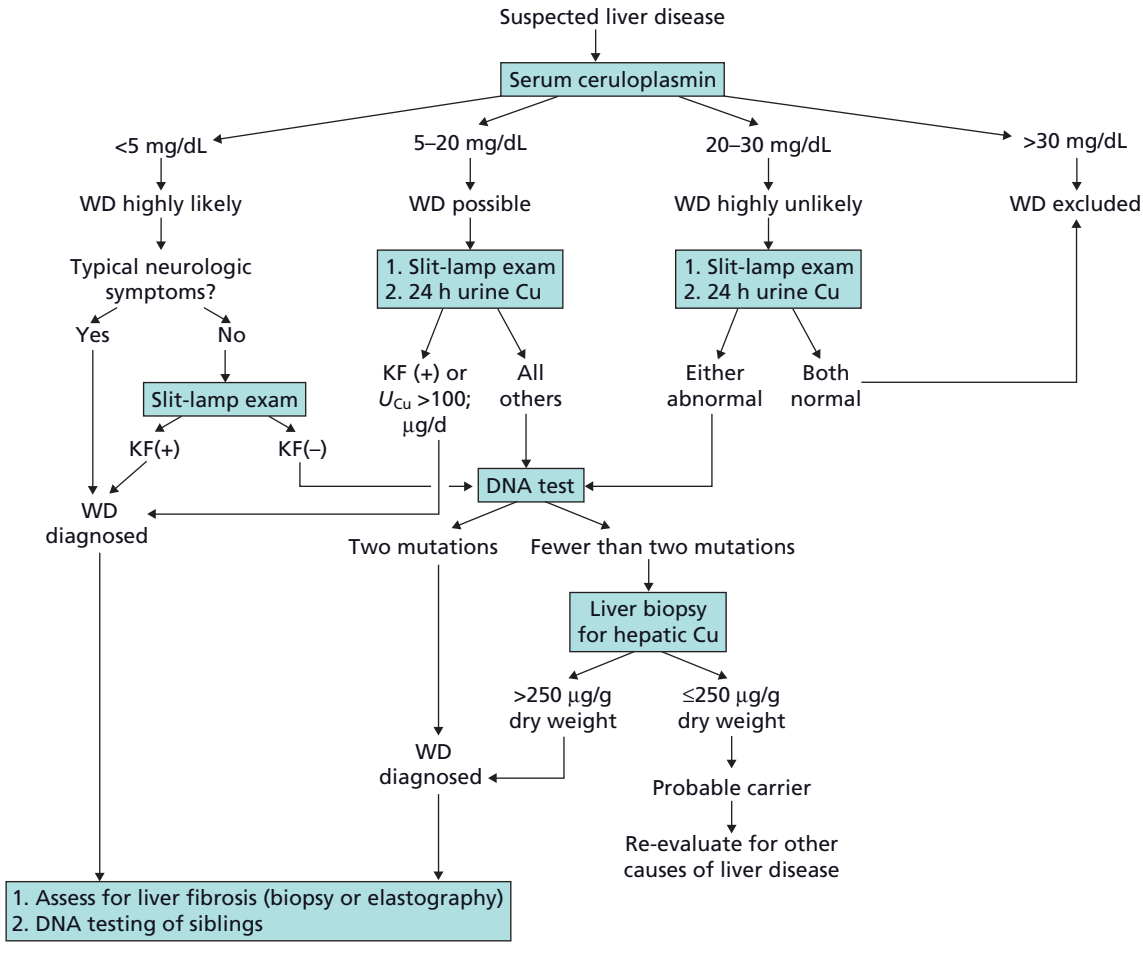

Figure 21.1 Algorithm for diagnosis of Wilson's disease (WD) in patients with abnormal liver tests or suspected liver disease. KF, Kayser–Fleischer rings; U_{Cu}, urinary copper excretion.

Table 21.1 Diagnostic tests for Wilson disease

Test	Typical finding	False negatives	False positives
Ceruloplasmin	Decreased	Acute inflammation Estrogens	Malabsorption Aceruloplasminemia Liver failure Wilson disease heterozygote
24-h urinary copper	>100 µg	Inadequate collection Presymptomatic Wilson disease	Hepatic necrosis Cholestatic diseases Copper contamination
Hepatic copper	>250 µg/g dry weight	Regional variation in cirrhosis	Cholestatic diseases
Kayser–Fleischer rings (slit-lamp)	Present	40–50% with hepatic Wilson disease Most presymptomatic siblings	Primary biliary cirrhosis

Modified from Scheinberg and Sternlieb [23] and Ferenci [24].

- KF rings
- Typical neurologic symptoms
- Low ceruloplasmin level.

Diagnosis is more difficult in cases where KF rings are absent and the individual is presymptomatic or presents with liver disease only. Over 90% of patients with Wilson disease have low serum ceruloplasmin (<20 mg/dL), so it remains the best starting point [22]. Although ceruloplasmin could be elevated by acute inflammation, pregnancy, or estrogen therapy, a level >30 mg/dL virtually excludes the diagnosis [23]. An extremely low ceruloplasmin (<5 mg/dL) is strong evidence of Wilson disease; levels of 5–20 mg/dL are consistent with the diagnosis but should be investigated further [22]. The diagnosis requires the simultaneous demonstration of low serum ceruloplasmin and copper overload. If KF rings are not present, an elevated 24-h urinary copper excretion can be taken as proof of excess body copper, usually >100 µg/24 h in symptomatic patients [22]. Other chronic liver diseases may be associated with urinary copper excretion in this range, however. Results in the range 40–100 µg/24 h are consistent with Wilson disease but require further proof.

The hepatic copper concentration measured in liver biopsy tissue remains the gold standard for demonstrating copper excess [22,23]. Values >250 µg/g dry weight were present in over 90% of patients in a large retrospective series [25]. Heterozygotes do not have copper concentrations in that range. Hepatic copper levels <50 µg/g dry weight generally exclude the diagnosis of Wilson disease, but there may be marked variation from one part of the liver to another if the patient has cirrhosis [22].

There are two types of molecular genetic tests available: linkage analysis of polymorphisms in genes flanking the *ATP7B* gene, and direct sequencing of the *ATP7B* gene itself [22,26]. The first of these has been available for some time and is of value in testing first-degree relatives once an index case has been clinically defined. Haplotype analysis of flanking markers indicates which family members are homozygous or heterozygous [24]. Siblings of patients with Wilson disease have a 25% chance of having the disease and family genetic analysis is required. Direct gene sequencing can be used in this way, but may also be used to confirm a primary diagnosis of Wilson disease [22]. The patient's *ATP7B* gene is completely sequenced and compared with the wild type. If both alleles have mutations, and if the initial test results and clinical syndrome are consistent with Wilson disease, the diagnosis is established [24]. If no mutations are identified but the clinical syndrome is consistent with Wilson disease, then a liver biopsy is necessary to determine the copper concentration. The gene-sequencing test is available through Mayo Medical Laboratories.

Treatment

Drugs approved for the treatment of Wilson disease include trientine, *d*-penicillamine, and zinc [22]. Trientine and penicillamine promote the urinary excretion of copper; zinc blocks copper absorption and promotes fecal excretion [22,27]. Although *d*-penicillamine is an

effective anti-copper treatment and many patients continue to take it, it has been superseded by other treatments because of the relatively high frequency of adverse effects, including hypersensitivity reactions, a lupus-like syndrome, proteinuria, and serious skin disorders [22]. In addition, 15–20% of patients have the appearance or worsening of neurologic symptoms after starting treatment [25].

Trientine is now preferred as the initial treatment for Wilson disease because it has few side effects and has a low incidence of neurologic exacerbation [22]. It is given as 1000–1500 mg/day in two or three divided doses, or 20 mg/kg per day in children. Treatment is monitored by checking the 24-h urinary copper excretion within the first 2 weeks, then every 1–2 months. In the first phase of treatment, urinary copper excretion may be 1000–2000 μg/24 h or more. Over a period of months, excretion declines as available copper is removed, usually plateauing at 200–500 μg/24 h. Once this maintenance phase has been reached, urinary monitoring can be done every 6–12 months. Values <200 μg/24 h should raise suspicion of non-compliance with treatment, whereas values that are suddenly higher than previously may indicate non-compliance, with a brief resumption of treatment before the test. If KF rings were present, their gradual disappearance would confirm adequate treatment.

Another way to check the adequacy of treatment is to monitor the concentration of non-ceruloplasmin-bound copper in the blood [28]. This is calculated from simultaneous measurements of the total serum copper and the ceruloplasmin, and is equal to the total copper in micrograms per deciliter minus three times the ceruloplasmin concentration in milligrams per deciliter. Normal values are <15 μg/dL, whereas patients with untreated Wilson disease usually have values >25 μg/dL. During the maintenance phase of therapy, the non-ceruloplasmin-bound copper should be <20 μg/dL.

Zinc was first used over 40 years ago to treat Wilson disease in Europe. After subsequent testing in the USA, it was approved by the Food and Drug Administration (FDA) in 1997 for maintenance treatment of Wilson disease [29]. It has few side effects, mainly stomach irritation. It is given as 50 mg elemental zinc (as zinc acetate) three times a day on an empty stomach; 25 mg three times a day may be sufficient. As a result of the slower onset of efficacy than with trientine, and because deterioration of liver disease has been reported after starting zinc [22], it is not indicated as the initial therapy for symptomatic patients. The adequacy of therapy is monitored by ensuring that the urinary excretion of copper is <75 μg/day, while compliance with therapy is demonstrated by a urinary zinc excretion >2000 μg/day. Experience has shown that zinc is effective as initial and long-term treatment for presymptomatic patients [22].

Acute liver necrosis and chronic hepatitis may respond to anti-copper therapy quite dramatically. Almost 90% of patients with chronic liver disease have improvement or stability of liver function during long-term treatment [25]. Occasionally, patients who comply with long-term treatment may nevertheless have progression of underlying cirrhosis and require eventual transplantation. Neurologic symptoms may start to improve after 5–6 months of treatment and may continue to improve slowly over 12–18 months [27]. About 75% of patients with neurologic disease have improvement or stability in their symptoms while on treatment [25]. Among the neurologic symptoms, tremor often regresses but improvement in dysarthria and spasticity is variable.

Liver transplantation is indicated for patients with Wilson disease and fulminant hepatic failure or decompensation of chronic liver disease despite medical therapy [20]. Patients who discontinue long-term medical therapy in the mistaken belief that they do not need it have an unfortunately high likelihood of progression to fulminant hepatic failure or hepatic decompensation within 2–3 years of discontinuation [30]. This emphasizes the critical importance of monitoring patients for compliance with treatment. Transplantation corrects the metabolic defect, and copper depletion treatment is not needed thereafter [20]. Neurologic symptoms may improve after liver transplantation, but this is unpredictable and transplantation for neurologic indications remains controversial.

α_1-Antitrypsin Deficiency

Pathogenesis

α_1-Antitrypsin (A1AT) deficiency is inherited in an autosomal recessive pattern with co-dominant expression [20]. Liver disease associated with A1AT deficiency is not due to lack of the anti-protease function, but, rather, to accumulation of an abnormal form of the protein in the liver cells that secrete it. The mutant form of the A1AT

glycoprotein, defined electrophoretically as PiZ, polymerizes spontaneously in the endoplasmic reticulum (ER) of the hepatocyte and cannot complete the secretory pathway [31]. The accumulated protein can be removed from the ER and destroyed by a vesicular process known as autophagy wherein an autophagosome merges with a lysosome [32]. Individual variation in the efficiency of this alternate destructive pathway may explain the incomplete clinical penetrance observed among ZZ homozygotes. The presence of two Z alleles is independently associated with liver disease, whereas the presence of one Z allele appears to increase the risk of developing serious liver disease from other causes [32].

Clinical Features

A1AT deficiency is the most common hereditary cause of liver disease in children, appearing as neonatal hepatitis and cholestatic jaundice [31]. There is a bimodal age distribution of disease, with another epidemiologic peak appearing as chronic liver disease in adults. A Swedish case–control study showed that adults who are homozygous for the Z allele have an eightfold risk of developing cirrhosis and a twentyfold risk of developing hepatocellular carcinoma [4]. Interestingly, among adults who develop liver disease, the average age at presentation is 15 years older for Z heterozygotes than for ZZ homozygotes [33]. Moreover, 80–90% of adult heterozygotes with either cirrhosis or chronic hepatitis are found to have another identifiable cause of liver disease [4], suggesting that partial A1AT deficiency is a co-factor that increases the risk of serious liver disease from other causes.

Diagnosis

Only the Z allele is associated with liver disease, so diagnosis requires determination of the serum electrophoretic A1AT phenotype, not the serum level. Liver biopsy tissue stained with periodic acid–Schiff and treated with diastase shows the characteristic globular, red–purple intracellular inclusions, most commonly in periportal areas and at the periphery of regenerating nodules [4,31].

Treatment

As the liver abnormalities are due to hepatic accumulation of abnormal A1AT, treatments aimed at increasing the level of the enzyme are not effective for the liver disease. Liver transplantation is indicated for those with decompensated cirrhosis and selected individuals with hepatocellular carcinoma. A1AT deficiency is the most common metabolic liver disease requiring transplantation in children [31]. Transplantation cures the metabolic defect: the A1AT phenotype becomes that of the donor, and liver disease has not been documented to recur [31]. Whether liver transplantation can prevent the onset or progression of lung disease is not clear [20].

Take-home points

- Hereditary hemochromatosis (HH) is most commonly due to a deficiency or dysregulation of hepcidin, the liver-derived hormone that regulates the iron transporter ferroportin.
- The transferrin saturation varies widely and may be normal in HH.
- Elevation of the transferrin saturation or the serum ferritin should be evaluated further with *HFE* gene testing.
- The *C282Y/C282Y* genotype accounts for 90% of cases and the *C282Y/H63D* genotype for 5%; non-HFE hemochromatosis is rare.
- Most cases of HH do not have clinically apparent disease and are discovered through laboratory testing.
- Patients with HH and serum ferritin >1000 ng/mL should undergo assessment for possible cirrhosis.
- Phlebotomy is still the best overall treatment, but the oral compound deferasirox is an alternative.
- Hepatic copper toxicity in Wilson disease is due to mutations affecting the copper transport protein ATP7B.
- Wilson disease should be in the differential diagnosis of virtually every liver disease syndrome.
- The treatment of choice for Wilson disease is now trientine and/or oral zinc.
- α_1-Antitrypsin deficiency (ZZ) can cause liver disease; partial deficiency (MZ) can increase the risk of serious liver disease from other causes.
- Only the Z allele is associated with liver disease, so diagnosis requires determination of the α_1-antitrypsin phenotype, not the serum level.

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22

CHAPTER 22

Hepatic Steatosis and Non-alcoholic Fatty Liver Disease

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Summary

Non-alcoholic fatty liver disease (NALFD) encompasses a wide spectrum of liver injury ranging from bland hepatic steatosis to non-alcoholic steatohepatitis (NASH). Bland steatosis follows a relatively benign clinical course, but NASH may progress to cirrhosis. NAFLD affects about a third of the adult US population and up to 10% of children and teenagers. The demographics of NAFLD in the general population mirror those of the metabolic syndrome, which is characterized by obesity, diabetes, hypertension, and dyslipidemia. The real prevalence of NASH in the general population remains unknown, but up to 15% of patients with NASH on liver biopsy may progress to cirrhosis within 15 years. Several clinical and laboratory markers of liver injury can be used to predict the severity of NAFLD and help in deciding the need for a liver biopsy. Pharmacologic therapy holds promise, but lifestyle intervention with diet and increased physical activity remain the only treatment recommendation.

Case

A 38-year-old nursing student was doing well until 3 months earlier when she noticed abdominal distension associated with discomfort in the right side of her abdomen and occasional nausea. Abdominal discomfort increased with movements, bending, and breathing. Alcohol consumption was no more than 1–2 glasses of wine per week. She had not received a blood transfusion and was on no medications. She had a history of tonsillectomy and bladder augmentation surgery. She was divorced and living with her three daughters. Her weight was 80.1 kg, height 161 cm, body mass index (BMI) 30.9 kg/m^2, waist circumference 90 cm, and blood pressure 132/69 mmHg. Her abdomen had moderate tenderness in the right upper quadrant; the liver edge was palpable about three fingerbreadths below the costal margin and was tender. There was no palpable spleen and no ascites. The rest of the physical examination was unremarkable. Laboratory studies showed total cholesterol 400 mg/dL, high-density lipoprotein (HDL) 35 mg/dL, triglycerides 522 mg/dL, fasting glucose 83 mg/dL, alanine transaminase (ALT) 64 IU/L (normal 9–29 IU/L), aspartate transaminase (AST) 58 IU/L (normal 12–31 IU/L), normal alkaline phosphatase, bilirubin, albumin, and international normalized ratio (INR); antinuclear antibody (ANA) positive 1:40, antismooth muscle antibody (ASMA) and antimitochondrial antibody (AMA) negative; total proteins 7.23 g/dL (normal 6.3–7.9 g/dL), γ-globulins 1.09 g/dL (normal 0.7–1.7 g/dL), negative hepatitis serology, serum iron 118 μg/dL (normal 35–145 μg/dL), ferritin 500 μg/L (normal 20–120 μg/L), transferrin saturation 28% (normal 14–50%). Abdominal ultrasonography and CT scan showed hepatomegaly with fatty infiltration of the liver.

Definition and Epidemiology

Hepatic steatosis refers to the accumulation of fat (mainly triglycerides) in hepatocytes that results from insulin resistance. Non-alcoholic fatty liver disease (NAFLD)

Practical Gastroenterology and Hepatology: Liver and Biliary Disease, 1st edition. Edited by Nicholas J. Talley, Keith D. Lindor and Hugo E. Vargas.

Table 22.1 Causes of non-alcoholic fatty liver disease.

Primary	Secondary				
	Nutritional	**Drugs**	**Metabolic**	**Toxins**	**Infections**
Obesity Glucose intolerance Type 2 diabetes Hypertriglyceridemia Low HDL-cholesterol Hypertension	Protein–calorie malnutrition Rapid weight loss Gastrointestinal bypass surgery Total parental nutrition	Glucocorticoids Estrogens Tamoxifen Amiodarone Methotrexate Diltiazem Zidovudine Valproate Aspirin Tetracycline Cocaine	Lipodystrophy Hypopituitarism Dysbetalipoproteinemia Weber–Christian disease	*Amanita phalloides* mushroom Phosphorus poisoning Petrochemicals *Bacillus cereus* toxin	Human immunodeficiency virus Hepatitis C Small bowel diverticulosis with bacterial overgrowth

HLD, high-density lipoprotein.

encompasses a wide spectrum of disease from bland hepatic steatosis, which is generally benign, to non-alcoholic steatohepatitis (NASH), which may progress to cirrhosis and liver failure. Hence, simple hepatic steatosis represents only one side of the spectrum of NAFLD. NAFLD is recognized as the most common chronic liver disease in the Western world [1].

NAFLD may be categorized as primary or secondary depending on the underlying pathogenesis (Table 22.1). Primary NAFLD occurs most commonly, and is associated with insulin-resistant states, such as obesity, type 2 diabetes, and dyslipidemia. Other conditions associated with insulin resistance, such as polycystic ovarian syndrome and hypopituitarism, have also been described in association with NAFLD. Distinction from secondary types is important because these have different treatment and prognosis. Primary NAFLD has reached epidemic proportions in many countries around the world as demonstrated in several population-based studies. In the USA, 34% of the population aged 30–65 years and 9.6% of the population aged 2–19 years have hepatic steatosis [2,3]. If these figures are extrapolated to the 2007 US population, over 55 million Americans have NAFLD. The prevalence of NAFLD in the general population in the USA is almost 14-fold higher than the prevalence of hepatitis C virus (HCV) infection—which affects about 4 million people—and almost threefold higher than alcohol-induced liver disease; about 20 million people in the USA have some degree of alcohol-induced liver disease.

Pathophysiology

It is now well established that insulin resistance is the principal pathophysiologic driver of NAFLD, with adipose tissue playing a key role in the early events leading to insulin resistance. In human obesity, adipose tissue, particularly that with an intra-abdominal (visceral) location, is characterized by inflammation with increased number of infiltrating CD14+ macrophages. Macrophages in adipose tissue correlate directly with adipose tissue mass (body mass index—BMI) and even more strongly with visceral adipose tissue [4]. Weight gain is associated with the appearance of macrophages within the adipose tissue, and these changes predate the development of insulin resistance and its attendant metabolic abnormalities [5,6]. Macrophages, adipocytes, preadipocytes, and endothelial cells within the adipose tissue produce a number of adipocytokines with either pro- or anti-inflammatory effects. In the insulin-resistant states, the profile of adipocytokines produced is predominantly proinflammatory, prothrombotic, and profibrogenic. A key metabolic effect of these adipocytokines is a relatively greater activity of hormone-sensitive lipase, resulting in a net increase in peripheral lipolysis and release of free fatty acids (FFAs) into the circulation. FFAs impair insulin signaling in striated muscle, decreasing the metabolic clearance of glucose. The pancreas responds to the increased glucose and FFAs by increasing insulin secretion. Over time, sustained overproduction of insulin induces injury of islet β cells, causing a failure to produce

Table 22.2 Main clinical, laboratory, and diagnostic characteristics of non-alcoholic fatty liver disease.

Clinical features	Laboratory abnormalities	Liver biopsy features	Imaging features	Exclusion of
Usually asymptomatic, sometimes mild right-upper quadrant discomfort, hepatomegaly, acanthosis nigricans, 'cryptogenic' cirrhosis Often associated with features of the metabolic syndrome: hyperglycemia or type 2 diabetes, obesity, dyslipidemia (hypertriglyceridemia, low HDL-cholesterol), hypertension	Elevated ALT and AST (usually less than fivefold normal) Elevated alkaline phosphatase and γ-glutamyltransferase (usually less than threefold normal) AST:ALT ratio <1; hyperinsulinemia, hyperglycemia, and insulin resistance; dyslipidemia, elevated ferritin	Steatosis (fatty infiltration >5% hepatocytes) Necroinflammation, typically with a zone 3 lobular distribution Mallory bodies; hepatocyte ballooning Fibrosis (perisinusoidal, perivenular, bridging, cirrhosis) Portal-based injury common in children	Imaging indicative of fatty infiltration of the liver (ultrasonography, CT, MRI, magnetic resonance spectroscopy)	Alcohol intake <140 g/week (women) or <210 g/week (men) Liver disease of viral, autoimmune, genetic origin; hemochromatosis

ALT, alanine transaminase; AST, aspartate transaminase; HDL, high-density lipoprotein.

enough insulin to maintain euglycemia and resulting in diabetes [7].

Fat accumulated in hepatocytes (steatosis) can be traced to three main sources, namely circulating FFAs, dietary content, and new synthesis. In patients with NAFLD on a normal diet, approximately 60% of hepatic fat derives from circulating FFAs. Peripheral insulin resistance and its resulting increase in lipolysis provide increased FFAs. Further, increased delivery of FFAs to the liver induces lipotoxicity and hepatocyte injury [8]. Hepatic steatosis leads to increased nuclear factor (NF)-κB signaling in the liver [9]. NF-κB activation then induces the production of local and systemic inflammatory mediators such as tumor necrosis factor (TNF)-α, interleukins IL-6, and IL-1β, and activation of Kupffer cells and macrophages within the liver. In addition, several of the proinflammatory adipocytokines induce activation of hepatic stellate cells, resulting in increased production of collagenous matrix and development of live fibrosis. Matrix production is also modulated by hepatic stellate cell apoptosis, which can be affected by cannabinoid receptor activation as well [10].

Clinical Features (Table 22.2)

Symptoms and Signs

Patients may complain of fatigue or malaise and a sensation of fullness or discomfort in the right upper abdomen. Hepatomegaly and acanthosis nigricans in children are common physical findings, although stigmata of chronic liver disease suggestive of cirrhosis are uncommon. The impact of NAFLD on health-related quality of life is currently being evaluated. However, several studies have found a significant detrimental impact on health-related quality of life from the several comorbidities that comprise the metabolic syndrome and often cluster with NAFLD.

The most common comorbidities associated with NAFLD are the components of the metabolic syndrome [11–13]. The current definition of the metabolic syndrome includes three or more of the following features: fasting glucose ≥100 mg/dL, central obesity with waist circumference >102 cm (40 inches) in men and >88 cm (35 inches) in women, blood pressure ≥130/85 mmHg, fasting triglyceride ≥150 mg/dL, and low HDL-cholesterol (<40 mg/dL in men, <50 mg/dL in women) [12]. About 90% of NAFLD patients have a BMI ≥25 kg/m^2. Obesity (BMI ≥30 kg/m^2) is present in 50% of patients with NAFLD, type 2 diabetes in 28%, dyslipidemia (hypertriglyceridemia, hypercholesterolemia, or low HDL-cholesterol alone or in combination) in 55%, and hypertension in 60%; almost half of patients with NAFLD have the metabolic syndrome, i.e., have at least three features of the metabolic syndrome (Figure 22.1). Also, about 75% of lean patients (BMI <25 kg/m^2) with NAFLD have at least one feature of the metabolic syndrome [13].

Most patients with NAFLD and a BMI ≥35 kg/m^2 also meet the criteria for central obesity as defined above. The

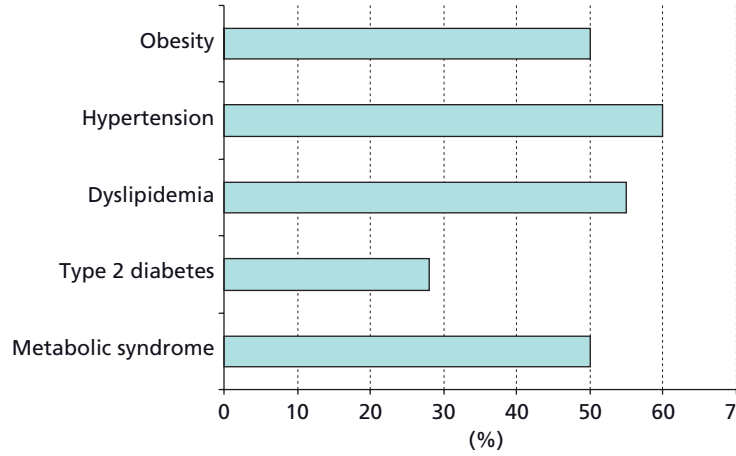

Figure 22.1 Prevalence of features of the metabolic syndrome in non-alcoholic fatty liver disease [13].

presence and severity of NAFLD correlate with central obesity more strongly than with the BMI, supporting the notion that fat with an intra-abdominal (visceral) location is metabolically different from fat with a more peripheral or subcutaneous location [14]. Some patients with NAFLD may have a BMI <35 kg/m^2 and still have central obesity, whereas many individuals with a high BMI do not have NAFLD. There are differences in body fat distribution among the different ethnic groups, which may be one of the factors explaining the different NAFLD prevalence among the different ethnic groups in the USA, with a higher prevalence among adult Hispanic individuals (45%) as compared with white adults (33%) and African–American adults (24%). In the USA, a prevalence difference between adult men and women is found only among white people (42% men vs 24% women) [2].

Laboratory Abnormalities

Serum liver enzyme abnormalities are often restricted to elevations of alanine transaminase (ALT) and/or aspartate transaminase (AST), and usually at levels below fivefold normal. Transaminase levels among NAFLD patients fluctuate, with normal levels present in up to 78% of patients at any one time, but are elevated in more than 20% of these patients if repeated at several points during the follow-up. Alkaline phosphatase and γ-glutamyltransferase levels may be modestly elevated (generally less than threefold normal) in a third of cases but are rarely elevated in isolation. Hyperbilirubinemia, low albumin levels, or increased INR usually indicates decompensated cirrhosis.

Serum iron tests are commonly abnormal, with elevated ferritin levels observed in up to 50% of patients and raised transferrin saturation in up to 10% of cases. These findings may potentially lead to confusion regarding a diagnosis of hemochromatosis. Whether there is an increased prevalence of heterozygous *HFE* gene mutations among patients with NAFLD is controversial; however, their presence does not appear to be associated with increased hepatic iron or liver fibrosis. Serum ANAs and/or ASMAs are present in 23–36% of NAFLD patients and may rarely indicate coexistent autoimmune liver disease. In one series of 225 NAFLD patients, 8% of autoantibody-positive patients also had coexistent features of autoimmune hepatitis on liver biopsy, but the liver biopsy features helped to exclude the diagnosis of autoimmune hepatitis in the vast majority of patients with NAFLD who were ANA and/or ASMA positive [15]. Other laboratory abnormalities commonly seen in patients with NAFLD are hyperglycemia, hyperinsulinemia, and increased levels of triglycerides and total cholesterol, and decreased levels of HDL-cholesterol.

Imaging Features

Ultrasonography, CT, and MRI can non-invasively diagnose fatty infiltration of the liver. Hepatic steatosis increases the liver echogenicity on ultrasonography, which can be contrasted against the lower echogenicity of the spleen or renal cortex. A similar pattern can be seen with diffuse fibrosis, giving rise to the term "fatty-fibrotic pattern," although the echo shadows tend to be coarser in the presence of pure fibrosis. The sensitivity

and specificity of ultrasonography for detecting hepatic steatosis vary from 60% to 94% and 88% to 95%, respectively. However, the sensitivity of ultrasonography decreases with lower degrees of fatty infiltration. In the presence of ≥30% fatty infiltration, the sensitivity of ultrasonography is 80% compared with a sensitivity of 55% when hepatic fat content is 10–19% [16]. Similarly, the sensitivity and specificity of ultrasonography decrease in the presence of morbid obesity to 49% and 75%, respectively [17].

On non-contrast images on CT scans, hepatic steatosis has a low attenuation and appears darker than the spleen. The sensitivity of CT at detecting >33% hepatic steatosis is up to 93%, with a positive predictive value of 76% [16]. Both MR phase contrast imaging techniques and magnetic resonance spectroscopy (MRS) are reliable at detecting steatosis and offer good correlation with hepatic fat volume. More than 5% of hepatic fat content on MRS indicates the presence of steatosis [18]. However, the routine application of MR images is limited by cost and lack of availability.

Histologic Features

NAFLD is histologically indistinguishable from liver damage resulting from alcohol abuse. Liver biopsy features include steatosis, mixed inflammatory cell infiltration, hepatocyte ballooning and necrosis, glycogen nuclei, Mallory hyaline, and fibrosis [19]. The presence of steatosis alone or in combination with the other features accounts for the wide spectrum of NAFLD (Figure 22.2). Steatosis is present predominantly as macrovesicular fat, although some hepatocytes may show an admixture with microvesicular steatosis. Fatty infiltration when mild is typically concentrated in acinar zone 3, whereas moderate-to-severe fatty infiltration shows a more diffuse distribution. The inflammatory infiltrate usually consists of mixed neutrophils and lymphocytes, and predominates in zone 3. Ballooning degeneration of hepatocytes results from intracellular fluid accumulation and is characterized by swollen cells typically noted in zone 3 near the steatotic hepatocytes. Mallory hyaline is found in about half adult patients with NAFLD and is usually located in ballooned hepatocytes in zone 3, but it is neither unique nor specific for NAFLD. The pattern of fibrosis is one of NAFLD's characteristic features. Collagen is first laid down in the pericellular space around the central vein, and in the perisinusoidal region in zone 3. In some areas, the collagen invests single cells in a pattern referred to as "chicken-wire" fibrosis as described in alcohol-induced liver damage. This pattern of fibrosis helps to distinguish NAFLD and alcoholic liver disease from other forms of liver disease in which fibrosis shows an initial portal distribution.

Portal tracts are relatively spared from inflammation, although children with NAFLD may show a predominance of portal-based injury as opposed to a lobular pericentral injury. Mallory hyaline is notably sparse or absent in children with NAFLD. In some patients at the cirrhotic stage, the features of steatosis and necroinflammatory activity may no longer be present.

The histologic distinction between hepatic steatosis and NASH with high-grade inflammation and fibrosis is relatively clear; however, differentiating more subtle changes in the middle of the spectrum can be difficult. Furthermore, different histologic definitions have been used to categorize NASH. The most accepted definition of NASH requires the presence of zone 3 accentuated macrovesicular steatosis together with mild mixed lobular inflammation and hepatocellular ballooning. Although liver biopsy is the gold standard for NASH diagnosis and staging fibrosis, sampling variability may underestimate the severity of liver injury.

Assessment of Disease Severity

Liver biopsy is the only investigation that can differentiate NASH from simple steatosis, and stage the extent of fibrosis. Imaging studies such as ultrasonography, CT, and MRI are not able to distinguish between steatosis and NASH, nor can they stage the degree of hepatic fibrosis. Recently, measuring the liver stiffness with ultrasound- or MR-based elastography has been proposed as potentially useful for quantification of liver fibrosis in patients with a wide range of chronic liver disease [20]; however, further evaluation of these techniques in patients with NAFLD is necessary.

The potential benefits of liver biopsy must be weighed against the small risk of complications, including pain, bleeding, and death. The decision to pursue biopsy needs to be individualized and discussed with each patient. A number of clinical and laboratory features may facilitate separation of patients with simple steatosis from those with NASH, and distinguish between those with and

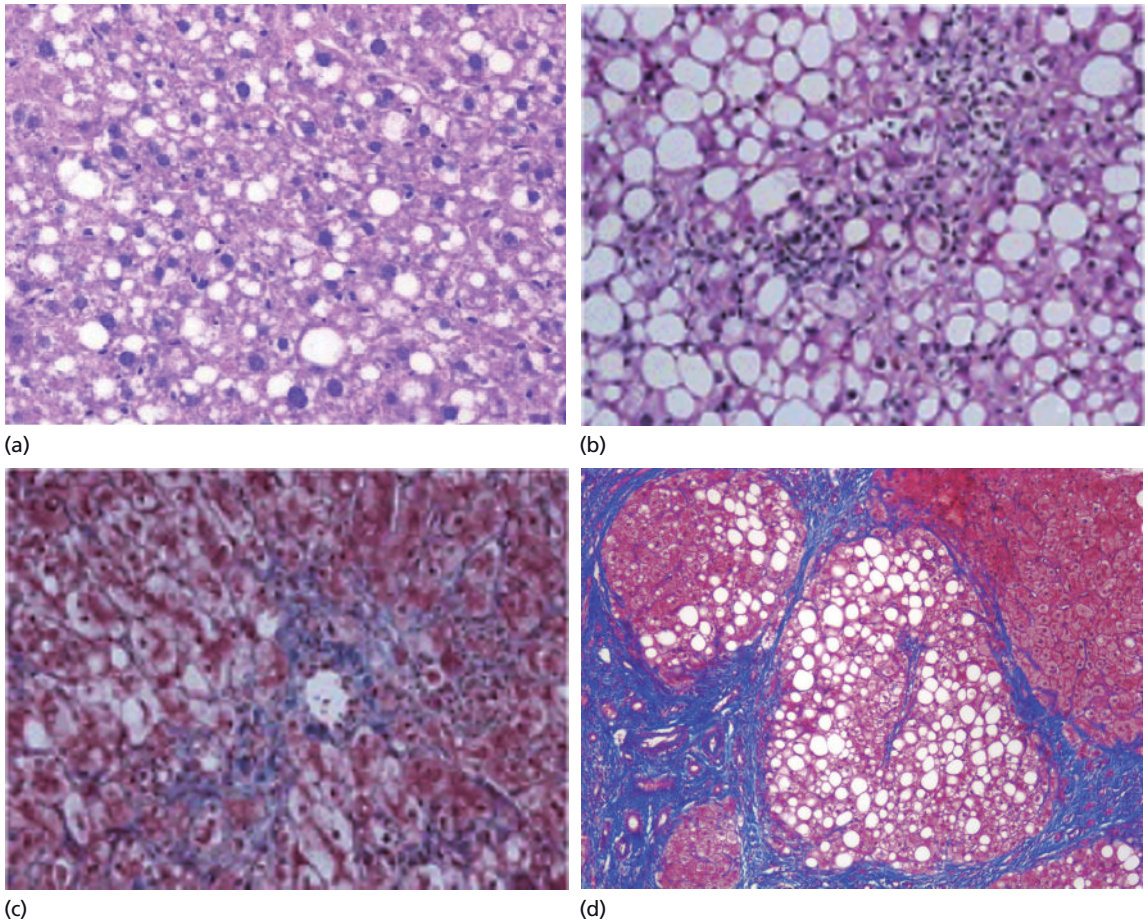

Figure 22.2 (a) Liver biopsy showing bland steatosis (H & E, × 100). Steatosis is present predominantly as macrovesicular fat, although some hepatocytes may show an admixture with microvesicular steatosis. (b) Liver biopsy showing non-alcoholic steatohepatitis (NASH) with steatosis, inflammatory infiltrate, Mallory hyaline, and hepatocyte ballooning (H & E, × 100). (c) Liver biopsy showing pericellular and perisinusoidal fibrosis in zone 3 (Masson trichrome, × 400). (d) Liver biopsy showing cirrhotic stage NAFLD (Masson trichrome, × 100).

those without advanced fibrosis. Caspase-3-generated cytokeratin (CK)-18 fragments, a marker of apoptosis measured in plasma, have been evaluated in distinguishing simple steatosis from NASH [21]. In a recent study on 44 patients with NAFLD, a CK-18 value of 395 U/L had a specificity of 99.9%, a sensitivity of 85.7%, and positive and negative predictive values of 99.9% and 85.7%, respectively, for the diagnosis of NASH [21]. The severity of fibrosis can also be predicted using a combination of routine clinical and laboratory variables such as older age, presence of diabetes, higher BMI, higher AST:ALT ratio, and low albumin and platelet count [13,22]. These features have been combined in numerical scores aimed at predicting the presence or absence of advanced fibrosis in NAFLD (Table 22.3).

Advanced fibrosis among NAFLD patients has been associated with levels of novel serum markers of fibrogenesis, including hyaluronic acid, propeptide of type III collagen, and the tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) [23]. These serum markers have been combined in a numerical score named the enhanced liver fibrosis panel to predict presence and severity of liver fibrosis in NAFLD (Table 22.3). Similarly, the fibrotest, which has been extensively studied in viral hepatitis to

Table 22.3 Clinical and serum markers of fibrogenesis proposed as predictors of advanced (stage 3–4) fibrosis in patients with non-alcoholic fatty liver disease.

Reference	n	Clinical score/Serum marker	AUC	Sensitivity (%)	Specificity (%)
13	733	–1.675 + 0.037 × age (years) + 0.094 × BMI (kg/m^2) + 1.13 × IFG:diabetes (yes = 1, no = 0) + 0.99 × AST:ALT ratio –0.013 × platelet (× 10^9/L) – 0.66 × albumin (g/dL)	0.88		
		Score <–1.455		82	77
		Score >0.676		51	98
21	827	BMI ≥28 kg/m^2 = 1 AST:ALT ratio ≥0.8 = 2 Presence of diabetes = 1			
		Score = 2–4	0.81	PPV = 43	NPV = 96
22	192	–7.412 + (ln(HA)[a] × 0.68) + (ln(P3NP)[a] × 0.775) + (ln(TIMP-1)[a] × 0.494) ELF = 0.3576	0.93	80	90
23	267	Fibrotest >0.30	0.88	92.0	71.0
		Fibrotest >0.70	0.88	25.0	97.0

[a]Predicting presence of fibrosis vs absence of fibrosis.
AUC, area under the receiver operator characteristic curve; ELF, enhanced liver fibrosis; HA, hyaluronic acid; IFG, impaired fasting glucose; ln, logarithm negative; NPV, negative predictive value; P3NP, propeptide of type III collagen; PPV, positive predictive value; TIMP-1, tissue inhibitor of matrix metalloproteinase-1.

predict severity of fibrosis, has been evaluated in NAFLD [24] (Table 22.3). Although all these scores, which are based on clinical and laboratory markers, aid in the decision about who should be biopsied, further validation is required before they can routinely be used in clinical practice.

Diagnosis

The most common clinical scenario leading to diagnosis of NAFLD is asymptomatic elevation of serum transaminase (ALT, AST) levels not due to viral hepatitis, iron overload, or alcohol abuse. When these other liver diseases are ruled out, NAFLD is the likely cause in most cases. Transaminases, however, are elevated in only 20% of the general population with NAFLD [2]. The AST:ALT ratio is usually <1, but this ratio increases as fibrosis advances to the cirrhotic stage [25,26]. Fatty infiltration of the liver as detected by ultrasonography is also likely to be due to NAFLD in most cases. These findings by themselves are not, however, sufficient to make a diagnosis of NAFLD. Supportive clinical, serologic, and sometimes histologic evidence is also required. The presence of features of the metabolic syndrome increase the likelihood of NAFLD, but these features are common in the general population and not specific for the diagnosis.

The gold standard for diagnosing NAFLD is clinicopathologic correlation, based on confirmation of steatosis by liver biopsy and appropriate exclusion of other etiologies (see Table 22.2). It is important to exclude alcohol abuse as the cause of fatty liver. It is known that a minimal amount of alcohol of 20 g/day (1–2 standard drinks) in women and 30 g/day (2–3 standard drinks) in men can induce fatty liver and these limits are commonly used to distinguish between alcoholic and non-alcoholic fatty liver. Secondary causes of NAFLD (see Table 22.1) should be ruled out because NAFLD associated with these conditions has a different course and treatment.

Differential Diagnosis

Patients with chronically elevated serum liver enzymes should have other causes excluded by clinical review and

laboratory testing. The extent of laboratory evaluation should be individualized [26]. Although 66–90% of individuals with chronically elevated liver enzymes with a negative laboratory evaluation have NAFLD, other potential diagnoses in these patients are drug-related liver injury, normal or non-specific changes on liver biopsy, autoimmune hepatitis, chronic biliary disease, and granulomatous liver disease. A liver biopsy may be useful to diagnose NAFLD when a potentially different diagnosis is suggested by clinical or laboratory testing. These situations include the presence of autoantibodies or raised iron indices, a history of recent medication change, or the absence of detectable hepatic steatosis on cross-sectional imaging. Also, persistence of elevated transaminases after 3–6 months of lifestyle intervention with appropriate weight loss and control of lipids and glucose levels may suggest another diagnosis and dictate the need for a liver biopsy.

NAFLD should be considered as a possible differential diagnosis among patients with "cryptogenic" cirrhosis. The prevalence of metabolic risk factors such as diabetes and obesity is similar among patients with cryptogenic cirrhosis and NAFLD. In addition, the prevalence rates of these risk factors are higher when compared with patients with cirrhosis of other etiologies, suggesting that NASH accounts for a substantial proportion of cases of cryptogenic cirrhosis. Rarely, NASH is a consideration in patients with subacute liver failure, having been observed among individuals who have silently progressed to cirrhosis before an unknown stimulus precipitates liver failure.

Case

The clinical diagnosis of NAFLD in the patient described is pretty straightforward based on the presence of features of the metabolic syndrome (central obesity, hypertriglyceridemia, and low-HDL cholesterol), elevated transaminases (less than threefold normal), confirmation of fatty infiltration of the liver on imaging studies, and a negative alcohol and medication history and negative viral serology. The presence of ANA at low titers without other laboratory features of autoimmune hepatitis, and increased ferritin with normal serum iron and transferrin saturation, are not uncommon in patients with NAFLD as described previously. The need for a liver biopsy to confirm the diagnosis of NAFLD and stage the disease was extensively discussed with the patient who opted to have her case re-evaluated after treatment.

Prognosis

The high prevalence of NAFLD in the general population contrasts with the relatively small proportion of individuals with NAFLD who will show evidence of disease progression or will develop complications of end-stage liver disease. The natural history of uncomplicated hepatic steatosis is relatively benign, with follow-up of 239 patients for an average of 12 years demonstrating progression to cirrhosis in three (1.3%) patients and liver-related death in only two patients (0.8%) [27,28]. In contrast, up to 15% of patients with NASH, particularly those with fibrosis, may progress to cirrhosis within 15 years of diagnosis [28,29]. The presence of advanced fibrosis or cirrhosis should initiate screening for hepatocellular carcinoma and esophageal varices with closer monitoring for disease-related complications. Histologic staging is also valuable for tracking disease progression or monitoring response to therapy. It is important to keep in mind, however, that changes in transaminase levels do not reliably correlate with histologic changes over time.

Treatment (Table 22.4)

Treatment of NAFLD is aimed at correcting the underlying risk factors and comorbid conditions, but there are no proven therapies at this point [30].

Treatment of Associated Conditions

A large body of clinical and epidemiological data gathered over the last three decades indicates that obesity, type 2 diabetes mellitus, and dyslipidemia are major associated conditions or predisposing factors leading to the development of NAFLD. Hence, it is reasonable to believe that the prevention or appropriate management of these conditions would lead to improvement or arrest of the liver disease. Weight loss, particularly if gradual, may lead to improvement in liver histology in NAFLD. However, rate and degree of weight loss required for normalization of liver histology have not been established. Total starvation or very-low-calorie diets may cause worsening of liver histology and thus should be avoided. The National Heart, Lung, and Blood Institute and the National Institute of Diabetes and Digestive and Kidney Diseases expert panel clinical guidelines for weight loss recommend that

Table 22.4 Therapeutic options in non-alcoholic fatty liver disease/non-alcoholic steatohepatitis.

Lifestyle changes	Insulin-sensitizing agents	Antioxidants and cytoprotective agents	Other treatments and future areas of research
Weight reduction	Metformin	Vitamins E and C	Anti-TNF-α antibodies
Reduce total fat intake to <30% energy	Pioglitazone	Betain	Pentoxifylline
Replace saturated with unsaturated fats	Rosiglitazone	Taurine	Antifibrotic medications
Increase fiber intake to >15 g/day		*N*-Acetylcysteine	Angiotensin II receptor antagonists
Increase physical activity		Sibilin	CB-1 receptor antagonists
		Ursodeoxycholic acid	Caspase inhibitors
		Fibrates and statins	
		Orlistat, sibutramine, phentermine	

Other than ursodeoxycholic acid, none of these medications has been evaluated in well-controlled, appropriately powered, randomized trials.

CB, cannabinoid; TNF, tumor necrosis factor.

the initial target for weight loss should be 10% of baseline weight within a period of 6 months. For most, this can be achieved by losing about 0.45–0.90 kg (1–2 lb) per week. With success, further weight loss can be attempted if indicated. The panel recommended weight loss using multiple interventions and strategies, including lifestyle modification (i.e., diet modifications and increased physical activity), behavioral therapy, pharmacotherapy (i.e., orlistat, phentermine, sibutramine), and surgery, as well as a combination of these treatment modalities. The recommendation for a particular treatment modality or combination should be individualized, considering the BMI and presence of concomitant risk factors and other diseases. The panel did not make specific recommendations for the subgroup of patients with NAFLD; however, given the lack of clinical trials in this area, the overall panel recommendations may be a useful and safe first step for obese patients with NAFLD. Similarly, no specific recommendations for liver test monitoring during weight loss were made, but measurement of liver enzymes monthly during weight loss seems appropriate.

Different dietary caloric restrictions have been used. However, further studies are necessary to determine the most appropriate content of the formula to be recommended for obese and/or diabetic patients with NAFLD. In the absence of well-controlled clinical trials in patients with NAFLD, it may be tempting to recommend a heart-healthy diet as recommended by the American Heart Association for those without diabetes, and a diabetic diet as recommended by the American Diabetes Association for those with diabetes. Dietary supplementation with *n*-3 polyunsaturated and monounsaturated fatty acids may improve insulin sensitivity and prevent liver damage. Saturated fatty acids worsen insulin resistance whereas dietary fiber can improve it. Nevertheless, the effect of such a dietary modifications in patients with fatty liver remains to be established. Diet to produce weight loss should always be prescribed on an individual basis and considering the patient's overall health. Patients who have obesity-related disease, such as diabetes mellitus, hyperlipidemia, or cardiovascular disease, will require close medical supervision during weight loss to adjust medication dosage as needed.

Improving insulin sensitivity with lifestyle changes or medications usually improves glucose and lipid levels in patients with diabetes and hyperlipidemia. Improving insulin sensitivity in these patients is expected to improve the liver disease, but, in many diabetic/hyperlipidemic patients with NAFLD, the appropriate control of glucose and lipid levels is not always accompanied by improvement of the liver condition.

Pharmacologic Treatment

Based on the fact that achieving and maintaining appropriate weight control is a difficult task to accomplish for most obese patients, the use of medications that can directly reduce the severity of liver damage independently of weight loss is a reasonable alternative. Pharmacologic therapy may also benefit those patients who lack risk factors or associated conditions such as non-obese, non-diabetic patients and those with a normal lipid profile. However, pharmacologic therapy directed specifically at the liver disease has only recently been evaluated in patients with NAFLD. Most of these studies have

been uncontrolled, open label, and lasting 1 year or less, and only a few of them have evaluated the effect of treatment on liver histology. Results of pilot studies evaluating insulin sensitizer medications, antioxidants, lipid-lowering medications, and some hepatoprotective medications suggest that these medications may be of potential benefit, but well-designed controlled trials are needed before any of these medications can be recommended for patients with NAFLD.

General Recommendations

An attempt at gradual weight loss is a useful first step in the management of patients with NAFLD as well as making a concerted effort to maintain appropriate control of serum glucose and lipid levels. Perhaps this, along with appropriate exclusion of other liver disease, may be the only treatment recommendation for those patients with pure steatosis and no evidence of necroinflammation or fibrosis, who seem to have the best prognosis within the spectrum of NAFLD. Patients with NASH, particularly those with increased fibrosis on liver biopsy, should be monitored closely, make a greater effort for adequate metabolic control, and be offered enrollment in well-controlled clinical trials, if available. Pharmacologic therapy holds promise, but data from well-controlled clinical trials are still needed to determine not only the efficacy but also the long-term safety of the several medications.

For those patients with cirrhotic stage NAFLD and decompensated disease, liver transplantation is a potential life-extending therapeutic alternative although some cirrhotic patients with NAFLD suffer from comorbid conditions that often preclude liver transplantation.

Case

A low-calorie, low-saturated fat diet, tailored to the patient's preferences, plus increased physical activity with aerobic exercise for 30–45 min a day at least four times a week was recommended. At her 3-month re-evaluation she had managed to lose 5 kg and her ALT and AST were within the normal range. Her total cholesterol had decreased to 290 mg/dL, and her triglyceride levels to 230 mg/dL. Treatment continued and at her 6-month evaluation she had managed to lose a total of 9 kg, her laboratory tests showed normal transaminases levels, a total cholesterol level of 189 mg/dL, an HDL-cholesterol level of 40 mg/dL, and a triglyceride level of 200 mg/dL.

Take-home points

- Non-alcoholic fatty liver disease affects a substantial proportion of the general population and represents the most common cause of elevated liver enzymes.
- Simple hepatic steatosis follows a relatively benign clinical course but steatohepatitis associated with increased fibrosis may progress to cirrhosis and liver cancer.
- The diagnosis of NAFLD requires exclusion of other causes of liver disease along with confirmation of fatty infiltration of the liver on imaging studies.
- Liver biopsy is the only tool that allows differentiation between simple steatosis and steatohepatitis and fibrosis staging.
- Lifestyle modification with diet and increased physical activity represent the only treatment modality potentially effective for patients with NAFLD.
- Pharmacologic therapy holds promise but large well-controlled trials are needed before any medication can be recommended for the treatment of this condition.

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CHAPTER 23
Drug-induced Liver Injury

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Summary

Drug-induced liver injury (DILI) is a rare but significant health problem. It is generally classified into intrinsic and idiosyncratic types: intrinsic DILI is generally dose dependent and predictable (e.g., acetaminophen toxicity), whereas idiosyncratic DILI is unpredictable and is generally not dose related. The clinical picture of DILI can range from asymptomatic elevation in liver biochemical tests to acute or chronic liver injury and acute liver failure. DILI is characterized into hepatocellular, cholestatic, or a mixed pattern based on liver biochemistries at clinical presentation. The diagnosis of DILI requires a high degree of clinical suspicion and exclusion of appropriate competing etiologies. In patients with idiosyncratic DILI, prompt withdrawal of the offending agent vastly improves the prognosis whereas its inadvertent continuation may lead to serious consequences including liver failure and death.

Case

A 55-year–old woman presented with a few days' history of lethargy, nausea, and abdominal pain. She is originally from Mexico and had a longstanding history of Crohn's disease, which lately has been difficult to control. Her gastroenterologist planned therapy with biologic agents but she was found to be PPD (purified protein derivative) positive. She was subsequently placed on isoniazid to treat her latent tuberculosis 2 months before current presentation. Due to upper right quadrant pain she was admitted to the surgery service. Clinical examination revealed right upper quadrant tenderness and abdominal ultrasonography showed sludge in the gall bladder which had wall thickening but no dilation of the biliary tree. Her serum AST was 1110 IU/L and ALT 1600 IU/L, alkaline phosphatase 300 IU/L, total bilirubin 2.0 mg/dL, and INR (international normalized ratio) 1.7. She underwent laparoscopic cholecystectomy which was uneventful but postoperatively her liver tests deteriorated (INR increased to 5.5 and bilirubin to 12 mg/dL) and developed severe lethargy. A hepatology consult was sought and a prompt transfer to a liver transplant center was recommended. She was put on the waiting list for liver transplantation with a working diagnosis of isoniazid-induced fulminant liver failure, but she died while waiting on the list a week later.

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Definition and Epidemiology

An adverse drug reaction can be defined as any drug response that is unintended and noxious and occurs at the normal dose of the drug. Drug-induced liver injury (DILI), hepatotoxicity, and adverse liver reactions are terms used interchangeably in this context. In general, DILI is broadly categorized into intrinsic and idiosyncratic types: intrinsic DILI is dose dependent and predictable (e.g., acetaminophen [paracetamol] toxicity), whereas idiosyncratic DILI is unpredictable and generally thought not to be dose related. Most liver injuries resulting from acetaminophen are associated with its intentional or unintentional overdose [1]. Although acetaminophen toxicity accounts for most DILI cases, a significant number of cases still result from idiosyncratic

injury caused by a variety of medications and herbal agents. Although traditionally idiosyncratic drug reactions have not been considered to be dose dependent, recent data suggest that oral medications with average daily dose <50 mg are very rarely associated with idiosyncratic DILI [2].

For most drugs, hepatotoxicity is extremely rare with an estimated risk ranging from 1 in 10 000 to 1 in 100 000 of those who are exposed to the drug [3]. However, in most clinical trials, the number of patients included is generally fewer than 10 000 and thus the risk of hepatotoxicity is not evident until the compound is in the post-marketing phase [3]. Lack of systematic surveillance for adverse events makes it very difficult to accurately estimate the frequency of DILI and there is no doubt that the incidence of DILI is greatly underestimated. Thus, the true incidence of idiosyncratic DILI remains unclear.

Based on retrospective data from the General Practice Research Database in the UK [4], an annual crude incidence of 2.4 cases/100 000 inhabitants was found and a very similar incidence was extrapolated from a Swedish study over a 10-year period [5]. More reliable data on the true incidence of DILI was provided by a prospective survey conducted on the general population of a French city [6]. The incidence of DILI was found to be 13.9 cases/100 000 inhabitants, which was approximately 16 times more frequent than the estimates based on spontaneous reporting [6]. Although these estimates indicate relatively low frequency of DILI in the general population, one should not underestimate the disease burden caused by DILI. The data from the US Acute Liver Failure Study Group show that acetaminophen (paracetamol) and idiosyncratic drug reactions were responsible for approximately 50% of cases of acute liver failure [1]. DILI has been reported to occur in 2–10% of patients hospitalized for jaundice [3]. A total of 77/1164 (6.6%) patients in an outpatient hepatology clinic in Sweden were the result of DILI, half of these being new consults and the other half followed up after hospitalization for DILI [5].

Clinical Presentation and Clinical Evaluation of DILI

Idiosyncratic DILI

Patients with DILI have a wide variety of clinical presentations. Both clinically and histologically, DILI can simulate almost all forms of acute and chronic liver injury. Thus, patients with DILI can present with acute liver failure, acute hepatitis, chronic hepatitis, steatohepatitis, granulomatous hepatitis, and very rarely cirrhosis [3,7]. Before patients develop jaundice, symptoms of liver dysfunction are usually non-specific but lethargy and nausea are common and in some patients severe biochemical liver test abnormalities are detected with no attributable symptoms. Some patients with DILI (about 30%) present with symptoms suggestive of immunoallergic drug reactions with fever, rash, and eosinophilia [8,9]. In cases where histology is available, the presence of eosinophilia and centrilobular necrosis may support the diagnosis of DILI. However, in most cases liver histology is not specific for DILI and pathologists generally report it as "consistent with" DILI.

Most idiosyncratic drug reactions occur within 6 months of starting the drug, although there are some exceptions (e.g., nitrofurantoin). Although a single drug may cause DILI with variable phenotypic expression (e.g., hepatitic vs cholestatic) in different patients, most hepatotoxic drugs have a "signature" pattern of liver injury. A hepatitic pattern is typically observed in patients with isoniazid-, disulfiram-, and diclofenac-associated hepatotoxicity, whereas cholestatic injury is seen most often with amoxicillin/clavulanate, macrolide antibiotics, and estrogens [3]. The most important initial approach to a patient with liver test abnormalities is to keep in mind DILI as a differential diagnosis. The initial evaluation should include a thorough history of drug exposure, including over-the-counter (OTC) medications and herbal remedies, duration of therapy, information about hepatotoxic potential of the implicated drug, and severity of liver injury.

Acetaminophen

Similar to idiosyncratic drug reactions, symptoms of liver injury due to acetaminophen are non-specific. Patients with unintentional acetaminophen toxicity have typically used OTC formulations or acetaminophen co-formulated with opiates and physicians should be aware of the possibility of such a "therapeutic misadventure." Acetaminophen hepatotoxicity should be suspected in patients with extremely high transaminases and coagulopathy but relatively milder hyperbilirubinemia at presentation [1]. Hepatic injury typically develops 12–72 h after and liver failure 72–96 h after ingestion of toxic

doses. Very high transaminase levels that rapidly decline on a daily basis also point toward acetaminophen toxicity, although hepatic ischemia has a similar biochemical pattern.

Diagnosis and Causality Assessment

Idiosyncratic DILI

To establish a relationship between a drug and liver injury can be a very difficult task. As mentioned earlier the clinical and biochemical abnormalities are usually non-specific and there are no markers or tests to confirm the causal relationship. For some compounds with typical "signature" and associated immunoallergic manifestations, the causality assessment can be straightforward. However, given the heterogeneity of its presentation, the diagnosis of DILI greatly relies on circumstantial evidence and "guilt by association" [10]. In most cases with a strong suspicion of DILI, there is a temporal relationship between starting the suspected drug and onset of DILI. There is also a temporal relationship between the discontinuation of the drug and improvement of liver tests (dechallenge). However, there are number of pitfalls to the causality assessment process.

An important question in this context is whether the drug treatment was started before the patient developed symptoms attributable to liver injury (e.g., lethargy, nausea, and/or dark urine or pale stools) or due to the very clinical entity for which the implicated drugs were given (e.g., non-steroidal anti-inflammatory drugs or NSAIDs for flu-like illness, and proton pump inhibitors for abdominal symptoms). It is essential to exclude other causes of liver diseases with great caution before implicating a particular compound. When possible, information about baseline liver tests before starting the implicated drug can be of great value. Information about the duration of drug therapy is crucial in order to evaluate the time to onset of the drug reaction. For most idiosyncratic reactions the latency period is approximately 1 week to a few months. Typically, immunoallergic reactions (fever, rash, and eosinophilia) occur within a few weeks of exposure. For the metabolically induced DILI, the latency period is in most cases <3 months. However, there are important exceptions. Patients receiving certain medications with well-documented hepatotoxicity (e.g., nitrofurantoin, diclofenac, troglitazone, and ximelagatran) can develop severe DILI after a prolonged latency during which liver tests can be entirely normal.

An important part of the causality assessment is to observe for biochemical and clinical improvement after discontinuation of the implicated drug—called positive dechallenge. However, for some drugs that cause hepatotoxicity, liver injury may worsen initially for days or sometimes weeks even after stopping the implicated medication. A good example is troglitazone, an agent removed from the market as a result of many cases of fatal hepatotoxicity, which in clinical trials was associated with liver test abnormalities that were misinterpreted because they continued to rise for a period after its discontinuation [11]. Furthermore, it is well known that DILI can worsen and lead to fatality even after timely discontinuation of the implicated compound [12]. Occasionally, for some drugs with hepatotoxicity potential, liver tests can improve in some patients despite continuation of therapy, examples being ximelagatran and tacrine [11]. However, it is obvious that some individuals may not achieve such an "adaptation" to the liver injury and may go on to develop serious liver injury [11]. Compared with hepatocellular or hepatitic reactions, improvement in liver tests is slower with cholestatic DILI [13]. The course of liver injury after the discontinuation of an implicated agent can aid in the diagnosis of DILI (albeit, retrospectively) because some compounds have fairly typical recovery patterns.

Although there is a strong suspicion of a drug etiology, exclusion of other causes of liver disease is mandatory for establishing the diagnosis of DILI. How extensive this diagnostic work-up should be depends on the clinical context. In general, serological testing for acute viral hepatitis and autoimmune hepatic disorders (autoimmune hepatitis, primary biliary cirrhosis) and abdominal imaging to exclude biliary tract/hepatic parenchymal pathology are essential. History of alcohol abuse should be documented, as well as recent episodes of hypotension that can cause hepatocellular liver injury. The role of a liver biopsy in the diagnostic work-up of DILI is controversial. There are several instruments to evaluate DILI causality but the Roussel Uclaf Causality Assessment Method (RUCAM) is the most commonly used [14]. This causality assessment method is mainly used in research but is being further developed by the US Drug Induced Liver Injury Network to make it more accurate and user friendly [14].

Acetaminophen (paracetamol)

Many of the principles of the diagnostic work-up and the causality assessment are similar in cases of acetaminophen-induced liver injury. However, measurement of blood concentration of acetaminophen can be obtained at least early in the course and is an important part of the management of patients with suspected or confirmed acetaminophen toxicity. Late in the course of the liver injury, blood concentrations of the drug are not reliable. A recently developed assay for the acetaminophen–cysteine protein adducts may identify acetaminophen toxicity in instances lacking clarity [1]. However, this assay is not commercially available and its validity in clinical practice needs further study.

Causative Drugs

A large number of medications and herbal agents have been associated with DILI [13]. Some drugs have well-characterized hepatotoxicity, examples being isoniazid, phenytoin, disulfiram, and amoxicillin/clavulanate, whereas hepatotoxicity from some other drugs has been reported only as isolated case reports [13]. The main classes of drugs reported in case series of patients with DILI have consistently been antimicrobials [5,6,8,12,15], followed by NSAIDs. The most common antimicrobials to be implicated are amoxicillin/clavulanate, isoniazid, erythromycin, flucloxacillin, trimethoprim–sulfamethoxazole, and nitrofurantoin [5,6,8,12,15]. However, among patients with acute liver failure due to drugs in the USA, acetaminophen was the most common causative drug, followed by antibiotics, NSAIDs, antiepileptics, and herbal drugs [16]. Although widely recognized, hepatotoxicity caused by herbal remedies and other natural products has not been studied systematically. Approximately 11% of patients in a prospective study in Spain developed serious acute liver injury caused by herbal remedies [17]. In the DILIN experience, 9% of the prospectively identified DILI cases were caused by the dietary supplements [16]. Although there are numerous herbal remedies that have been reported to cause hepatotoxicity, agents used to promote weight loss (e.g., Herbal Life) and to promote muscle building (dihydroepiandosterone, testosterone analogues) are the most common in the USA [15].

Risk Factors

To predict the susceptibility for DILI in an individual patient for a specific compound is almost impossible. Obviously if the patient has already experienced liver injury from a particular drug, there is significant risk of recurrence on rechallenge Also a past history of DILI from one drug has been shown to be a predictor of future DILI from other compounds [7,13]. Genetic susceptibility is considered to be the most important risk factor for DILI [3], but the genetic basis has not been identified for most of the compounds.

The pathogenesis of DILI is complex and its discussion is beyond the scope of this chapter. In general, increasing age appears to be a risk factor for development of DILI but it is not entirely clear whether this might reflect exposure to multiple concomitant drugs in the older age group. Increasing age has been shown to be a risk factor for halothane, isoniazid, nitrofurantoin, and flucloxacillin hepatotoxicity [3]. It has also been convincingly shown that the appearance of the cholestatic type of DILI is more common in elderly people and hepatocellular damage seems to be inversely related to age [18]. Younger age is a risk factor for certain drugs such as valproic acid and the risk for Reye syndrome with aspirin [3]. DILI has been reported to occur more often in women in some studies [5,6,12,15], whereas a similar preponderance between men and women has been found in other studies [8,18,19]. In a prospective study from France, similar rates of DILI were observed in men and women before the age of 50 [6]. After the age of 50, DILI became twice as high in women, suggesting an increased risk of DILI after the menopause [6]. Women have been found to be more susceptible to liver injury associated with halothane, flucloxacillin, isoniazid, nitrofurantoin, chlorpromazine, and erythromycin [3,4,12,13], whereas men have been found to have an increased risk of azathioprine-induced liver injury [3]. Recently, in a prospective study from Spain with more than 600 DILI cases, female sex was not found to be a predisposing factor to overall DILI [18]. The late Hyman Zimmerman observed that autoimmune type DILI was seen almost exclusively in women [13] and this has recently been confirmed [7]. Although the gender-based risk to develop DILI is unclear, women were more represented among patients with acute liver failure undergoing a liver transplantation in the USA [16].

Malnutrition and chronic alcohol abuse seem to increase the risk of liver injury due to acetaminophen [1,13], whereas their role in idiosyncratic DILI is less clear. Chronic alcohol use has been reported to increase the likelihood of DILI for selected compounds such as methotrexate, isoniazid, duloxetine, and halothane [13]. It is controversial whether pre-existing liver disease makes patients more susceptible to develop DILI. Patients with non-alcoholic fatty liver disease with elevated baseline levels of transaminases were not at an increased risk for development of hepatotoxicity from statins [20]. Similarly, treatment with statins in patients with hepatitis C and elevated liver tests seemed to be safe [21]. Pre-existing hepatitis B and C or coinfection with HIV has been reported to increase the risk of hepatotoxicity from antiretroviral agents in HIV-infected patients [22,23]. However, these studies did not include a control group with HIV and concomitant hepatitis B or C not treated with the implicated drug. It is generally believed that chronic liver disease is probably more important in terms of the tolerance and recovery from a DILI event rather than conferring significant susceptibility [13].

Prognosis

Idiosyncratic DILI

Previous studies consisting of unselected patients with idiosyncratic DILI have revealed that the prognosis of DILI is generally favorable [8,12]. The prognosis of DILI is dependent on the severity of liver injury and the comorbidity status. The prognosis of DILI patients with acute liver failure is usually poor without transplantation, with approximately 20–50% transplant-free survival [24,25]. Hyman Zimmerman, the legendary investigator in the field of drug hepatotoxicity, observed that the combination of hepatocellular injury (high transaminases) and jaundice was associated with a poor prognosis, with a fatality rate of 10–50% [13]. This observation is called "Hy's rule" and is currently used in its modified version by the US Food and Drug Administration for assessing the hepatotoxic potential of compounds in clinical trials. Studies from Spain and Sweden have recently confirmed these early observations and showed approximately 9–12% mortality/liver transplantation in patients with hepatocellular jaundice [8,12]. In general, the prognosis of hepatocellular DILI is worse than cholestatic/mixed types of DILI [8,12]. Studies have shown that older age, female gender, aspartate transaminase (AST) levels, and diabetes are associated with an unfavorable outcome [8,12,15]. Recently, the presence of both peripheral and hepatic eosinophilia in idiosyncratic liver injury has been reported to be associated with a better prognosis [9]. In general, the level of transaminases is not a reliable indicator of the severity of the DILI event in an individual patient [8,9,15]. In fact, a decrease in AST and ALT (alanine transaminase) after drug discontinuation in severe DILI may not reflect improvement, but rather suggests limited hepatic reserve and threatens acute liver failure.

Although recovery is complete both biochemically and histologically in a vast majority of DILI cases that improve, a small proportion may evolve into chronic liver disease (chronic DILI) [26]. One study that investigated the natural history of DILI found that a high proportion of cases had persistent abnormalities during the follow-up but these patients were identified through a histologic database, indicating a selection bias [27]. A prospective follow-up of DILI patients registered in the Spanish Hepatotoxicity Registry revealed 5.7% incidence of chronic DILI [28]. Patients with cholestatic/mixed pattern of liver injury were more prone to develop chronic liver injury [28]. More recently, in the DILIN prospective study, it has been reported that 14% of patients had persistent laboratory abnormalities at 6 months after DILI onset [15]. However, whether these patients or other patients reported to have chronic DILI [20,26–28] will experience liver-related morbidity or mortality is not known. A follow-up study of DILI patients from Sweden with a mean follow-up of 10 years revealed that development of a clinically important liver disease after severe DILI (all had jaundice initially) was rare [7]. A total of 23/685 DILI patients who had survived acute DILI were hospitalized for liver disease during the study period and 5 had liver-related mortality [7]. In this series, there were eight patients with cirrhosis during the follow-up and five of them had no etiology other than a previous DILI event [7]. A significantly longer duration of drug treatment before the diagnosis of DILI has been found to be a risk factor for developing chronic liver injury after clinical recovery of DILI [7,27,28]. All available data indicate that continuing medication after DILI onset is ominous. Thus, prompt recognition of DILI and cessation of therapy is important not only to decrease the

risk for the acute liver injury but also to avoid chronic consequences of DILI.

Acetaminophen (paracetamol)

Prognosis is generally better in acetaminophen-induced acute liver failure (ALF) than with ALF due to other drugs, with a 60–80% transplant-free survival rate [1,24,25]. In general the presence of encephalopathy and renal impairment are predictors of an unfavorable prognosis [1]. In a recent prospective study of patients hospitalized for acetaminophen-induced liver failure in the USA, 178 patients (65%) survived, 74 (27%) died without transplantation, and 23 (8%) underwent liver transplantation [29]. Transplant-free survival rate and rate of liver transplantation were similar between those with intentional (suicide attempt) and unintentional overdose [29].

Management

Once DILI is suspected in a patient with new-onset liver disease, the prompt cessation of drug(s) implicated is usually the first step in the management of these patients. It is obviously of crucial importance to assess the severity of the liver disease, and symptomatic patients with jaundice, encephalopathy, and/or coagulopathy should be hospitalized. An early contact should be made with a transplant center if the patient does not have an obvious contraindication for liver transplantation. Patients with suspected DILI and concomitant jaundice should be carefully looked after and liver transplantation considered before they develop severe encephalopathy.

In acetaminophen-induced liver failure, *N*-acetylcysteine (NAC) should be given immediately [1]. Other than NAC, specific treatment options for the liver injury associated with drugs are very limited. In valproate-associated hepatotoxicity, which is associated with mitochondrial dysfunction, carnitine is recommended, because it is an important cofactor in mitochondrial β-oxidation of fatty acids [30]. Although steroids are commonly used in patients with acute liver injury due to idiosyncratic drug reactions, their use is not supported by any controlled studies. Small cases series and case reports suggest that they may be used in patients with DILI and marked autoimmune features. The use of steroids may be justified when DILI is associated with concomitant Stevens–Johnson syndrome as can be the case with phenytoin-induced hepatotoxicity or when the autoimmune hepatitis is considered to be induced by drugs such as nitrofurantoin, halothane, minocycline, or diclofenac.

The patients with severe liver failure are generally hospitalized within the intensive care unit (ICU), particularly those who reach grade III encephalopathy and/or those with renal failure. Treatment within the ICU of renal impairment, encephalopathy, and infectious complications is beyond the scope of this chapter. Last, it should be pointed out that patients with DILI-related acute liver failure should be considered for liver transplantation early in the course of the disease. As pointed out earlier, patients with acetaminophen-induced liver failure generally have better prognosis without transplantation than those with acute liver failure caused by idiosyncratic drug-induced DILI [24,25]. In the US Acute Liver Failure Study Group experience, patients with ALF due to acetaminophen are less frequently placed on the transplant list than other etiologies, and only 7% of patients with acetaminophen toxicity received a graft compared with more than 40% of idiosyncratic DILI cases [24]. This may reflect the fact that a large proportion of acetaminophen cases have a contraindication for transplantation due to history of substance abuse, repeated suicidal behavior, and other psychosocial issues [1].

In summary, DILI should be considered in the differential diagnosis of every patient with new-onset liver disease. A careful history about prescription medicines, OTC agents, herbal remedies, and dietary supplements should always be undertaken. Implicated agent(s) should be promptly discontinued and thorough testing should be performed for the exclusion of competing etiologies. Patients with DILI and concomitant jaundice and/or coagulopathy should be hospitalized until there is evidence of significant improvement. NAC is the treatment of choice in acetaminophen-induced liver toxicity. Liver transplantation should be considered early in the course of severe DILI accompanied by liver failure.

Take-home points

- DILI can mimic any form of liver disease and thus a thorough history of all prescription and over-the counter medicines and herbal remedies should be obtained from all patients presenting with new liver disease.

- Idiosyncratic DILI is a diagnosis of exclusion, so even when it appears obvious one must rule out appropriate competing etiologies.
- Idiosyncratic DILI is classified into hepatocellular, cholestatic, and mixed types based on serum liver biochemistries.
- Antimicrobials are the single most common class of prescription agents to cause idiosyncratic DILI followed by NSAIDs and central nervous system agents.
- Patients with DILI and concomitant jaundice and/or coagulopathy indicating liver failure should be hospitalized until there is evidence of significant improvement.
- Patients with DILI and acute liver failure should be referred for liver transplantation if there are no obvious contraindications.

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CHAPTER 24
Alcoholic Liver Disease

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Summary
Alcoholic liver disease is a major driver of liver-related morbidity and mortality in the USA and worldwide. Diagnosis is made by a combination of clinical, histologic, and laboratory findings. Disease includes a spectrum ranging from fatty liver, which is generally benign, to hepatitis and cirrhosis, which can carry a poor prognosis. Although various pharmacologic therapies have been utilized, the most established treatments include supportive care, abstinence, and liver transplantation when appropriate.

Introduction

Alcohol-associated liver disease results in a broad spectrum of histologic and clinical symptoms. Conditions such as fatty liver, alcoholic hepatitis, and alcoholic cirrhosis are induced by excessive alcohol consumption. Although fatty liver is still reversible by alcohol abstinence, alcoholic hepatitis and cirrhosis are critical and potentially life-threatening manifestations of extended duration alcohol abuse [1].

Case
A 50-year-old man is brought to the emergency room by the emergency services after a syncopal episode. Some history is obtained from the patient's wife who says that the patient has had a drinking problem for some years and has been feeling generally unwell for the past few days. The patient is alert and shows no signs of altered mental status or fever, but feels weak. Physical exam is significant for spider angiomas on his chest and palmar erythema. Liver edge is firm and span is increased. Spleen is palpable. No ascites or lower extremity edema is detected.

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Definition and Epidemiology

Alcohol-related liver disease (ALD) has become a global burden for countries in the Western world. As a major cause of morbidity and mortality, alcoholic liver disease has become a substantial health care problem, accounting for 40% of deaths from cirrhosis and 30% of hepatocellular carcinoma in the USA and Europe [2].

Chronic alcohol abuse can result in an overlapping spectrum of histopathologic processes, ranging from steatosis (alcoholic fatty liver) and alcoholic hepatitis, to alcoholic cirrhosis. However, finding these entities in their isolated histopathologic state is uncommon, as they often tend to overlap. Steatosis, the infiltration of liver cells with fat, develops as a short-term response to excessive alcohol consumption, occurring in 90% of heavy drinkers. In general, fatty liver is an asymptomatic, benign condition that is entirely reversible within a few weeks of abstinence. However, 15–20% of affected individuals may subsequently develop fibrosis, alcoholic hepatitis, and/or cirrhosis as concomitantly existing diseases. Approximately 10–35% of people who abuse alcohol develop acute alcoholic hepatitis, characterized by necroinflammation and fibrosis as a result of the hepatocellular damage. In its initial stages, alcoholic hepatitis, similar to steatosis, can be reversed by abstinence. However, alcoholic hepatitis can be a serious condition;

patients with severe alcoholic hepatitis have an exceptionally high short-term mortality rate and, with continued alcohol abuse, cirrhosis may develop. The mortality rate of acute alcoholic hepatitis varies and can be predicted by various quantitative scoring systems as described later. Chronic inflammation triggers fibrotic lesions in a characteristic perivenular and pericellular dissemination, leading to alcoholic cirrhosis [2].

Pathophysiology

Alcoholic liver disease has a multifactorial pathogenesis and can be induced by a variety of mechanisms (Figure 24.1). The two most important may be ethanol metabolism and its noxious metabolites, as well as genetic factors that predispose to alcohol-induced hepatic inflammation and fibrosis. Ethanol consumption obviously is the most prominent risk factor for liver injury [3,4].

Metabolic Mechanisms

In the liver, alcohol is metabolized by several different enzyme systems: alcohol dehydrogenase (ADH), aldehyde dehydrogenase, and the microsomal ethanol-oxidizing system (MEOS). When blood alcohol levels are low, ADH is the main enzyme that breaks down ethanol in the liver by catalyzing the conversion of alcohol to acetaldehyde. MEOS also converts alcohol to acetaldehyde, but with two important differences: (1) the conversion is achieved with the MEOS-specific cytochrome P-450 enzyme CYP2E1, and (2) when alcohol blood levels are moderate to high. These two major metabolizing pathways play a fundamental role in the development of alcohol-induced chronic liver disease.

Acetaldehyde

Acetaldehyde is the most potent ethanol metabolite leading to liver damage. It directly affects many aspects of hepatocyte signaling. The liver utilizes ethanol as its preferred energy source, forgoing other available fueling substrates in its presence. Ethanol metabolism operates through oxidative and non-oxidative pathways. In the first step of oxidation, ethanol is converted to acetaldehyde through the gastric isoenzyme ADH. A portion of ethanol undergoes first-pass metabolism, disrupting intracellular pathways and altering the functional properties of the cell membranes. This allows free fatty acids to diffuse liberally across hepatocyte plasma membranes. Under physiologic circumstances, fatty acids undergo β-oxidation inside the hepatocyte; this mechanism is disturbed in people with alcohol problems. ADH is believed to wield an inhibitory effect on the peroxisome proliferator-activated receptor α (PPAR-α), a transcription factor that regulates the synthesis of enzymes involved in fatty acid catabolism. Over time, more fatty acids accumulate in the liver, with increasing inability of the liver to use them as energy substrates. Esters form and accumulate as triglycerides within the hepatocytes. Triglycerides are usually exported from the liver in very low-density lipoproteins (VLDLs). However, ethanol interferes with microtubule-mediated protein secretion, including VLDLs. Hence, triglycerides cannot be effectively transported out of the liver cell due to ethanol-generated disruption of VLDL secretion, leading to steatosis.

Oxidative Stress and MEOS

Oxidant stress is an important contributing factor in ethanol toxicity. The MEOS is another enzyme compound involved in ethanol metabolism. It operates through several cytochrome P-450 isoenzymes, of which CYP2E1 is a key player: chronic alcohol intake stimulates CYP2E1 expression, which fuels hepatic ethanol oxidation. Tissue-damaging reactive oxygen species (ROS) are released, which can attack cellular lipids and cause peroxidation. These free radicals interact with proteins, lipids, and nucleic acid, especially mitochondrial DNA. Mitochondria become susceptible to tumor necrosis factor α (TNF-α), eventually leading to cell apoptosis and necrosis, and histologic liver inflammation ensues.

Genetic and Hereditary Factors

The discrepancy between people who drink an equal amount of alcohol and the consequent development of liver disease has led to the theory of a genetically determined predisposition to alcohol-related liver disease. Certain genetic factors may make a person more susceptible to alcohol-induced liver toxicity. Of two people who consume the same amount of alcohol, one may be more likely to develop the disease because of this genetic variability than the other. In patients with alcohol-induced liver disease, gene-linked polymorphisms have been

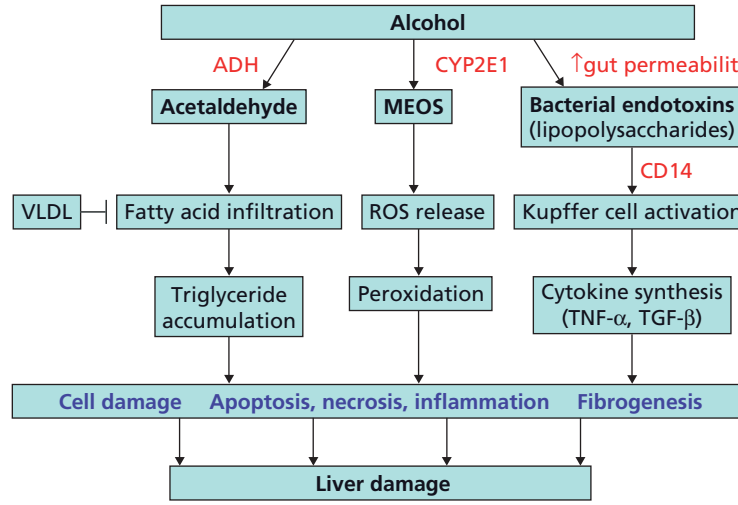

Figure 24.1 Mechanisms of alcohol-induced liver injury.

found to cause mutations in the TNF promoter and in alcohol-metabolizing enzyme systems. Polymorphisms of ADH may cause reduced enzyme activity, leading to high levels of acetaldehyde that enhance liver injury. However, currently no specific polymorphism has been definitely linked to alcoholic liver disease. Furthermore, genetic factors are assumed to play a role in an individual's inclination toward alcoholism.

Alcoholic liver disease is more prevalent in men, but women are more likely to develop severe forms of the disease with less alcohol consumption than men. Even with weight adjustment, a similar amount of alcohol consumption results in higher blood alcohol levels in women than in men. Attempts at explaining this trend include a relative deficiency of gastric ADH in women, differences in alcohol bioavailability, and female hormone-related causes [5].

Immunologic Mechanisms

Alcohol may impair the body's immune response. The extent of its influence, however, remains to be defined. Chronic ethanol consumption increases the intestinal permeability to substances that include bacterial endotoxins such as lipopolysaccharide (LPS). LPS binds with the CD14 receptor, thereby activating nuclear factor κB (NF-κB). The result is an augmented transcription of proinflammatory cytokines such as interleukin 6 (IL-6), transforming growth factor β (TGF-β), and TNF-α. TNF-α and IL-6 are primarily involved in cholestasis and production of acute-phase proteins, whereas TGF-β may stimulate fibrogenesis in hepatic stellate cells. The result is necroinflammation, apoptosis, and fibrosis, which promote the progression of liver disease [6].

Clinical Features

Most patients with fatty liver are asymptomatic. Patients who have alcoholic hepatitis and cirrhosis may also be asymptomatic, but many present with non-specific symptoms such as nausea, vomiting, weight loss, weakness, pain, fever, jaundice, and diarrhea. In the end-stages of cirrhosis, symptoms of liver failure may develop.

On physical examination, 75% of patients with steatosis and alcoholic hepatitis present with hepatomegaly, regardless of the degree of liver damage. In addition, hepatic tenderness, splenomegaly, varices, and peripheral edema may occur. In patients with a more extensive disease severity, approximately 60% present with jaundice and ascites. In the initial stages of cirrhosis, well-compensated patients present with no abnormalities on physical examination. As the disease progresses, compensation mechanisms gradually collapse and patients have variable degrees of hepatic failure as well as muscle wasting, ascites, spider angiomas, portal hypertension, and in severe cases, hepatic encephalopathy [7].

Diagnosis

A detailed drinking history should be obtained. In mild forms of liver disease, the patient often presents with no complaints. In patients with chronic alcohol problems, hepatomegaly is the most common symptom of alcohol-related hepatitis and cirrhosis. The onset of fever, jaundice, scleral icterus, or upper right quadrant tenderness is highly suggestive of liver damage as well. Other diagnostic findings that point to liver damage are neutrophilic leukocytosis, thrombocytopenia, an AST:ALT ratio >1, mixed hyperbilirubinemia (elevated levels of both conjugated and unconjugated bilirubinemia), hypoalbuminemia, and increased prothrombin time (PTT). High serum immunoglobin levels and low peripheral lymphocyte count are common [2].

Alcoholic hepatitis can be difficult to distinguish from non-alcoholic steatohepatitis (NASH) histologically, but can be predicted by specific lab-based criteria. NASH occurs frequently in people who are obese or have hyperliproteinemia or type 2 diabetes mellitus, and in chronic parenteral hyperalimentation-treated patients, as a side effect of certain drugs, such as estrogens and glucocorticoids. NASH is indolent in most cases, with an AST:ALT (aspartate transaminase:alanine transaminase) ratio <1. The differential diagnosis between alcoholic hepatitis and NASH can be difficult where there is an unreliable alcohol history. The AST:ALT ratio, body mass index, and gender are the most important variables to accurately differentiate patients with ALD from non-alcoholic fatty liver disease (NAFLD). Combined, these variables determine the ALD/NAFLD Index (ANI) (see www.mayoclinic.org/gi-rst/mayomodel10.html). An ANI >0 is more likely in alcoholic hepatitis patients [8].

To definitely confirm the diagnosis of alcoholic hepatitis, a percutaneous or transjugular liver biopsy is required. However, the use of biopsy varies depending on clinical suspicion and diagnostic plan. Liver biopsy is most useful in cases where the alcohol etiology is clinically undetermined and confirmation of the diagnosis is desired before starting any treatment. Histologic features of moderate-to-severe alcoholic liver disease include steatosis, fibrosis, inflammation, Mallory bodies, ballooning necrosis of hepatocytes and hemosiderin deposits. Ultrasonography with duplex is also useful to help exclude biliary tract obstruction and other conditions such as the Budd–Chiari syndrome [9].

Case

The patient has been subjected to blood tests, with the following results: ALT 32 IU/L, bilirubin 1.4 mg/dL, albumin 3.6 g/dL, alkaline phosphatase 100 IU/L, INR 1.6. Hepatitis serologies show no evidence of hepatitis A, B, or C. An abdominal ultrasound scan is performed and shows an enlarged liver suggestive of fatty infiltration. The DF score is 35.

As a supportive measure, the patient was administered intravenous fluids and vitamins. He was soon started on a course of prednisone. In addition, he received counseling on his drinking behavior as well as his nutritional choices.

Prognosis

The prognosis is largely dependent on alcohol abstinence and the degree of liver decompensation. Patients with clinically decompensated alcoholic cirrhosis have a 5-year mortality rate of 90%. The 5-year survival rate of decompensated cirrhosis patients who continue drinking is at best 30% [1]. Alcohol abstinence is the most effective way to prevent progression of alcoholic liver disease. Up to a certain point, already acquired pathologic liver alterations, such as steatosis, acute alcoholic hepatitis, inflammation, or mild collagen deposition, are for the most part reversible. Alcoholic steatosis has been shown to resolve completely with abstinence. However, more advanced fibrosis is less likely to resolve. Regardless, alcohol abstinence is the primary and most fundamental approach to therapy.

The severity of alcoholic hepatitis can be assessed using a prognostic index. There are several frequently applied scoring systems predicting survival in patients with alcoholic hepatitis. The Maddrey Discriminant Function (DF) is most commonly used and is calculated by the follow equation:

$$\mathrm{DF} = 4.6 \times (\text{prolongation of PTT in seconds}) + \text{bilirubin (in mg/dL)}.$$

If DF >32, patients have a 30-day survival rate of less than 50%; when DF <32, the probability of survival in 30 days is 80–100%.

An alternative prognostic quantitative index is the Mayo End Stage Liver Disease (MELD), a modified version of DF, which takes bilirubin, international normalized ratio (INR), and creatinine levels into account:

$$DF = 3.8 \log_e \text{bilirubin (in mg/dL)} + 11.2 \log_e \text{INR} + 9.6 \log_e \text{creatinine (in mg/dL)}.$$

When the MELD index is ≥25, the short-term survival rate is about 50% (see www.mayoclinic.org/meld/mayomodel7.html) [10].

The Glasgow alcoholic hepatitis score (GAHS) is calculated using values for age, white cell count, urea, PTT ratio, and bilirubin level. Patients with a GAHS ≥9 have a 30-day survival rate of 46% and an 80-day survival rate of 40%.

Management

Even in patients with severe liver cirrhosis, alcohol abstinence was shown to be beneficial for patient survival. Effective therapy is based on a combination of lifestyle changes and perhaps pharmacologic treatment than either alone or when compared with no treatment (Figure 24.2). Treatment consideration is based on the extent of the alcoholic liver injury. Isolated fatty liver requires no treatment other than alcohol abstinence. For alcoholic hepatitis, a number of pharmacologic treatment options have been evaluated and are discussed below, but current therapy still focuses on supportive care.

Lifestyle Modification

The ultimate goal is to prevent disease progression and the possible development of decompensated cirrhosis and hepatocellular carcinoma. Lifestyle modification is an important cornerstone of therapy. People with alcohol problems are often heavy smokers as well, which may be a risk factor for progression of liver disease. Patients with end-stage liver disease have some degree of malnutrition, due to low nutrient intake and intestinal malabsorption. Nutritional deficiency disrupts the integrity of the immune system and impairs the efficiency to respond to infection. Patients should follow a high-protein diet supplemented with vitamins B, C, and K, and folic acid. Obesity is also a risk factor for the development of steatosis, alcoholic hepatitis, and cirrhosis. The approach to lifestyle modification begins with reduction of alcohol intake, smoke cessation, weight control, and nutritional supplementation.

Drug Therapy

Corticosteroids

Corticosteroids are the most extensively studied treatment for alcoholic hepatitis, but no consensus conclusion has been reached about their effectiveness. Studies on the subject have often led to conflicting conclusions concerning the benefit of corticosteroids to patient survival. Examination of study results suggests that corticosteroids improve survival in patients who have hepatic encephalopathy and are therefore at a higher risk for premature mortality. The available data further suggest that corticosteroids should not be used in mild alcoholic hepatitis cases or those with either gastrointestinal bleeding requiring blood transfusion or an indication of current infection. When administering glucocorticosteroids to patients with hepatic encephalopathy, a course of prednisone 40 mg daily for 30 days is recommended [5].

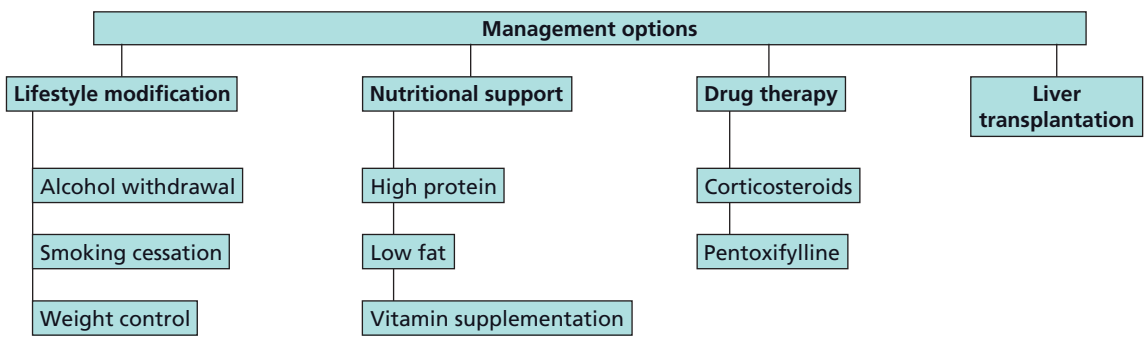

Figure 24.2 Management options in various stages of the spectrum of alcoholic liver disease. Precise interventions will vary according to the severity of the condition.

Pentoxifylline

Pentoxifylline is a non-selective phosphodiesterase inhibitor used as a supplemental drug for peripheral vascular disease. It improves blood flow by decreasing blood viscosity and aggregation properties of red blood cells and platelets. Increases of organ microcirculation, tissue oxygenation, and antifibrinogenic efficacy, and lowering of portal hypertension have been observed as well. In clinical trials, pentoxifylline has been shown to improve short-term (4 weeks) survival of patients with alcoholic hepatitis. The drug's positive effects may be attributable to decreased development of hepatorenal syndrome. Observed side effects were vomiting, epigastric pain, and dyspepsia, which quickly resolved after pentoxifylline treatment was discontinued.

Anti-TNF Therapy

Tumor necrosis factor (TNF)-α is a major factor in the pathogenesis of alcoholic hepatitis and is associated with a worse prognosis. Although anti-TNF was thought to be a promising approach to therapy, randomized trials have not shown a benefit [11].

Other Treatment Options

Other drug groups have been discussed as possible treatment alternatives, but have failed to achieve beneficial results in clinical trials. Colchicine has therapeutic potential as an anti-inflammatory and collagen-inhibiting drug, but with no beneficial effects on overall or liver-related mortality. Propylthiouracil is a substance with antioxidant and portal circulation-enhancing properties, but a number of large randomized trials could not detect a significant beneficial effect in patients with alcoholic liver disease.

Liver Transplantation

End-stage alcoholic liver disease is one of the most common indications of liver transplantation. In the USA, only 6% of patients with end-stage alcoholic liver disease are transplanted, the prime reason being donor scarcity and suboptimal patient population. The 7-year survival rate after liver transplantation is an excellent 60%. Postoperative complications such as organ rejection, graft failure, or retransplantation are less common for alcoholic liver disease patients than for those undergoing transplantation for other conditions. Many transplantation units demand a 6-month alcohol abstinence period before considering transplantation. Many patients with apparently advanced alcoholic liver disease who successfully reduce their alcohol intake recover during that time and no longer need transplantation. About a third of transplant recipients relapse back to alcoholism, but consumption usually remains at low-to-moderate levels. However, graft loss as a consequence of continued drinking after transplantation is less common, especially when proper selection criteria are observed [2].

Complications

Alcoholic liver disease can aggravate through exposure to several factors, such as acetaminophen (paracetamol), but the most concomitant hepatic disease is hepatitis C. Chronic alcohol abuse is a major risk factor for the development of hepatitis C virus (HCV) infection, and appears to accelerate the progression of chronic HCV liver disease as well. Patients with acute liver disease are at very high risk for HCV infection. Although intravenous drug abuse is often responsible for the high prevalence of HCV in ALD patients, 40% of patients have no additional distinguished risk factors for HCV other than alcohol abuse. The coexistence of HCV in alcoholic liver disease patients may be responsible for the intensified disease progression of liver injury. Studies have shown that HCV-positive individuals with alcohol problems had had more severe liver disease than those who tested HCV negative. These patients also respond less successfully to therapy for their liver disease, and have a less favorable prognosis than HCV-negative ALD patients. Chronic alcoholism also appears to reduce the response rate of HCV liver disease to therapy, making alcohol a risk factor for HCV disease progression as well, even when alcohol-induced liver injury is not present.

Take-home points

- Alcoholic liver disease encompasses a clinicohistologic spectrum (fatty liver, alcoholic hepatitis, cirrhosis).
- Metabolic and immune mechanisms as well as hereditary factors contribute to the pathogenesis of alcoholic liver disease by altering hepatocytic functioning.

- The two main alcohol metabolizing pathways are alcohol dehydrogenase and MEOS.
- Alcoholic fatty liver develops in response to short periods of alcohol abuse; hepatitis and cirrhosis are the result of long-term drinking.
- Accurate diagnosis of alcoholic liver disease is oriented by the clinical history, histology, and laboratory findings.
- Early forms of alcohol-induced liver damage can be reversed by alcohol abstinence.
- Effective treatment focuses on combining supportive measures and in some cases drug therapy.
- Liver transplantation is the only available long-term treatment for end-stage liver disease.

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CHAPTER 25
Autoimmune Liver Diseases

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Summary
Autoimmune hepatitis (AIH), primary biliary cirrhosis (PBC), and primary sclerosing cholangitis (PSC) are considered the most common autoimmune liver diseases. While the underlying etiopathogenesis for these disorders are considered diverse, the clinical and biochemical presentations can be similar with histologic findings in some cases overlapping between disorders. The purpose of this overview is to describe advances in the diagnosis and management of AIH, PBC, PSC, and celiac disease affecting the liver. In addition to discussing criteria which may suggest an overlap between AIH with either PBC or PSC, practical approaches to therapy for individual diseases will also be presented.

Case
A 52-year-old woman is referred for evaluation of abnormal serum liver enzymes for 6 months. She has no prior history of liver disease, and only complains of fatigue and intermittent dry eyes. She is taking no medications. Past medical history is unremarkable, and her family history is noted for rheumatoid arthritis and hypothyroidism. Physical examination is unremarkable, and there are no signs of chronic liver disease. Laboratory tests are noted for a normal complete blood count, international normalized ratio (INR), and electrolyte panel. Serum alkaline phosphatase is 400 IU/dL, aspartate transaminase (AST) is 205 IU/L, alanine transaminase (ALT) is 220 IU/L, and total bilirubin is 0.9 mg/dL. Abdominal ultrasound is negative for biliary obstruction. Further testing is negative for chronic viral hepatitis and metabolic liver disease. Serum autoantibodies are noted for antinuclear (ANA) of 1.2, smooth muscle (SMA) of 1:40, and antimitochondrial (AMA) antibodies of 1.8, and a gamma-globulin level of 2.2 g/dL.

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Autoimmune Hepatitis

Definition and Epidemiology

Autoimmune hepatitis (AIH) is a chronic inflammatory disease of the liver characterized by serum autoantibodies, hypergammaglobulinemia, and histologic features including interface hepatitis. The mean incidence and prevalence rates of AIH are 19 and 169 per 1 000 000 population among white Northern Europeans, yet many ethnic groups can develop AIH. Women are nearly four times more susceptible to AIH compared to men, while all age groups can be affected.

Pathophysiology

The interaction between immunoglobulin G and normal hepatocytes is thought to trigger natural killer cells to bind with Fc receptors, resulting in an antibody-mediated form of cell-mediated cytotoxicity. In cell-mediated damage without antibody mediation, a disease-specific autoantigen is expressed on antigen presenting cells which stimulate cytotoxic T-cell invasion. Genetic predisposition for AIH is also recognized, with an increased frequency of selected major histocompatibility class

(MHC) class II DRB1 alleles (such as DRB1*0301 and DRB1*0401).

Clinical features

The clinical presentation of AIH ranges widely from asymptomatic mild disease to fulminant hepatic failure. Common features in symptomatic patients include fatigue and jaundice. Symptoms including pruritus, nausea, vomiting, skin rash, and joint pain are less commonly observed [1].

Diagnosis

For clinical purposes, a modified version of the International Autoimmune Hepatitis Group (IAHG) scoring system recognizes definite and probable cases of AIH. This version requires only four criteria for assessment, including autoantibody titers, serum IgG, histology, and the absence of viral hepatitis (Table 25.1). Assessment of the initial performance of this scoring system demonstrates excellent accuracy for diagnosing AIH in clinical practice [2].

Table 25.1 Simplified diagnostic criteria for autoimmune hepatitis.

Variable	Cut-off	Points
ANA or SMA	≥1:40	1
ANA or SMA	≥1:80	
or LKM	≥1:40	2*
or SLA	Positive	
IgG	>Upper normal limit	1
	>1.10-fold upper normal limit	2
Liver histology (evidence of hepatitis is a necessary condition)	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis	Yes	2
		Total ≥ 6: probable AIH
		Total ≥ 7: definite AIH

*Addition of points achieved for all autoantibodies (maximum 2 points).
AIH, autoimmune hepatitis; ANA, antinuclear antibody; SMA, smooth muscle antibodies; LKM, liver–kidney antibody; SLA, soluble liver antigen; IgG, immunoglobulin G.

Biochemical Features

Elevations in serum AST and ALT aminotransferase levels are often 2–10-fold above the upper limit of normal, while elevated serum alkaline phosphatase levels occur in 20% of cases without significant biliary-type injury on histology. Total bilirubin and albumin levels are usually normal unless advanced cirrhosis or severe inflammation is present.

Serologic Features

Serum ANA and SMA antibodies are observed together in 60% of cases. Serum titers greater than 1:40 suggest the presence of AIH, while titers greater than 1:80 are more indicative of AIH. Elevated serum gamma-globulin levels (>2.0 g/dL) are considered essential for diagnostic verification, while serum perinuclear antineutrophil cytoplasmic (p-ANCA) or liver–kidney microsomal (LKM) antibody levels may be helpful for the small percentage of cases with negative ANA and SMA, and gamma-globulin levels less than 2.0 g/dL.

Histologic Features

Interface hepatitis and/or piecemeal necrosis are the most specific histologic criteria for AIH. Complementary features include rosette formation and the absence of bile duct injury. The inflammatory reaction is mainly made up of lymphocytes and plasma cells, and may be found in portal, periportal, or lobular areas. The pattern of fibrosis development is similar to that observed in chronic viral hepatitis.

Differential Diagnosis

The differential diagnosis of AIH includes drug-induced liver injury with minocycline, nitrofurantoin, isoniazid, and propylthiouracil recognized as known culprits; AMA-negative primary biliary cirrhosis (PBC); small duct primary sclerosing cholangitis (PSC); acute infectious hepatitis from cytomegalovirus (CMV), Epstein–Barr (EBV), parvovirus 19, and adenovirus; chronic hepatitis associated with rheumatologic disorders such as systemic lupus erythematosus; and celiac disease.

Therapeutics

Indications

The absolute indications for treatment include (1) AST greater than 10-fold normal; (2) AST greater than five-fold normal with gamma-globulin greater than two-fold normal; (3) bridging or confluent necrosis on liver biopsy; or (4) symptomatic disease (fever, nausea/vomiting, jaundice). Treatment is not typically required for patients with (1) asymptomatic disease and interface hepatitis on liver biopsy; (2) AST less than five-fold normal; (3) inactive or minimal inflammation with cirrhosis; and (4) end-stage liver disease.

Medical Therapy

Induction therapy may consist of monotherapy with prednisone or combined treatment with azathioprine and prednisone (Table 25.2). Both treatment regimens can induce remission in greater than 80% of patients on therapy, yet a lower rate of side effects with the combined regimen is observed (10% versus 44%) (1). Maintenance therapy should be provided for 12–18 months to increase the likelihood of histologic remission. Importantly, cessation of therapy before 12 months because of normal serum liver biochemistries is associated with high rates of disease relapse. Despite its availability, there are no compelling data for routine testing of thiopurine methyltransferase activity to prevent azathioprine toxicity. Monitoring of complete blood counts every 3–4 months is the most common strategy for identifying long term hematologic toxicity from azathioprine [1].

With specific reference to pregnancy, immunosuppressive therapy is not contraindicated. AIH flares may occur during and immediately after pregnancy, and thus it is not safe to discontinue or excessively reduce immunosuppressive therapy during pregnancy. Concerns regarding teratogenicity from immunosuppressive medications have not been substantiated in cohort studies to date. However, a higher than normal frequency of prematurity, low birth weights, and fetal loss is observed in pregnant women with AIH compared to unaffected individuals [3].

Treatment End Points

Remission

Complete disease remission occurs in 65% of all treated patients after 18 months of therapy and 80% achieve remission within 3 years. Controversy exists as to whether complete withdrawal of medical therapy following remission is indicated, as the likelihood for indefinite remission off therapy is only 15–20%. To prevent early drug withdrawal, an end-of-treatment liver biopsy is recommended but rarely utilized in clinical practice unless complete medication withdrawal is planned. Subsequently, medication doses are tapered with the goal of maintaining azathioprine monotherapy or low dose prednisone.

Relapse Following Remission

Relapse following remission is characterized by a minimum three-fold increase in the serum aminotransferase level above normal limits and/or increased serum gamma-globulin level to greater than 2 g/dL. The frequency of relapse after remission is 50% within 6 months of treatment cessation, and up to 85% of patients develop a relapse within 3 years. In contrast, patients with a sustained remission (defined by > 6 months off therapy) have a 10% risk for relapse. Treatment with azathioprine (2 mg/kg/day) with or without prednisone or low-dose

Table 25.2 Immunosuppressive medication regimens for autoimmune hepatitis.

Interval	Prednisone (mg/day)	Prednisone (mg/day)	Azathioprine (mg/day)
Week 1	60	30	50
Week 2	40	20	50
Week 3	30	15	50
Week 4	30	15	50
Daily until end point	20	10	50

prednisone (10 mg daily or less) alone is associated with disease control (AST < five-fold and no symptoms) in almost 90% of patients.

Drug Toxicity

This occurs in 10–15% of all treated patients where dose reduction or premature drug withdrawal is necessary. The most common drug-related adverse events are obesity (50%), osteoporosis (30%), and diabetes mellitus (20%). For prednisone monotherapy, dose reduction or withdrawal may be required to minimize adverse effects. Conversion to azathioprine (if tolerated) is an option.

Incomplete Response

An estimated 10–15% of individuals will have an incomplete response despite an adequate duration of optimal therapy. For these patients, dose reduction to maintain AST levels less than five-fold normal is the goal. An increased risk for end-stage liver disease resides with this patient subgroup, necessitating referral for possible liver transplantation.

Treatment Failure

Treatment failure is rarely encountered (<10% of cases), and is defined by serum aminotransferase levels increased by at least 67% from pretreatment values. In this setting, high-dose prednisone (60 mg/day) or prednisone (30 mg/day) with azathioprine (150 mg/day) can induce biochemical remission in 75% of these patients after 24 months. Dose reduction is continued until conventional maintenance levels of medication are again achieved.

Salvage Therapies

Alternative medical management strategies, including cyclosporine, ursodeoxycholic acid, budesonide, 6-mercaptopurine, methotrexate, cyclophosphamide, and mycophenolate mofetil are not established as effective therapies overall. Liver transplantation is effective in patients who deteriorate in spite of corticosteroid treatment. The actuarial 10-year survival after transplantation is estimated at 75%. Disease recurrence occurs in some, but does not often progress to cirrhosis, graft failure, or disease refractory to conventional immunosuppressive regimens [4].

Case continued

The patient's symptoms, serum liver enzyme profile, and positive serum AMA test strongly suggest a diagnosis of PBC. However, the possibility of an overlap syndrome between AIH and PBC is suggested by the higher then expected serum AST and ALT levels and positive ANA and SMA antibodies. Liver biopsy was then performed, revealing histologic features, including chronic non-suppurative bile duct inflammation without evidence for interface hepatitis. These findings are consistent with PBC alone.

Take-home points

Diagnosis

- AIH is a clinical syndrome without specific diagnostic hallmarks.
- Clinical symptoms range from asymptomatic state to fulminant hepatic failure.
- Serum aminotransferase levels greater than five-fold the upper limit of normal are usual.
- Serum ANA and/or SMA are typically present at titers of 1:80 or higher.
- Serum gamma-globulin levels often exceed 2 g/dL.
- Interface hepatitis on liver histology is mandatory for the diagnosis.

Therapy

- Prednisone with or without azathioprine are first-line treatments.
- Treatment should be continued for 12–18 months.
- Complete remission is achieved in an estimated 80% of patients.
- Relapse can occur in up to 20% of patients at 1 year following complete discontinuation of therapy.
- Incomplete response, drug toxicity, and treatment failure occur in a minority of patients.
- Patients unresponsive to conventional therapies with progressive liver disease often require liver transplantation.

Primary Biliary Cirrhosis

Definition and Epidemiology

PBC affects all races and has no specific geographic predilection. Women are primarily affected with a female-to-male ratio of 9:1. The median age of disease onset is 50 years but varies between 20 and 90 years. The annual incidence of PBC ranges between 2 and 24 cases per

million population, while prevalence estimates range from 19 to 402 cases per million population.

Pathophysiology

The major finding is recognition of the AMA directed against the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2) along the inner surface of biliary epithelial mitochondrial membrane. Furthermore, direct cytotoxic activity is not attributed to AMA. Molecular mimicry from microbial infection inducing cross-reactivity with self-antigens and genetic predisposition have also been proposed as underlying mechanisms.

Clinical Features

The majority of contemporary patients (>60%) with PBC will be asymptomatic at initial presentation. Over 50% of asymptomatic patients, however, will develop symptoms of PBC within 10 years. Fatigue, dry eyes/dry mouth, and pruritus are the most commonly reported symptoms. Jaundice, cutaneous hyperpigmentation, hepatosplenomegaly, and xanthelasmas are now rarely observed at diagnosis.

Diagnosis

Biochemical Features

The most characteristic biochemical abnormality is an elevated serum alkaline phosphatase level (>1.5-fold the upper limit of normal). Modestly increased values for ALT and AST are common, but elevations greater than 200 IU/L are uncommon. Serum total bilirubin levels are commonly within normal limits. There may also be hypercholesterolemia and elevated serum IgM levels.

Serologic Features

Serum AMA is present in 90% and 95% of patients with the diagnosis of PBC at titers greater than 1:40. Serum ANA and/or SMA are observed in 35–66% of cases. Other serum autoantibodies include rheumatoid factor (70%), antithyroid antibodies (40%), and anti-sp-100 antibodies (25%).

Histologic Features

Stage I PBC is associated with portal tract inflammation with lymphoplasmacytic infiltrates affecting septal and interlobular bile ducts. Focal duct obliteration with granuloma formation, termed the "florid duct lesion", is considered almost pathognomonic for PBC when present. Stage II PBC is consistent with an extension of portal tract infiltrates with associated lymphocytic cholangitis and interface hepatitis. Stage III PBC is dominated by the existence of septal or bridging fibrosis. Stage IV disease is consistent with biliary cirrhosis [5].

Overlap Syndrome with Autoimmune Hepatitis

Selected patients with PBC may also have clinical and histologic features compatible with AIH. The term "overlap syndrome" has been used to describe this situation with original estimates of frequency as high as 20%. Refinement of diagnostic criteria, however, has reduced the prevalence rate of this condition to less than 5%. There are no prospective, long term data regarding prognosis and optimal therapy for overlap syndrome compared to patients with typical PBC [6].

Therapeutics: Disease-Related Complications

Fatigue

Attempts to identify effective medical treatment for fatigue in PBC patients have not been successful to date. Antioxidant therapy, ondansetron, and selective serotonin reuptake inhibitors are ineffective [5,7].

Pruritus

Antihistamines and phenobarbital have marginal clinical efficacy in the pruritus of PBC. Cholestyramine (a bile-acid binding resin) 4 g orally before and/or after breakfast is thought to maximize bile acid sequestration resulting in symptom improvement. The use of divided doses of cholestyramine spaced several hours apart from other medications is recommended to prevent reduction in gastrointestinal absorption of other drugs. Sertraline at 75–100 mg/day may be effective therapy for mild-to-moderate itching. Rifampin (150–450 mg/day) is highly effective for moderate-to-severe pruritus, yet may cause liver injury in 15% of cases and bone marrow aplasia on rare occasions. Parenteral naloxone and oral nalmefene can result in symptomatic improvement. Among patients with pruritus refractory to medical therapy; liver transplantation is the most effective therapeutic option [5,8].

Keratoconjunctivitis Sicca

Secondary involvement of salivary and lacrimal glands with inflammation is thought to be the underlying cause

of dry eyes and dry mouth. The majority of patients, however, do not satisfy criteria for the diagnosis of Sjögren syndrome. Treatment is directed at symptomatic improvement using artificial tears and oral sialagogues as first-line agents. Topical cyclosporine for keratoconjunctivitis has not been tested in PBC. Oral pilocarpine and cemeviline may be effective on an individual basis [5].

Dyslipidemia

In early-stage disease, total serum cholesterol levels tend to be markedly elevated and may fall to low levels once end-stage liver disease has developed. Two published investigations have independently concluded there is no increased risk of death from cardiovascular disease in PBC patients with severe hypercholesterolemia compared to the general population [8]. Statin-based therapy, however, may have an important role in patients with a genetic predisposition for atherogenic lipid disorders.

Metabolic Bone Disease

Metabolic bone disease in PBC is related to osteopenia rather than osteomalacia (defective bone mineralization). Risk factors for metabolic bone disease in PBC include age, body mass index, and stage 3 or 4 histologic disease. First-line therapies include weight-bearing exercise, oral calcium (1000–1200 mg/day), sun exposure, and vitamin D replacement (25 000–50 000 IU two to three times weekly) when low serum levels are documented. Alendronate have been associated with improvements in lumbar spine bone mineral density, and intravenous preparations should be considered in patients with known esophageal varices [8].

Fat-Soluble Vitamin Deficiency and Steatorrhea

Malabsorption of fat-soluble vitamins from cholestasis is exceedingly uncommon in the absence of cirrhosis, but should be checked in these individuals, with oral replacement only indicated when suboptimal levels are identified. Steatorrhea in PBC may be attributed to a number of potential causes. Impaired bile acid delivery to the small intestine can be treated with oral median-chain triglycerides. Celiac disease should be treated with a gluten-free diet. Exocrine pancreatic insufficiency and bacterial overgrowth syndrome may also occur, with pancreatic enzyme replacement therapy and rotating empiric antibiotic use, respectively, as the treatments of choice [8].

Cancer

There is an increased occurrence of hepatocellular carcinoma (HCC), which commonly occurs in men with cirrhosis from PBC. Surveillance imaging to identify HCC is indicated in this subgroup.

Therapeutics: Primary Underlying Disease

D-penicillamine, corticosteroids, azathioprine, cyclosporine, and methotrexate are not considered effective treatments for PBC. A recent meta-analysis failed to identify any significant clinical benefit with colchicine therapy [5].

Ursodeoxycholic Acid

Randomized controlled trials, in addition to recent observational cohort studies, have identified a survival benefit with ursodeoxycholic acid (UDCA) at a dose of 13–15 mg/kg/day for patients with early-stage PBC, which is similar to matched general populations [9]. However, an estimated 50% of patients do not achieve a complete biochemical response to UDCA (defined by alkaline phosphatase and/or AST levels > 1.5-fold normal). A number of factors must be considered as possibly contributing to an incomplete response to UDCA. These include medication non-compliance, inappropriate dosing by weight, concomitant use of cholestyramine impairing UDCA absorption, or concomitant disease, e.g. autoimmune hypothyroidism, celiac disease, or overlap syndrome, as a cause of elevated serum liver enzymes [5] (Figure 25.1).

Combination and Novel Therapies

Combination therapy with UDCA and several adjunctive therapies including corticosteroids, azathioprine, colchicine, and methotrexate have been ineffective.

Liver Transplantation

The most effective therapeutic alternative for patients with end-stage PBC is liver transplantation. Patient and graft survival rates remain excellent at 90–95% and 80–85% at 1- and 5-year intervals, respectively. Recurrent PBC occurs in at least 30% of patients by 10 years following liver transplantation. The use of tacrolimus and older donor age are associated with developing recurrent disease. The efficacy of UDCA therapy for recurrent PBC in halting disease progression remains unknown [10].

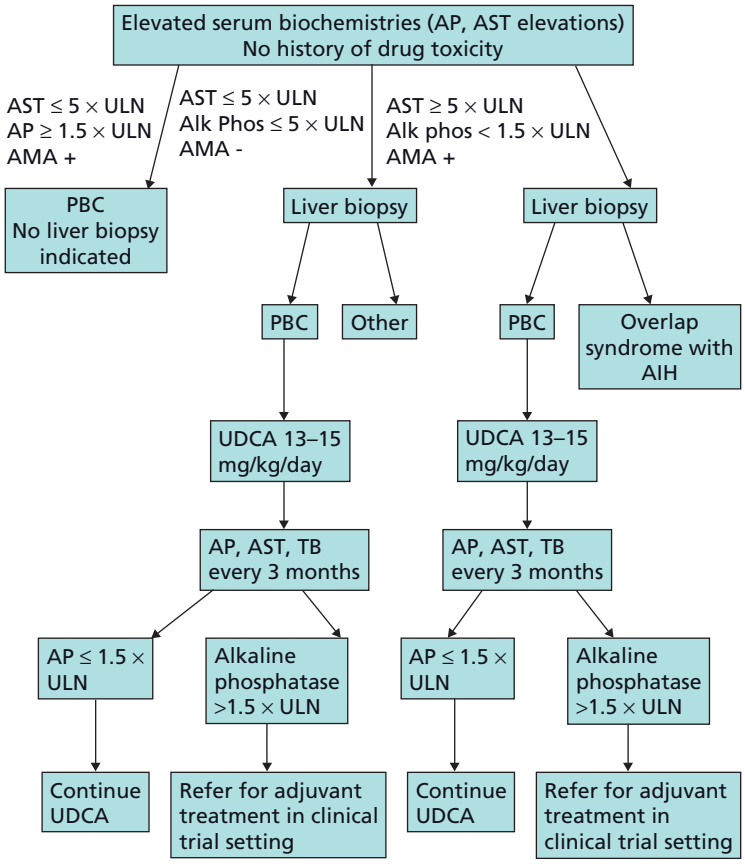

Figure 25.1 Proposed clinical algorithm for the diagnosis and treatment of primary biliary cirrhosis. AP, alkaline phosphatase; AST, aspartate transaminase; ULN, upper limit of normal; AMA, antimitochondrial antibodies; PBC, primary biliary cirrhosis; AIH, autoimmune hepatitis; UDCA, ursodeoxycholic acid; TB, total bilirubin.

Take-home points (Table 25.3)

Diagnosis

- The diagnosis of PBC should be considered when the following clinical features are present:
  - Cholestatic serum liver profile;
  - Serum AMA positivity;
  - Liver histology compatible with PBC.

Therapy

- Medical therapy with ursodeoxycholic acid (UDCA) can halt disease progression in most individuals and improves survival free of liver transplantation.
- Initial therapy with UDCA at 13–15 mg/kg/day is recommended. The treatment goal is to achieve reduction in serum alkaline phosphatase level less than or equal to 1.5-fold the upper limit of normal (complete response).
- If a complete response to UDCA therapy is not observed, consider adjuvant therapy in the setting of ongoing clinical trials.
- Liver transplantation is a life-extending procedure for patients with end-stage liver disease from PBC.

Table 25.3 Monitoring of patients with primary biliary cirrhosis and primary sclerosing cholangitis.

- History and physical exam every 6–12 months
- Serum liver biochemistries and prothrombin time every 3–6 months
- Serum thyroid stimulating hormone (TSH) at diagnosis and yearly thereafter
- Serum vitamin A, D, and E levels at diagnosis in advanced hepatic disease
- Liver ultrasound at diagnosis and yearly in patients with advanced liver disease
- Bone mineral density test at diagnosis and 2 years later if therapy initiated
- Ultrasound and serum alpha-fetoprotein every 6–12 months with cirrhosis
- Screening endoscopy for esophageal varices if cirrhosis present

Primary Sclerosing Cholangitis

Definition and Epidemiology

Fifty to 70% of affected individuals are men with a mean age of 40 years at diagnosis. Annual incidence rates between 9 and 13 cases per million population, with point prevalence rates of 85 and 136 cases per million population, are noted. Among European and North American populations, an estimated 70–80% of patients with PSC have inflammatory bowel disease (IBD). Conversely, about 2–4% of patients with IBD have or develop PSC.

Pathophysiology

Cellular immune abnormalities, including CD4 lymphocyte recognition of antigens expressed on biliary epithelia, is hypothesized to initiate histologic injury. The strong association between PSC and IBD suggests an underlying infectious etiology, although compelling data have not been presented. An increased frequency of human leukocyte antigen (HLA) alleles A1, B8, and DR3 is observed in PSC but remains non-specific for disease susceptibility. A number of non-MHC candidate genes may also influence susceptibility to clinical disease from PSC.

Clinical Features

A history of IBD and elevated serum liver biochemistries often prompts investigations to exclude PSC. Asymptomatic patients now represent 40–60% of patients in observational cohort studies.

Diagnosis

Biochemical Features

Elevations in serum alkaline phosphatase values are the biochemical hallmark of PSC, with values 3–10-fold the upper limit of normal in most cases. Serum alanine and aspartate aminotransferase levels are usually two- to three-fold above normal, while total bilirubin levels may be normal in 60% of individuals at diagnosis. Higher levels of total bilirubin are worrisome for advanced disease, superimposed choledocholithiasis, or malignancy.

Serologic Features

Serum ANA and SMA antibodies occur in 20–50% of cases, while AMA are rarely found in PSC. p-ANCA are detected in frequencies ranging between 30% and 80% but lack diagnostic specificity for PSC.

Radiographic Features

Cholangiography remains the gold standard for diagnosis in PSC, characterized by segmental bile duct fibrosis with saccular dilation of normal intervening areas resulting in the characteristic "beads on a string" appearance. Magnetic resonance cholangiopancreatography (MRCP) has been increasingly utilized, where an overall diagnostic accuracy rate of 90% is reported. Cholelithiasis is noted in 20% of individuals with PSC with the majority being asymptomatic [11]. The identification of gallbladder polyps on cross-sectional imaging requires consideration for elective cholecystectomy given the potential for neoplastic transformation in PSC [12].

Histologic Features

Liver biopsy is required for assessing the stage of histologic disease, but is not essential for making a diagnosis of PSC unless cholangiography is normal. Periductal fibrosis with inflammation, bile duct proliferation, and ductopenia constitute the main histologic findings. Fibro-obliterative cholangiopathy, the pathologic hallmark of PSC, is uncommonly observed. The histologic classification of PSC is based on four stages and is similar to other chronic liver diseases [11].

Therapeutics: Disease-Related Complications

Fatigue, Pruritus, and Metabolic Bone Disease

The approach to symptomatic medical therapy for patients with fatigue, pruritus, and metabolic bone disease is similar to that described for patients with PBC, and will not be discussed in detail here.

Symptomatic Choledocholithiasis

Choledocholithiasis is reported at frequencies around 15% among symptomatic individuals with the majority of calculi involving both central and peripheral bile ducts. Endoscopic or percutaneous methods to provide biliary decompression and stone extraction have been successful. Biliary surgery, including stone extraction and bilioenteric anastomosis, may be considered when non-operative approaches have been ineffective in patients with early-stage PSC.

Dominant Stricture

Dominant strictures occur in 5–10% of patients with PSC. Clinical manifestations include a sudden asymptomatic increase in serum alkaline phosphatase and/or

bilirubin, progressive jaundice, and bacterial cholangitis. Following empiric broad-spectrum intravenous antibiotic therapy, endoscopic or percutaneous therapy with balloon dilation of identified stenoses can provide significant clinical improvement [11]. The efficacy and safety of endoscopic stents versus balloon dilation alone has not been determined in a controlled trial setting to date [13]. In all patients with dominant strictures, endoscopic brushings and biopsy are required to exclude malignancy.

Peristomal Variceal Bleeding

Peristomal variceal bleeding occurs among subjects with IBD who have undergone proctocolectomy with ileostomy formation. Newer surgical techniques including ileal pouch–anal anastomosis are indicated to prevent this complication. Beta-adrenergic blockers and endoscopic sclerotherapy are not associated with long term efficacy, while transjugular intrahepatic portosystemic shunt (TIPS) can be effective in treating refractory bleeding.

Colonic Dysplasia/Carcinoma

Several large studies have supported the association between an increased risk for colorectal neoplasia in PSC. For invasive carcinoma or high-grade dysplasia, surgical colectomy is the treatment of choice. Patients with low-grade or indefinite histology for dysplasia may be followed with heightened endoscopic surveillance and biopsy protocols. UDCA cannot be currently recommended for chemoprevention given the absence of a prospective controlled trial [11].

Cholangiocarcinoma

The estimated annual risk for cholangiocarcinoma is 0.5–1.5%, and the prevalence rates vary between 4$ and 20%. In addition, 30–50% of individuals are ultimately diagnosed with cholangiocarcinoma within 2 years of identifying PSC. Risk factors for cholangiocarcinoma in PSC remain poorly understood. Serum tumor markers including carbohydrate antigen 19-9 (CA 19-9) levels greater than or equal to 100 IU/L have a sensitivity of 89% and specificity of 86%, but do not have support as a tool for detecting early-stage disease. Cross-sectional imaging can be helpful when a periductal mass is located in patients suspected to have cholangiocarcinoma. Endoscopic biopsy and brushings for routine and advanced cytologic techniques enhance the sensitivity for tissue-based diagnosis [14].

Therapeutic options for cholangiocarcinoma in PSC are limited. Systemic chemotherapy and radiation for patients with advanced disease provide a limited survival advantage. In a protocol for highly selected patients with unresectable localized cholangiocarcinoma, a 5-year actuarial survival rate greater than 70% after liver transplantation has been reported [15].

Therapeutics: Primary Underlying Disease

Medical Therapies

D-penicillamine, colchicine, corticosteroids, azathioprine, cyclosporine, and methotrexate are not considered effective treatments for PSC. Randomized controlled trials have not identified a survival benefit with UDCA at a dose of 13–15 mg/kg/day [11]. Two randomized controlled trials of higher-dose UDCA also failed to identify clinical and survival benefits when compared to placebo [16,17]. Novel therapies including oral nicotine, pirfenidone, pentoxifylline, silymarin, mycophenolate mofetil, and tacrolimus have not been associated with clinical benefit in patients with PSC [11].

Endoscopic Therapy

The use of endoscopic dilation with sphincterotomy and/or stenting is associated with clinical response rates in 60–90% of patients. The use of short term stenting for dominant strictures is associated with an 83% improvement in symptoms and liver biochemistries in a small number of patients. No prospective study has been performed to determine if stent therapy following balloon dilation is superior to balloon dilation alone.

Biliary Reconstructive Surgery

Surgical resection has been performed among precirrhotic individuals with extra-hepatic biliary strictures refractory to endoscopic/percutaneous therapy. A number of concerns exist, however, with regard to long term consequences of surgical therapy. For patients requiring liver transplantation, a prior history of operative bile duct resection has been associated with longer procedure times, greater intraoperative blood loss, and increased risks for subsequent biliary complications.

Liver Transplantation

PSC remains an important etiology for liver transplantation in the USA. Excellent patient survival rates between 90% and 97% at 1 year and 83–88% at 5 years are reported. Increased colonic disease activity following liver transplantation is reported in between 30% and 50% of patients, with some individuals requiring proctocolectomy for symptom control. Symptomatic pouchitis after liver transplantation is more common when compared to patients with ulcerative colitis transplanted for other liver diseases. PSC is a recurrent disease after liver transplantation in 10–20% of patients [11].

Take-home points (Table 25.3)

Diagnosis

- PSC is a chronic cholestatic liver disease characterized by inflammation and fibrosis of the intra- and extra-hepatic bile ducts.
- The majority of cases occur in association with IBD which often precedes the development of PSC.
- Elevated serum alkaline phosphatase is the biochemical hallmark for PSC.
- Cholangiography is required to verify a diagnosis of PSC.
- Liver biopsy is not essential for diagnosis but can aid in assessing stage of disease.

Therapy

- There are no effective medical therapies for halting disease progression in PSC.
- Endoscopic or percutaneous therapy for biliary obstruction provides symptom relief.
- Biliary surgery is rarely performed and is only indicated for relief of symptomatic biliary obstruction refractory to endosopic/percutaneous therapy.
- Liver transplantation is the optimal therapy for patients with end-stage complications of PSC.

Celiac Disease

Definition and Epidemiology

Celiac disease may cause elevated serum liver enzymes, which have been reported in up to 40% of adults at the time of diagnosis. In contrast, celiac disease is present in about 9% of patients with chronic liver enzyme elevations. A diagnosis of celiac disease should be suspected in those subjects with a positive family history of gluten-sensitive enteropathy or dermatitis herpetiformis.

Clinical Features

The majority of patients with liver injury from celiac disease are asymptomatic.

Diagnosis

Biochemical Features

Elevated serum AST and/or ALT levels less than five-fold the upper limit of normal may occur, whereas the total bilirubin is often normal. Serum alkaline phosphatase elevation from baseline may reflect secondary hyperparathyroidism.

Serologic Features

Serologic tests for the assessment of celiac disease may be less helpful in patients with chronic liver disorders. Immunoglobulin A gliadin antibody positivity occurs with increased frequency among patients with chronic liver disease, with most cases not reflecting the presence of celiac disease. The antigliadin antibody is not useful in screening, and human-based tissue transglutaminase (tTG) tests remain associated with increased false-positive rates in patients with chronic liver disease. The endomysial antibody assay may be helpful, with a positive result necessitating endoscopy and biopsy for confirmation of diagnosis.

Histologic Findings

Liver biopsy has been cited as useful when liver tests remain elevated despite adherence to a gluten-free diet or to exclude a concomitant liver disease. Notably, patients with celiac disease undergoing liver biopsy have mild or non-specific histologic changes often with steatosis, with advanced fibrosis or cirrhosis a rare observation.

Therapeutics

Treatment with a gluten-free diet is associated with normalization of serum aminotransferase values in 75–95% of patients within 1 year. It is recommended that an alternative etiology for liver disease be sought in unresponsive patients adherent to a gluten-free diet. The reversible nature of severe histologic changes in patients

with celiac disease is controversial [18,19]. Liver transplantation is rarely necessary for end-stage liver disease from celiac disease.

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26

CHAPTER 26
Vascular Diseases of the Liver

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Summary
Vascular disease of the liver can result from a number of conditions that alter the normal flow of blood within the hepatic vascular system. These diseases are usually categorized based on the location of the lesion or lesions responsible for altering the flow, in reference to the sinusoids. Thus vascular diseases of the liver can be presinusoidal, such as portal vein thrombosis and schistosomiasis, intrasinusoidal such as most cases of liver cirrhosis, or postsinusoidal such as Budd–Chiari syndrome or sinusoidal obstruction syndrome (veno-occlusive disease).

Budd–Chiari syndrome is a heterogeneous disorder characterized by partial or full occlusion at the level of the hepatic veins or the suprahepatic portion of the inferior vena cava. It typically presents with painful hepatomegaly, ascites, and abnormal liver tests. Most cases occur in the setting of myeloproliferative disorders or hypercoaguable states. Diagnosis is usually established non-invasively with Doppler ultrasonography, computed tomography, or magnetic resonance angiography. Venography and liver biopsy are rarely needed. Treatment is determined by the disease severity, underlying etiology, and duration of the disease. Treatment options include medical (supportive care, diuretics, anticoagulation, thrombolysis), radiological intervention with transjugular intrahepatic portosystemic shunt, or rarely surgical (surgical shunts or liver transplantation).

Portal vein thrombosis (PVT) refers to thrombosis that involves the trunk of the portal vein and represents the classic form of presinusoidal portal hypertension. It occurs in both children and adults and is the leading cause of extrahepatic portal hypertension in non-cirrhotic patients in Western countries. Clinical presentation is usually subtle and most patients will present with manifestations of portal hypertension: abdominal pain, abdominal distension due to ascites, variceal bleeding, and splenomegaly. Liver cirrhosis is the most common acquired cause of PVT in adults. Other causes include neoplastic disorders, infections, and hypercoaguable disorders. Ultrasonography is the first-line diagnostic modality with high sensitivity and specificity. Contrast CT scan and magnetic resonance imaging usually help to confirm the diagnosis and determine the extent of the thrombus. Treatment is directed at management of portal hypertension complications; the role of anticoagulation remains controversial.

This chapter addresses both Budd–Chiari syndrome and PVT. Sinusoidal obstruction syndrome is discussed in Chapter 27.

Budd–Chiari Syndrome

Case 1

A 40-year-old woman presents with a 2-week history of worsening right upper quadrant abdominal pain and progressive abdominal distension. Her past medical history is significant for a history of right leg deep venous thrombosis 3 years ago, treated with 6 months of anticoagulation, She has no known history of heart disease. On examination, she appears ill, and is tachypneic but hemodynamically stable. There are no spider angiomas or scleral icterus, the heart and lung exams are normal, and she has tense ascites with tenderness over the right upper quadrant.

Practical Gastroenterology and Hepatology: Liver and Biliary Disease, 1st edition. Edited by Nicholas J. Talley, Keith D. Lindor and Hugo E. Vargas.

Definition and Epidemiology

Budd–Chiari syndrome (BCS) is a rare, heterogeneous, and potentially fatal group of disorders related to hepatic venous outflow obstruction. This rare disorder is usually caused by multiple concurrent factors, including acquired and inherited thrombophilia. Venous outflow obstruction can occur at any level from the small hepatic veins to the suprahepatic inferior vena cava (IVC).

Accurate estimates of incidence are lacking in Western countries. Prevalence was estimated to be 2.4 cases/million people based on autopsy studies in Japan [1,2]. In Asian patients, obstruction is usually related to a thin membrane that involves the IVC at the level of the ostia draining the three major hepatic veins. In contrast, most cases reported in Western countries are due to pure thrombosis of the hepatic veins. Incidence and prevalence rates are expected to increase due to increased awareness and improved diagnostic methods.

BCS can be classified according to etiology, site of obstruction, manifestations, and duration of the disease (Table 26.1).

Table 26.1 Classification of Budd–Chiari syndrome.

Classification according to etiology	
Primary	Hepatic venous obstruction related to endoluminal pathology (thrombosis or webs)
Secondary	Obstruction secondary to a lesion outside the venous system (tumor, abscess) Flow is obstructed by invasion or compression
Classification according to site of obstruction	
Small hepatic veins	Obstruction at level of small hepatic venules that cannot be seen on venogram or Doppler ultrasonography
Large hepatic veins	Obstruction of large hepatic veins that can be seen on venogram or Doppler ultrasonography
Inferior vena cava (IVC)	Obstruction of IVC between the level of hepatic veins and right atrium
Combined obstruction	Obstruction of hepatic veins and IVC
Classification according to disease duration	
Acute	Symptoms within 6 weeks of disease onset: 20% of patients (5% with fulminant hepatic failure)
Subacute	Symptoms over weeks up to 6 months (40%)
Chronic	Symptoms >6 months with portal hypertension and cirrhosis (40%)

Pathophysiology

There is marked clinical and pathological heterogeneity among patients with BCS. This heterogeneity remains poorly understood, in part due to the limitations in the assessment of hepatic hemodynamics, liver histopathology, and prothrombotic disorders [3,4].

In general, obstruction of the hepatic venous outflow tract results in increased hepatic sinusoidal pressure and portal hypertension. The ensuing venous stasis and congestion lead to hypoxic damage to the adjacent hepatic parenchymal cells. Furthermore, the ischemic injury to the sinusoidal lining cells results in the release of free radicals, and oxidative injury to the hepatocytes ensues. These mechanisms culminate in the development of hepatocyte necrosis in the centrilobular region (zone 3) [3]. Untreated, progressive centrilobular fibrosis will progress to liver cirrhosis and be complicated by portal hypertension with the formation of portal venous collateral systems. The latter may lead to reduction in the hepatic sinusoidal pressure and in turn lead to transient improvement in liver functions.

A universal observation has been a discordance between the duration of signs and symptoms and the actual age of venous thrombus or hepatic lesions found at pathologic examination: most patients with acute presentations have evidence of long-standing hepatic outflow obstruction, as indicated by extensive fibrosis or cirrhosis on liver biopsies [5].

Etiology

Secondary BCS can result from a lesion originating outside the venous system. Those lesions can be either malignant tumors (hepatocellular carcinoma [HCC], renal adenocarcinoma, adrenal adenocarcinoma, and atrial myxoma), benign mass lesions (large central nodule

in the setting of focal nodular hyperplasia), or infectious (hydatid disease, parasitic cysts, or abscesses). These lesions will lead to venous outflow obstruction by either venous invasion or extrinsic compression. Compression or kinking of the hepatic veins can occur after hepatic resection or transplantation.

Primary BCS results from an endoluminal venous pathology. An underlying etiology or risk factor that confers predisposition to the development of BCS can be identified in up to 75–85% of patients. The common causes are as follows:

- Hypercoaguable states (inherited):
  - Antithrombin III deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Factor V Leiden mutation
- Prothrombin mutation (acquired):
  - Myeloproliferative disorders
  - Paroxysmal nocturnal hemoglobinuria
  - Antiphospholipid syndrome
  - Pregnancy
  - Use of oral contraceptives.

The uncommon causes are:

- Tumor invasion:
  - HCC
  - Renal cell carcinoma
- Miscellaneous:
  - Behçet syndrome
  - IVC webs
  - Trauma
  - Inflammatory bowel disease.

There are also idiopathic causes.

Multiple factors acting in combination are seen in up to 25% of patients [6]. Hematologic disorders, particularly myeloproliferative disorders (MPDs), are the most common cause of BCS, accounting for half the cases. Most patients with an MPD at the time of presentation lack the classic diagnostic criteria of MPDs. Recent advances in diagnostic tools, including the recent discovery of the *V617F* mutation in the Janus Kinase 2 (JAK2) tyrosine kinase, have revolutionized the diagnosis of MPDs in BCS patients in the absence of the classic criteria [7].

The JAK2 tyrosine kinase mutation is a somatic point mutation that is extremely rare in healthy individuals (<1%). It is located on chromosome 9p and causes amino acid substitution in the antiregulatory domain of the *JAK2* gene. This gain-of-function mutation confers erythropoietin hypersensitivity and growth factor independence, and leads to enhanced hemopoiesis. Mutation prevalence is estimated at 90–95% for polycythemia vera, and 50–60% for both essential thrombocythemia and idiopathic myelofibrosis. Several clinical studies indicate that patients with MPDs who carry *JAK2* mutations have a higher risk of thrombosis [8]. As a consequence of these developments, the World Health Organization (WHO) guidelines for MPD diagnosis have been revised and *JAK2* mutation screening was added as a major diagnostic criterion for MPD in conjunction with bone marrow exam.

Factor V Leiden mutation, antiphospholipid syndrome, and *G20210A* prothrombin gene mutation are the next most common prothrombotic disorders in BCS. The diagnosis of inherited deficiencies in protein C, protein S, and antithrombin III in patients with BCS is difficult because acquired deficiencies can develop in the event of liver disease, liver failure, acute thrombosis, and anticoagulant therapy. The decreased levels of these coagulation inhibitors are significant only in the presence of normal or slightly reduced levels of coagulation factors.

Hormone replacement therapy, oral contraceptive pills, and pregnancy may exacerbate any of the abovementioned prothrombotic disorders (especially patients with heterozygous status) and lead to increased risk of BCS. Other miscellaneous causes include paroxysmal nocturnal hemoglobinuria, a rare disorder that is complicated by BCS in 30% of patients and accounts for 5% of BCS patients.

Clinical Manifestations

BCS typically presents with ascites (84% of patients), abdominal pain, and hepatomegaly (76%). However, 5–10% of patients can be asymptomatic if the liver sinusoids were decompressed by large intrahepatic and portosystemic shunts. The classic patient with BCS is a woman in her third or fourth decade, with an underlying prothrombotic disorder and taking an oral contraceptive. The clinical presentation of BCS depends on the extent and rapidity of hepatic venous occlusion, and on whether a venous collateral circulation has developed to decompress the liver sinusoids.

The syndrome can be classified, according to presentation, into fulminant, acute, subacute, and chronic forms. Fulminant presentation is rare, occurring in only 5% of patients. It leads to hepatic dysfunction and encephalopathy within 8 weeks of development of jaundice. This acute syndrome occurs in 15% of patients and is associated with severe symptoms of short duration—including jaundice, right upper quadrant pain, hepatomegaly, and ascites. Some patients will present with variceal bleeding. Subacute presentation is common and occurs in 40% of patients. It has a more insidious onset and typically presents more than 6 months after onset of thrombosis. Ascites and hepatic necrosis may be minimal because the hepatic sinusoids are decompressed by the collateral circulation. Chronic presentation is seen in approximately 40% of patients with BCS, who usually present with signs and symptoms of liver cirrhosis that result from chronic venous congestion of the liver. Portal hypertension and esophageal varices are commonly present.

Biochemical tests of liver functions are usually abnormal. The degree of abnormality varies from significant elevation (more than five times the normal level) of transaminases, bilirubin, and alkaline phosphatase in patients with acute and fulminant presentation, to mild elevation in patients with subacute or chronic presentation.

Diagnosis

Case 1

Laboratory data showed high ALT (alanine transaminase) (five times the normal level), high AST (aspartate transaminase) (three times the normal level), bilirubin 3 mg/dL, INR 1.5. Doppler ultrasonography assessment revealed moderate ascites, and thrombosis of all three hepatic veins with extension into the IVC. The portal vein was patent. Contrast-enhanced CT scan confirmed the above findings with no evidence of hepatic necrosis

Work-up for thrombophilia confirmed homozygous status for factor V Leiden.

BCS should be suspected in patients with unexplained liver dysfunction, ascites with high serum ascites–albumin gradient (SAAG >1.1) and high protein content (>2.5 g/dL), and painful hepatomegaly, particularly in patients with a known risk factor for BCS.

Advances in non-invasive vascular imaging with Doppler ultrasonography, magnetic resonance imaging (MRI), and contrast-enhanced computed tomography (CT) have allowed improved diagnosis, including the recognition of asymptomatic disease. Doppler ultrasonography of the liver, with sensitivity and specificity of 85%, is the technique of choice for initial investigation when BCS is suspected. The presence of hepatic vein collaterals (spider web) is particularly useful in differentiating BCS from other liver disease. Contrast-enhanced CT and MRI may help to confirm the diagnosis, better identify hepatic necrosis, differentiate between acute and chronic forms of BCS, and better delineate the venous anatomy, especially when a transjugular intrahepatic portosystemic shunt (TIPS) is being considered.

The progress in imaging has led to less emphasis on the use of angiography of hepatic veins and IVC for diagnostic purposes. Likewise, improved imaging techniques have reduced the need for liver biopsy. Biopsy is usually reserved for a small subset of patients in whom BCS is the result of isolated pure thrombosis of the small hepatic veins which cannot be seen on standard imaging techniques. Liver biopsy usually shows the classic sinusoidal dilation around the central veins with centrilobular necrosis (zone 3). Those findings can be seen also in patients with heart failure and constrictive pericarditis. Echocardiography may be needed in some patients to assess for congestive heart failure, constrictive pericarditis, or right atrial myxoma.

Therapy

Case 1

Patient was started on furosemide, spironolactone, and intravenous heparin. Her symptoms and liver tests continued to worsen and she required large-volume paracentesis twice. After completing an evaluation, she was listed for liver transplantation. A TIPS was placed on the fifth hospital day, after which liver tests stabilized and ascites became better controlled.

Within 8 weeks, ascites resolved and bilirubin returned to normal. Patient was placed on warfarin with a target INR of 2.5–3.0.

Over the last few years, considerable advances have been seen in the overall understanding and practical management of primary BCS. Many of those advances have

been made possible by the input of new knowledge from hematology, technical improvement in interventional radiology, and international collaborative efforts.

The goals of therapy are to prevent propagation of the clot, decompress the congested liver, and prevent complications related to fluid retention, malnutrition, and portal hypertension. The underlying cause of BCS should be investigated, and appropriate therapy administrated. Radiological imaging is usually adequate to rule out secondary BCS. Figure 26.1 outlines a proposed treatment algorithm for patients with BCS.

Medical Therapy and Management of Complications

All patients with BCS should receive anticoagulation, unless contraindicated, starting with intravenous heparin, followed by warfarin with a target international normalized ratio (INR) of at least 2.5. This should help to prevent progression of thrombosis. Although there are no randomized trials confirming the therapeutic benefit of anticoagulation, several reports attributed the recent improvement in BCS outcome to the routine use of anticoagulation. However, a few reports, most containing small numbers of patients, document higher rates of 6-month mortality in patients receiving anticoagulation and diuretics alone.

In general, medical therapy alone with diuretics and anticoagulation should be reserved for patients without ongoing hepatic necrosis, as indicated by mild symptoms, relatively normal liver injury tests and synthetic functions, and medically controlled ascites. Patients with significant portal hypertension or evidence of synthetic dysfunction (coagulopathy, encephalopathy or hepatorenal syndrome) should receive additional therapies [9]. Patients receiving medical therapy should be monitored closely for disease progression with regular assessment for liver functions and portal hypertension screening. Serial liver biopsies to confirm disease stability should also be considered.

Thrombolytic therapy can be used in patients with acute BCS who present within 72 h of diagnosis (in one report within 2 weeks of diagnosis). This treatment has had variable success and most data are based on small

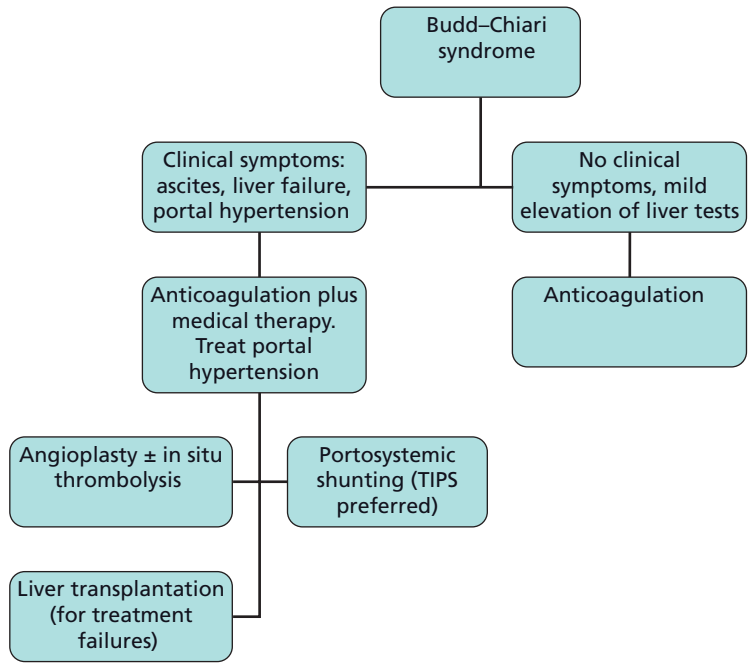

Figure 26.1 Strategy management of Budd–Chiari syndrome using stepwise implementation of therapeutic options. More invasive options are required in case of failure or absence of response to previous treatment. TIPS, transjugular intrahepatic portosystemic shunt.

case series. Treatment is usually infused into the clotted vein over 24 h [10]. The risk of serious complications (bleeding, stroke, pulmonary embolism), combined with low efficacy, limits this treatment to patients with acute presentation with a well-defined clot that is limited to hepatic veins.

In the presence of cirrhosis, varices should be assessed with endoscopy. Endoscopic eradication of varices or use of non-selective β-blockers to prevent bleeding is often necessary. Ascites is usually managed with diuretics or large-volume paracentesis.

Angioplasty

Short-segment obstruction or webs in the hepatic veins or the IVC are treated successfully with balloon dilation. Angioplasty can be combined with local thrombolytic therapy and stent placement to improve outcome and increase rates of long-term patency which can be as high as 80%. Optimal anticoagulation is essential in all patients to maintain patency. Factors associated with restenosis are unknown and frequent angiographic or Doppler assessment is recommended [3,11].

Transjugular Intrahepatic Portosystemic shunt

The therapeutic principle of portosystemic shunting is to convert the portal vein into an outflow tract, thus decompressing the sinusoids. TIPS has been increasingly used for BCS treatment in recent years; it is usually reserved for patients who have failed medical therapy (approximately two-thirds of patients), patients with acute BCS who failed thrombolytic therapy, and as a bridge for liver transplantation. It avoids laparotomy and overcomes caudate lobe compression and occlusion of IVC, with less periprocedural mortality than surgical shunting [9,12,13].

Successful placement of TIPS can be achieved in 85–95% of patients with few immediate complications. Long-term patency, despite routine anticoagulation, averages 30–50%. Those rates have improved since the introduction and wide use of polytetrafluoroethylene (PTFE)-covered stents (67% patency rate at 1-year compared with only 19% for non-covered stents) [14]. In some cases, portal hypertension may not progress even with stent dysfunction, possibly owing to new collateral circulation. The use of TIPS in patients who are potential candidates for a liver transplant should be coordinated with the transplant team, because a poorly positioned stent (extension into the suprahepatic portion of the IVC) may create significant difficulties during the hepatectomy portion of the transplantation procedure.

TIPS should be considered for patients who fail endoscopic therapy for variceal bleeding and a few case reports showed benefit in patients with fulminant BCS in whom a liver transplant was not promptly available.

Surgical Shunts

Patients with subacute and chronic presentation of BCS, in the absence of significant hepatic fibrosis, can be considered for surgical shunting, provided that the portal vein is patent. Portosystemic shunts, by relieving sinusoidal hypertension, may reverse hepatic necrosis and prevent cirrhosis. A pressure gradient between the portal vein and the IVC of more than 10 mmHg (required for adequate flow across the shunt) is essential for successful long-term outcome, even in the presence of IVC compression by the caudate lobe of the liver.

Surgical shunts that have been used in patients with BCS include side-to-side portacaval, splenorenal, and mesocaval shunts. Mesoatrial shunts have been used for patients with IVC occlusion, but, with low long-term patency rates, this shunt should not be used if a TIPS can be placed. The long-term patency rates are approximately 80–90%. The 5-year survival rate after surgical shunting ranges between 57% and 95%, and is affected by the severity of liver disease at time of surgery and long-term shunt patency. Surgical shunts require anticoagulation to maintain patency, with life-long periodic Doppler ultrasound assessment of the shunt, particularly ones in which a synthetic graft has been used.

Retrospective data have questioned the benefits of surgical shunts. Their data showed no long-term survival advantage except in patients with mild liver disease. The lack of effect on survival was related to high perioperative mortality in patients with advanced liver disease (Child–Pugh class B and C liver disease), and late shunt dysfunction and thrombosis. Some perioperative mortality is attributed to acute hepatic decompensation which may require emergency salvage liver transplantation. Shunting should therefore be performed in a transplant center where rescue therapy can be performed if needed.

Overall, recent advances in interventional radiology have limited the need for surgical shunting to patients in

whom TIPS cannot be performed and are poor candidates for liver transplantation.

Liver Transplantation

Liver transplantation may be the only option for patients with fulminant BCS and for patients with decompensated liver cirrhosis who are not candidates for surgical or radiological decompression. It is indicated only for patients in whom the underlying disease that led to BCS is associated with favorable long-term prognosis. The 5-year survival rate among patients undergoing liver transplantation for BCS is currently as high as 95% [15,16].

Appropriate patients selection is particularly important in patients with MPDs. Patients with essential thrombocytosis have good long-term prognosis and should be considered for liver transplantation. Patients with polycythemia vera who have a hemoglobin >10 g/dL, white blood cell counts <30 00/mm^3, and who do not have trisomy 8, circulating blasts, or profound hypercatabolic symptoms, have good long-term survival and are reasonable candidates for liver transplantation. Most patients have good outcome post-transplantation, and use of aspirin and hydroxyurea post-transplantation is safe and effective [17]. Malignant transformation has not been reported.

Although some genetic prothrombotic disorders are cured by transplantation (protein C, protein S, and antithrombin III deficiency), thrombosis still occurs and routine long-term anticoagulation is necessary. This is most likely related to the fact that multiple etiologic factors are present simultaneously in a patient with BCS. Careful monitoring is necessary post-transplantation, as 40% of patients have complications from anticoagulation.

Prognosis and Survival

The natural history of BCS is not well known, as most publications report on treated patients. Mortality rates have decreased over time, and are highest within the first 2 years of diagnosis. Retrospective studies suggest that the 5-year survival rates average around 65–75%.

Several clinicopathologic factors, including treatment variables, were identified through multivariant prognostic models and were found to correlate with long-term prognosis. In a large series of 237 patients, severity of encephalopathy, ascites, prothrombin time, and serum bilirubin resulted in defining three groups, with statistically different 5-year survival rates of 89%, 74%, and 42% [9]. In another study, the 5-year survival rate was 70% in patients with Child–Pugh class B or C, older age, ascites, and high serum creatinine, compared with 95% if all factors are absent [18]. Histopathologic features do not help in determining prognosis, although surgical shunt outcome may be worse in patients with advanced fibrosis.

IVC obstruction has a good short-term prognosis, but long-term data are few. In Japan, patients with obliterative cavopathy have a 25% mortality rate over 15 years, dying from variceal bleeding, liver failure, and HCC.

Portal Vein Thrombosis

Case 2

A 55-year-old woman with Child class B liver cirrhosis, currently listed for liver transplantation, presents for her routine 3-month follow-up. She reports increased abdominal distension and worsening fatigue, but no hematemesis or melena. On examination, she has spider angiomas, scleral icterus, and mild-to-moderate ascites.

Definition and Epidemiology

Portal vein thrombosis (PVT) refers to thrombosis developing in the trunk of the portal vein from where it can extend into both the left and the right intrahepatic branches of the portal vein, the splenic vein, and the superior or inferior mesenteric vein. Most acquired cases occur in the setting of existing liver cirrhosis. Noncirrhotic, non-tumoral PVT is one of the leading causes of portal hypertension in the world (5–10%), and accounts for up to 30% of variceal bleeding cases in Asia [19,20].

The incidence of PVT is very hard to define and varies depending on the patient population and the diagnostic method employed. It is increasingly being diagnosed by the wide use of Doppler ultrasonography and cross-sectional imaging. Autopsy studies report an overall risk of PVT in the general population to be close to 1% [21].

The prevalence of PVT in patients with liver cirrhosis appears to correlate with the severity of underlying liver disease and has been reported to range from 1% to 21% (mean 11%).

Pathophysiology

Under normal circumstances, the portal vein contributes two-thirds of the hepatic blood supply. However, portal vein occlusion with thrombosis often produces few clinical consequences or laboratory manifestations. Hemodynamic adaptations occur with immediate vasodilation of the hepatic arterial bed followed in the long term by development of collateral veins (cavernous transformation) that bypass the thrombosed portion of the portal vein. The latter process may take up to 12 months, although it has been reported to occur as early as 5 weeks after the thrombotic event. Portal pressure will continue to increase over time, leading to presinusoidal portal hypertension with the formation of varices, and splenomegaly with increasing risk of bleeding.

PVT can be classified anatomically into four grades according to thrombus extension in relation to the portal vein and superior mesenteric vein (SMV):

1 Grade 1: partially thrombosed portal vein with less than 50% occlusion of the lumen

2 Grade 2: total occlusion of the portal vein with or without limited extension into the SMV

3 Grade 3: complete thrombosis of the portal vein and proximal SMV; distal SMV is patent

4 Grade 4: complete thrombosis of the portal vein and SMV.

Etiology

In the second half of the 19th century, the Virchow triad (damage to the vein, slowing of the venous blood flow, and hypercoagulability) identified pathogenic factors for venous thromboembolism. By implication, a combination of the elements of this triad is also thought to explain the pathogenesis of PVT. Despite current knowledge and advanced diagnostic modalities, PVT is classified as idiopathic in 15–30% of cases.

Causes of PVT vary depending on patient age and can be classified as inherited or acquired (Table 26.2). Among the acquired causes, cirrhosis has long been considered the most common cause, and is present in approximately 25% of patients with PVT. The pathogenesis of PVT in cirrhosis is uncertain but most likely multifactorial and related to decreased and altered portal blood flow, presence of periportal fibrosis, and a possible thrombophilia (two-thirds of patients may have a deficiency of one or more natural anticoagulant proteins) [22].

Neoplastic disorders are the second most common cause of PVT in adults and are present in approximately 20% of patients. Pancreatic cancer tops that list followed by HCC.

Infection is an important cause of PVT and is the most common cause of PVT in children, accounting for 40–50% of cases. Omphalitis (neonatal umbilical sepsis) is

Table 26.2 Risk factors for PVT.

Primary risk factor	Prevalence (%)[a]
Prothrombotic disorders	40–50
Inherited (protein S and C deficiency)	
Acquired (factor V Leiden, prothrombin mutation, antiphospholipid antibody)	
Cirrhosis	10–18
Myeloproliferative disorder (MPD)	7–12
Polycythemia vera	
Thrombocytosis	
Paroxysmal nocturnal hemoglobinuria	
Neoplasm	5–8
Pancreatic cancer	
Hepatocellular carcinoma	
Intra-abdominal malignancy	
Infections	10–25
Neonatal umbilical sepsis	
Appendicitis	
Diverticulitis	
Miscellaneous	5
Abdominal surgery	
Transjugular intraheptic portosystemic shunt	
Variceal treatment	
Pancreatitis	
Idiopathic[b]	10–20

[a]Some patients have combined risk factors.
[b]Overt or latent MPD was found in 48% of those patients in one study.

present in close to 25% of children with PVT. Infection accounts for approximately 10–20% of PVT cases in adults with non-cirrhotic, non-tumoral PVT. Septic PVT is usually related to appendicitis, cholecystitis, or diverticulitis, and is strongly associated with bacteroides bacteremia of unknown origin.

MPDs account for 3–12% of adult patients with PVT. This diagnosis may not be evident at the time of initial diagnosis of PVT, but becomes evident years later. In one study, 48% of patients with idiopathic non-malignant PVT had either an overt or a latent MPD.

Inherited or acquired hypercoaguable states are another important etiology of PVT. In most patients, more than one procoagulant risk factor is usually identified. The most prevalent group of inherited disorders includes gene mutations in factor V Leiden, factor II, and methylenetetrahydrofolate reductase (MTHFR). Both factor V Leiden and prothrombin gene mutations are associated with a lower risk of thrombosis despite a higher prevalence (>2%) in the general population. The relative risk of PVT in patients carrying those gene mutations is approximately 2%. The antiphospholipid syndrome is the most important acquired prothrombotic disorder and has been reported in up to 10% of patients with non-cirrhotic, non-malignant PVT.

A variety of other causes of PVT in adults without cirrhosis has been described (see Table 26.2). These include abdominal surgery (including splenectomy), pancreatitis, inflammatory bowel disease, pregnancy, and the use of oral estrogens.

Clinical Features

Patients with PVT may manifest with an acute process characterized by abdominal pain, increased abdominal girth, or hematemesis. Signs suggestive of intestinal ischemia may be present if thrombus extends into the SMV system. However, most cases of PVT are asymptomatic or minimally symptomatic, and diagnosed only if complications of portal hypertension develop. Most patients with PVT will have portal hypertensive gastrointestinal bleeding within 4 years of diagnosis. In patients with underlying liver cirrhosis, PVT can lead to hepatic decompensation.

On physical examination, splenomegaly is seen in 50–75% of cases. Splenomegaly can be massive and associated with the additional findings of hypersplenism such as anemia, thrombocytopenia, and leukopenia. Ascites is infrequently seen with the acute presentation and usually disappears once collateral circulation has developed. Jaundice and abnormal liver tests are rare in the absence of liver cirrhosis.

Histologically, there is little alteration in the hepatic architecture and most patients with non-cirrhotic PVT will have normal histology.

Diagnosis

Case 2

Patient underwent ultrasonography with Doppler studies which showed absence of flow in the portal vein, patent hepatic veins, and a cirrhotic appearing liver. CT with intravenous contrast confirmed PVT with some extension into the SMV. The small bowel appeared normal and medium-sized varices were seen. The liver appeared cirrhotic without any enhancing masses to suggest HCC. A CT scan from 3 months ago showed patency of the portal vein.

Laboratory data revealed a minimal increase in bilirubin, low platelet count, and normal creatinine with no change in the prothrombin time (PTT).

Most cases of PVT have minimal signs and symptoms and a high index of suspicion continues to be the key to diagnosis. Several radiological techniques are available to help confirm the diagnosis. Ultrasonography with Doppler studies is the first-line diagnostic modality. It has a sensitivity that ranges from 70% to 90% with high specificity (95–99%). An echogenic thrombus within the portal vein lumen is the key finding to establish the diagnosis. Other less specific findings include lack of variation in portal venous diameter with respiration and a dilated portal venous system. Contrast-enhanced CT and MRI and MR angiography (MRA) can be used to confirm the diagnosis and provide additional information, especially regarding the extension of the thrombus, and the presence of periportal collaterals (cavernous transformation), varices, signs of bowel ischemia, and parenchymal hepatic abnormalities. Sensitivity of any of these tests can be as high as 85–90%, with 90–95% specificity. Invasive diagnostic techniques such as angiography are rarely needed.

Therapy

Case 2

Patient had an upper endoscopy that showed mild portal hypertensive gastropathy with small non-bleeding varices. Hypercoaguable disorder work-up was done and confirmed the presence of prothrombin (factor II) gene mutation.

Patient was started on low-molecular-weight heparin (LMWH) and warfarin for 5 days. When the INR was >2, LMWH was stopped.

Repeat Doppler ultrasonography in 3 months showed recanalization of the portal vein with resolution of the partial thrombus in the SMV. Patient received a liver transplant 3 months later without significant complications.

Assessment

There are few controlled studies to help establish treatment guidelines in patients with PVT, so treatment should be individualized according to the clinical presentation and pathophysiology involved. A thorough assessment of thrombus chronicity is essential in order to identify those conditions amenable to treatment and to tailor therapy. Figure 26.2 outlines the management algorithm for patients with PVT.

Management usually starts with radiological testing (ultrasonography, CT, MRI/MRA) to help confirm the diagnosis, establish the extent of the thrombus, and identify the presence of any local factors. The presence of varices or cavernous transformation of the portal vein indicates chronicity. PVT will be defined as recent or

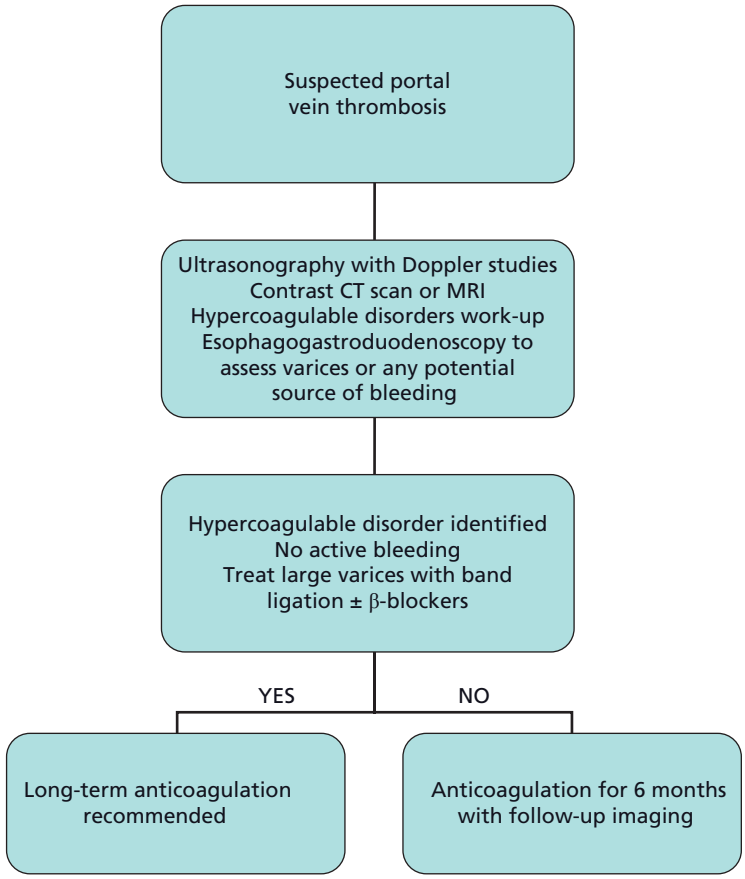

Figure 26.2 Proposed management algorithm for portal vein thrombosis.

acute in patients with acute presentation of abdominal pain, absence of findings that suggest portal hypertension (varices, ascites, and hypersplenism), and absence of cavernous transformation of the portal vein.

Early screening for varices is recommended in all patients with PVT. Gastroesophageal varices can be seen in 20–55% of patients and most will have large varices. Varices may develop as early as 1 month after the acute episode of PVT. However, patients with negative baseline endoscopy may still develop varices during follow-up; hence a repeat endoscopy is recommended in 6–9 months [23].

All patients with PVT (including those with liver cirrhosis) should undergo an extensive evaluation for both acquired and inherited hypercoagulable disorders. Levels of antithrombin III, protein C, and protein S can be difficult to interpret, especially in the presence of liver cirrhosis, as their plasma levels may be non-specifically decreased due to the underlying liver disease.

A potential MPD should also be carefully sought because these disorders can present with PVT years before the classic hematological manifestations. The current diagnostic approach in patients with PVT should include screening for the JAK2 mutation, and possibly a bone marrow aspiration if an MPD is suspected [8]. Presence of the JAK2 mutation is seen in 40% of patients with mesenteric venous thrombosis (including PVT) that do not fulfill the classic diagnostic criteria for an MPD [7].

Treatment

Outcome and Role of Anticoagulation

Acute PVT. Acute PVT refers to a recent formation of a thrombus that partially or totally occludes the portal vein. Goals of treatment are to avoid extension of thrombosis and to recanalize the obstructed vein, preventing thrombus extension and ischemic intestinal injury in the short term, and extrahepatic portal hypertension in the long term. Spontaneous recanalization of the portal vein is rare (<5%). As anticoagulation therapy is of proven benefit in patients with deep venous thrombosis, it was logical to extrapolate this principle to patients with PVT. Several retrospective studies that included consecutive patients have been published. Their combined data show that, when initiated immediately, anticoagulation therapy is associated with complete recanalization of the portal vein in 45%, partial recanalization in 35%, and no recanalization in 25% of patients [4,23]. These studies identified several factors associated with lack of recanalization: extent of the initial thrombus within the portal venous system, presence of ascites at time of diagnosis of acute PVT, presence of more than one prothrombotic disorder, and delay of anticoagulation treatment more than 1 week after the onset of symptoms. Severe complications of anticoagulation therapy were reported in less than 5% of treated patients.

Early initiation of anticoagulation therapy (within 1 month) of acute or recent PVT is recommended for most patients. Recanalization may occur 4–6 months after starting anticoagulation, so anticoagulation should be continued for at least 3 months and preferably for 6 months. Although there are no specific studies, long-term anticoagulation seems rational in patients with an identified prothrombotic disorder, recurrent episodes of thrombosis, or a familial history of venous thrombosis [4,8,24]. Anticoagulation should be initiated with heparin or LMWH. Oral vitamin K antagonists (warfarin) are usually started simultaneously with a target INR of 2–3. Bleeding complications are unlikely and can be minimized by the appropriate patient selection: absent or small varices without known bleeding, and no predictable bleeding sites outside the gastrointestinal tract.

The experience of other treatment modalities (surgical thrombectomy, *in situ* or systemic thrombolysis, or TIPS) is limited. One case series reported on the efficacy of thrombolytic agents in 28 patients who were treated within 4 weeks of the onset of symptoms. Treatment led to reinstitution of portal venous flow in 82% of patients, with 36% achieving complete recanalization and partial recanalization in 46% of patients [25]. As treatment can be associated with few but serious complications, it should be reserved for a highly selected group of patients.

Presence of intestinal infarction is a surgical emergency and will require emergency laparotomy with resection of necrotic bowel. Anticoagulation therapy appears to improve survival of patients who undergo surgery.

Chronic PVT. Chronic PVT is also known as portal cavernoma (cavernous transformation of the portal vein), a term that refers to the formation of a network of hepatopetal collateral veins which bypass the occluded portion of the portal vein. Most patients will present with

complications related to portal hypertension and hypersplenism. Bleeding is the most common complication encountered in these patients.

Management of chronic PVT is usually challenging and requires balancing the risk of bleeding against the risk of recurrence or extension of thrombosis. Several retrospective studies in patients with non-cirrhotic, nonmalignant PVT show a beneficial role of anticoagulation in recanalization of the portal vein and prevention of thrombus extension. Most of these patients have an identifiable prothrombotic disorder and 48% of patients have varices. Anticoagulation does not increase the risk or severity of bleeding or affect patients' mortality, provided that appropriate prophylaxis for bleeding has been instituted [24]. Therefore, there is mounting evidence that the benefit–risk ratio favors anticoagulation treatment in patients with chronic PVT [22,23]. Further prospective studies are needed, because the retrospective literature is hampered by inherent patient selection bias, lack of standardized anticoagulation and treatment duration, and frequent exclusion of patients with liver cirrhosis.

Treatment outcome in patients with chronic PVT is good. Patients are usually treated for 6 months without an underlying thrombophilia or life long in the presence of hypercoaguable disorder [26]. The mortality rate related to PVT complications (intestinal infarction or gastrointestinal bleeding) is less than 5% in patients followed for at least 5 years. The long-term mortality is usually related to the underlying disease especially in patients with MPDs [8,24].

Chronic PVT: Management of Varices and Role of Surgery

Acute bleeding from gastric or esophageal varices should be managed in the same manner as variceal hemorrhage in patients with cirrhosis. Treatment is usually a combination of a vasoconstrictor agent (octreotide, terlipressin), endoscopic band ligation, and antibiotic prophylaxis. Variceal bleeding is more common in children. Mortality in patients with non-cirrhotic PVT is lower than in patients with cirrhosis due to preserved liver function. For primary prophylaxis of variceal bleeding, there are insufficient data regarding the role of β-blockers or endoscopic therapy, and treatment should be individualized.

The role of surgical therapy in the management of PVT is still debatable. A shunting procedure that efficiently and permanently decompressed the portal venous system with a low complication rate would be ideal. Although the reported success rate is as high as 80%, the rate of shunt stenosis and thrombosis is high (8–24%), limiting its efficacy and making it the treatment option for those patients in whom medical and endoscopic therapy has failed to control variceal bleeding [27]. Splenectomy is curative in most patients with splenic vein thrombosis and isolated gastric varices. There are case reports of successful TIPS insertion in patients with portal cavernoma.

PVT: Patients with Liver Cirrhosis

The prevalence of PVT increases with the severity of liver disease, ranging from less than 1% in patients with well-compensated Child class A cirrhosis to as high as 10% in decompensated patients awaiting a liver transplant. Independent risk factors for thrombosis in patients awaiting a liver transplant include: severity of liver disease, low platelet count, history of variceal bleed, and prolonged interval from listing to liver transplantation. In most patients with liver cirrhosis, development of PVT is often accompanied by gastrointestinal bleeding, ascites, or encephalopathy. HCC should be excluded in all patients with recently identified PVT [28].

Patients with PVT, compared with those without it, have an increased prevalence of factor V Leiden, *MTFR* mutation, and prothrombin gene mutation (most frequently seen). However, an underlying prothrombotic disorder can be difficult to detect secondary to cirrhosis-related changes in markers of many prothrombotic disorders [28].

PVT in patients awaiting a liver transplant is a challenging clinical dilemma. Historically, PVT was a relative contraindication for liver transplantation because of technical difficulty. However, recent advances in surgical techniques made it feasible for patients with non-malignant PVT to undergo liver transplantation with comparable outcomes to those patients transplanted without PVT [29,30]. These techniques are most successful when the PVT is localized without extension into the SMV system—a serious complication that could preclude patients from being transplant candidates.

There are limited data regarding the role of anticoagulation therapy in patients with PVT and liver cirrhosis. Most of the reported case series are retrospective and include only patients awaiting liver transplantation. The

data are too limited to make solid recommendations, especially in patients with existing liver disease that increases risk of bleeding complications. As post-transplantation prognosis is strongly compromised by persistent complete PVT, an attempt at treatment with anticoagulation is reasonable in patients awaiting a liver transplant and in the absence of an active source of bleeding. One study showed a high rate of portal vein recanalization in patients receiving anticoagulation (42%), with no significant increase in the risk of bleeding complications. Patients transplanted with partial or complete recanalization of the portal vein had significantly better survival than those patients transplanted with PVT [28].

Prognosis

Based on early data, patients with acute PVT had high mortality rates (20–50%), with intestinal necrosis as the main cause of death even when surgery was performed. The outcome has improved through early diagnosis, early and increased use of anticoagulation, and use of antibiotics. Currently the 5-year survival rate is approximately 85% [24].

In patients with chronic PVT, morbidity is mainly related to variceal bleeding, recurrent thrombosis, and hypersplenism. Mortality rates are still low, with 5-year mortality rates of 5–10%. Mortality is mainly related to associated disease rather than portal hypertension-related complications [24].

Take-home points

Budd–Chiari syndrome:

- Budd–Chiari syndrome is more common in women and usually presents in the third to fourth decades.
- Suspect BCS in patients with acute or chronic liver disease and one of the following:
  - Ascitic protein content >3 g/dL
  - Personal or family history of idiopathic thrombosis
  - Platelet count >200 000 with signs of portal hypertension.
- Painful hepatomegaly, ascites, jaundice, and signs of portal hypertension are common clinical presentations.
- Non-invasive imaging with Doppler ultrasonography, contrast CT, or MRI is usually adequate to establish diagnosis. Venography and liver biopsy are rarely needed
- MPD and hypercoagulable disorders are among the most common causes of BCS.
- *JAK2* mutations help to identify patients with MPDs in the absence of the classic clinical presentation.
- Medical therapy with diuretics and anticoagulation is indicated for all patients, and most will require additional modalities to help control disease progression.
- TIPS has replaced surgical shunts as treatment of choice in patients with BCS.
- Liver transplantation is needed in 10–20% of BCS patients and is associated with an excellent 5-year survival.
- Post-transplantation, most patients will require long-term anticoagulation.

Portal vein thrombosis:

- PVT is the main etiology of presinusoidal portal hypertension.
- Causes of PVT vary depending on age. Infection is the most common cause in children. Liver cirrhosis, hypercoaguable disorders, and neoplastic process are the most common causes in adults.
- Hypercoaguable disorders can be found in up to 50% of patients with PVT, and MPDs can be seen in 10–15% of patients.
- Work-up for hypercoaguable disorders and possible *JAK2* mutation should be performed on all patients with PVT.
- Anticoagulation should be used for patients with PVT, in the absence of clinical contraindications, and duration should be individualized based on etiology.
- Patients with liver cirrhosis can develop PVT spontaneously but a work-up should be done to rule out MPDs, hypercoaguable disorders, and HCC.
- Limited data show a high rate of PVT recanalization in patients with liver cirrhosis and PVT. This correlated with better prognosis post-transplantation. Still further studies are needed to confirm safety
- In the absence of liver cirrhosis, PVT has a good prognosis, with <10% mortality rate at 5 years.

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CHAPTER 27
Hepatic Complications of Bone Marrow Transplantation

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Summary

Hepatic complications of hematopoietic stem cell transplantation (HSCT) are common. Sinusoidal obstruction syndrome (SOS), acute/chronic hepatic graft-versus-host disease (HGVHD), infection, and drug-induced hepatotoxicity (DIH) are the most common reasons for liver abnormalities following HSCT.

SOS, characterized by rapid weight gain due to fluid retention, hyperbilirubinemia, and hepatomegaly with right upper quadrant pain, can be difficult to diagnose. Liver biopsy is the gold standard. Treatment options include tissue-type plasminogen activator with heparin, defibrotide, and antithrombin III. A majority of patients recover.

Acute HGVHD generally occurs with skin and gastrointestinal tract GVHD. Chronic HGVHD presents with other manifestations of chronic GVHD, closely resembling an autoimmune disorder much like scleroderma. Immunosuppression is the mainstay of therapy, with a majority of patients requiring long-term treatment.

Viral, fungal, and bacterial infections, as well as DIH, are also common after HSCT. Treatment with appropriate antibiotics, or withholding liver-toxic medications, results in liver function improvement for most patients.

Case

A 32-year-old white female with a history of myeloproliferative disease (MPD) complains of abdominal pain 4 days following a myeloablative, matched related-donor allogeneic hematopoietic stem cell transplantation (HSCT). The patient was given busulfan 0.8 mg/kg (33.5 mg) i.v. for 4 days and cyclophosphamide 60 mg/kg (3400 mg) i.v. for 2 days for conditioning. She was maintained on ursodeoxycholic acid (UDCA) 300 mg orally twice daily and enoxaparin 30 mg s.c. twice daily for sinusoidal obstruction syndrome (SOS) prophylaxis.

On evaluation, she is complaining of severe generalized abdominal pain, rated at 10 on a scale of 1–10 pain intensity. She is not jaundiced. Abdominal examination reveals ascites with a fluid wave and generalized tenderness to palpation. The patient's weight has increased from 55.6 kg on admission to 61.6 kg.

Laboratory studies show serum aspartate aminotransferase (AST) 71 IU/L [reference range (RR): 8–43 IU/L]; serum alanine aminotransferase (ALT) 117 IU/L (RR: 7–45 U/L); serum alkaline phosphatase (AP) 120 IU/L (RR: 37–98 IU/L); serum total bilirubin 3.7 mg/dL (RR: 0.1–1.1 mg/dL); serum direct bilirubin 2.6 mg/dL (RR: 0–0.3 mg/dL). These values were normal 5 days prior. Abdominal ultrasound reveals mild ascites, hepatosplenomegaly, unremarkable liver parenchyma, normal appearing biliary ducts, normal hepatic artery waveform, and a previously identified portal vein thrombosis, attributed to the underlying MPD.

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Definition and Epidemiology

HSCT is a commonly used treatment for hematologic and non-hematologic malignancies. More than 80% of patients will develop hepatic complications in the aftermath of HSCT [1]. Mortality rates from liver damage following HSCT are between 4% and 15% [2,3].

SOS [also called hepatic veno-occlusive disease (VOD)], acute or chronic hepatic graft-versus-host disease (HGVHD), infection, drug-induced hepatotoxicity (DIH) and liver dysfunction due to the underlying malignancy are the most common reasons for liver abnormalities following HSCT [4,5]. Among these disorders, HGVHD accounts for 33–40.6% of liver dysfunction; DIH (19–30%); and post-transplantation viral hepatitis (7–15%) [6,7]. SOS incidence is variable, with rates between 5% and 70% in different reports [8–11].

Pathophysiology

Sinusoidal Obstruction Syndrome

Endothelial injury from drugs or total body irradiation (TBI) used as a part of the conditioning regimen triggers SOS [8]. Early in the course, edema causes subintimal zone thickening within sublobular venules. Erythrocyte fragments are seen in the extravascular space of Disse. Fibrin and factor VIII are found deposited in venule walls on immunohistochemical (IHC) staining [8]. Edema results in venule lumen narrowing and increased venule resistance to blood flow with portal hypertension. Increased venule resistance causes low-flow states, leading to hepatocyte ischemia [8]. With ongoing SOS, fibrosis forms within sinusoids, leading to destruction of sublobular venules and chronic venous outflow obstruction [12].

Disorders of hemostasis are believed to contribute to the process. Although thrombi are not commonly seen in venules on histologic examination [12], prophylaxis and treatment with anticoagulants are known to be effective for SOS, suggesting a potential role for thrombosis in the disease. Levels of protein C, protein S, antithrombin III (ATIII), and fibrinogen are lower in patients with SOS. Levels of factor VIII, von Willebrand factor (vWF), and tissue plasminogen activator (tPA) are higher [13–15]. These findings suggest initiation of the coagulation cascade in response to endothelial injury.

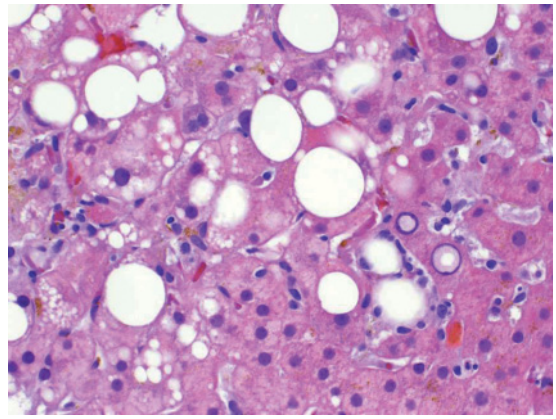

Figure 27.1 Hematoxylin and eosin stain of a liver biopsy from a 66-year-old white male, status—post matched-related allogeneic hematopoietic stem cell transplantation for myeloproliferative disorder. The patient presented 150 days post-transplant with elevated serum aspartate aminotransferase and alanine aminotransferase, unresponsive to withholding of hepatotoxic medications. Cholestasis and a necroinflammatory infiltrate in the lobule are observed, consistent with acute hepatic graft-versus-host disease (40× magnification) (courtesy of Giovanni De Petris MD).

Hepatic Graft-versus-Host Disease

Histologic changes are observed within 1–2 weeks of the clinical appearance of acute HGVHD [16]. Figures 27.1 and 27.2 depict common histopathologic findings. Bile duct damage, cholestasis, and endothelitis of central or portal veins are specific features. Following allogeneic HSCT, increased expression of major histocompatibility complex, blood group antigens, and minor transplantation antigens on biliary epithelial cells leads to antigen recognition by T lymphocytes and cytotoxicity [17]. The recruitment of non-specific effector cells (eosinophils, neutrophils, and macrophages) amplifies bile duct damage [16]. Furthermore, expression of Fas by cholangiocytes and hepatocytes is upregulated; the binding of Fas ligand from CD8+ cytotoxic T lymphocytes to Fas on cholangiocytes and hepatocytes results in a death-inducing signaling complex, leading to apoptosis [18]. After weeks to months of acute HGVHD, cholestasis, hepatocyte injury and dropout, and bridging fibrosis occur. Cirrhosis is uncommon [16].

In chronic HGVHD, patterns include a loss of small bile ducts with minimal inflammation and cholestasis, to

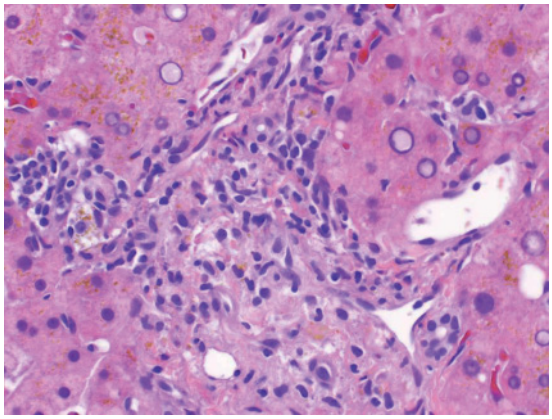

Figure 27.2 Hematoxylin and eosin stain of a liver biopsy from a 66-year-old white male, status—post matched-related allogeneic hematopoietic stem cell transplantation for myeloproliferative disorder. The patient presented 150 days post-transplant with elevated serum aspartate aminotransferase and alanine aminotransferase, unresponsive to withholding of hepatotoxic medications. Diffuse bile ductule damage in a portal area is seen, consisted with acute hepatic graft-versus-host disease (40× magnification) (courtesy of Giovanni De Petris MD).

chronic active hepatitis [5], or portal inflammation [19]. A review of 48 HGVHD biopsy specimens found that only portal inflammation was significantly more likely to be seen in chronic HGVHD compared to acute HGVHD. Otherwise, the patterns of the two forms of HGVHD largely are indistinguishable [19].

Infection

Viral hepatitis following HSCT is most commonly caused by hepatitis C virus (HCV) and cytomegalovirus (CMV). Other potential viral causes include hepatitis B virus (HBV), herpes simplex virus (HSV), varicella zoster virus (VZV), human herpesvirus-6 (HHV6), adenovirus, Epstein–Barr virus (EBV), parvo- and papova-viruses [16]. Histopathologic features of selected liver viral infections following HSCT are shown in Table 27.1. Bacterial sepsis is evidenced by non-dilated ducts without suppuration, bile thrombi in bile ducts, and central venous ischemia [20]. Fungal infections have various histopathologic findings, including formation of abscesses and granulomas in *Candida* infection, or invasion of

Table 27.1 Histopathologic and clinical features of selected liver viral infections following hematopoietic stem cell transplantation.

Virus	Histopathologic features	Clinical features
Chronic HCV	Portal inflammation	Asymptomatic *or* Fatigue, arthralgia, myalgia, weight loss Normal to mildly elevated serum ALT
CMV	Intranuclear inclusions bordered by a clear region [20]; mononuclear cell infiltrate in sinusoids; lymphocyte infiltration into portal areas; microabscesses; cholestasis [16]	Asymptomatic *or* Invasive disease with: colitis, pneumonitis, encephalitis and/or hepatitis
HSV	Intranuclear inclusions, hemorrhage, ghost cells, extensive necrosis [20]	Right upper quadrant pain, jaundice, fatigue, anorexia, nausea, absence of rash Elevated serum AST/ALT
VZV	Similar to HSV [20]	Similar to HSV
Adenovirus	Similar to HSV [20]	Similar to HSV
EBV	Sinusoidal lymphocytes and cellular apoptosis [20]	Lymphadenopathy, hepatosplenomegaly, pancytopenia Elevated serum AP

HCV, hepatitis C virus; CMV, cytomegalovirus; HSV, herpes simplex virus; VZV, varicella zoster virus; EBV, Epstein–Barr virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AP, alkaline phosphatase.

vasculature with fungal organisms leading to infarction with *Aspergillus, Rhizopus, Mucor* or *Absidia* infections [20].

Drug Toxicity

Medications used frequently in HSCT that may cause DIH are shown in Table 27.2. Histologically, acute liver injury from drugs has one of four patterns: hepatocellular, cholestatic, mixed or acute steatosis. Hepatocellular injury is demonstrated by the presence of cellular degeneration, necrosis, and steatosis. Cholestatic liver injury is suggested by one of two patterns: (1) canalicular pattern (bland/non-inflammatory pattern with cholestasis); or (2) hepatocanalicular pattern (cholestasis, portal inflammation with some hepatocellular destruction). Microvesicular steatosis, mainly with triglycerides, represents the acute steatosis class of liver injury. Any of these liver injury patterns may be seen with DIH in HSCT [20].

Clinical Features

Sinusoidal Obstruction Syndrome

Risk factors for SOS are listed in Table 27.3. There are four categories of risk factors: risks due to pre-existing liver dysfunction; risks due to the conditioning regimen; risks related to other drugs administered; and patient/transplant-type specific risks.

SOS is characterized by a triad of features: rapid weight gain due to fluid retention, hyperbilirubinemia, and hepatomegaly with right upper quadrant pain [22], often appearing in the first or second week after HSCT [6,22]. SOS may develop up to 3–4 weeks after HSCT [22]. Azotemia, elevation in other liver transaminases, and thrombocytopenia are also found. Symptoms include right upper quadrant abdominal pain. Jaundice, hepatomegaly, and ascites may be found on examination.

Over one-half of patients develop multiorgan failure, including congestive heart failure, hepatorenal syndrome, and respiratory failure in some case series [4,16]. For patients surviving SOS, bilirubin values peak around 10 days following their first increase, returning to baseline within an additional 10 days [11].

Hepatic Graft-versus-Host Disease

Risk factors for acute GVHD following HSCT include [22]:

- Stem cell product from an unrelated human leukocyte antigen (HLA)-matched donor;
- Stem cell product from an HLA-mismatched donor;
- Female donor–male recipient;
- Advanced age of donor or recipient;
- Suboptimal GVHD prophylaxis;
- Prior herpesvirus infections.

Table 27.2 Drugs associated with liver toxicity following hematopoietic stem cell transplantation.

- Busulfan
- Cyclophosphamide
- Cyclosporine
- Fluconazole
- Itraconazole
- Melphalan
- Methotrexate
- Tacrolimus
- Total parenteral nutrition
- Trimethoprim–sulfamethoxazole

Table 27.3 Risk factors for sinusoidal obstruction syndrome.

- **Liver related:**
  - Hepatitis C [21]
  - Pre-existing liver disease (fibrosis, cirrhosis, low serum albumin) [4]
  - Pretransplant elevated serum AST/ALT [22]
  - Previous hepatic irradiation [4]
- **Conditioning regimen-related:**
  - Myeloablative conditioning regimen (especially high-dose busulfan and/or TBI with cyclophosphamide) [4]
- **Drug therapy-related:**
  - Acyclovir [4]
  - Amphotericin B [4]
  - Gemtuzumab ozogamicin (Mylotarg) [23]
  - Methotrexate (for GVHD prophylaxis) [8]
  - Vancomycin[4]
- **Transplant-related factors:**
  - Advanced age [8]
  - Allogeneic HSCT > autologous HSCT [8]
  - Prior HSCT [4]
  - Unrelated-donor HSCT or HLA mismatched related-donor HSCT [4]

AST, aspartate aminotransferase; ALT, alanine aminotransferase; TBI, total body irradiation; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplantation; HLA, human leukocyte antigen.

Acute HGVHD generally occurs along with skin and gastrointestinal tract GVHD, only rarely occurring in isolation [16]. Historically, acute GVHD was defined as occurring within the first 100 days of allogeneic HSCT, but this definition has become less favored. A diagnosis of acute GHVD should be based on clinical signs and symptoms rather than timing alone [24]. Acute HGVHD is suggested by the onset of cholestatic jaundice (elevated serum AP, hyperbilirubinemia, mild hepatomegaly). The increase in serum AP is often dramatic, as much as 10–20-fold above normal; AST and ALT values also may increase as much as 10-fold. If acute HGVHD is accompanied by sepsis or renal failure, bilirubin values above 50 mg/dL may be seen [16]. If GVHD progresses, severe hepatic dysfunction with ascites, coagulopathy, and encephalopathy is observed.

Chronic HGVHD is usually found in patients with other manifestations of chronic GVHD, which closely resembles an autoimmune disorder much like scleroderma. Affected systems include mucosa (sicca symptoms, oral mucositis), skin (pigmentation changes, loss of hair and sweat glands), ophthalmic (keratoconjunctivitis), gastrointestinal (esophageal strictures, malabsorption), pulmonary (bronchiolitis obliterans), and hematologic (suppressed hematopoiesis). Chronic HGVHD findings include elevations of serum AP and hyperbilirubinemia, but the magnitude of hyperbilirubinemia does not correlate with the degree of liver involvement [5].

Infection

Many viral infections following HSCT may affect the liver. Infection with adenovirus or EBV, along with reactivations of CMV, HBV, HCV, HSV, VZV, and HHV6, typically occur following engraftment of stem cells [5]. Clinical features of these viruses are summarized in Table 27.1. Note that patients may develop all, some or none of the features noted in Table 27.1.

Fever, painful hepatomegaly, and elevated serum AP are features of fungal liver infections following HSCT, but are non-specific symptoms. The incidence of fungal infections following HSCT has decreased with use of triazole prophylaxis, especially the incidence of *Candida* infections, but resistant organisms have emerged (e.g. *C. glabrata, C. krusei*) [5]. *Aspergillus* infections of the liver are seen usually with infections of other organs [5].

Isolated bacterial infections of the liver after HSCT are rare, usually due to empiric antibiotics started for fevers during the HSCT course. Reactivation of *Mycobacterium* species is a recognized (though rare) complication of HSCT; liver involvement has been reported [25].

Drug Toxicity

Hepatic injury from drugs used during the HSCT process is suggested by abnormalities in serum AST, ALT, or AP levels. A clinical picture resembling acute hepatitis may be seen in severe cases.

Diagnosis

Sinusoidal Obstruction Syndrome

The diagnosis of SOS is challenging due to the overlap of signs and symptoms of SOS with other conditions. A diagnosis of SOS is established by liver biopsy [8]; however, thrombocytopenia following HSCT, often refractory to platelet transfusions, may preclude the ability to obtain a liver biopsy. Thus, the diagnosis of SOS is based frequently on clinical findings and suspicion. Several sets of criteria for making an SOS diagnosis have been developed; all incorporate the three features of rapid weight gain due to fluid retention, hyperbilirubinemia, and hepatomegaly with right upper quadrant pain developing within 3–4 weeks of HSCT. For example, the Seattle criteria define SOS as development of two of three clinical features within 30 days of HSCT: (1) jaundice; (2) hepatomegaly with right upper quadrant pain; (3) ascites and/or unexplained weight gain. These criteria have a specificity of 92% and sensitivity of 56% [26].

Imaging studies, such as Doppler ultrasound and magnetic resonance imaging (MRI), aid in establishing a diagnosis of SOS, but do not rule out SOS if they are unrevealing. On ultrasound, splenomegaly, ascites, and flow within the periumbilical vein confer 100% sensitivity and 49% specificity for SOS [27]. Portal hypertension, reversal of portal flow, hepatomegaly, and thickening of the gall-bladder wall also may be observed. Although less well studied for SOS, MRI may reveal hepatomegaly, thickening of the gall-bladder wall, reduced portal flow, ascites, narrowing of hepatic vein, and periportal cuffing [28].

The gold standard for SOS diagnosis is liver biopsy. Percutaneous, laparoscopic, and transjugular approaches are used. Sufficient samples are generally obtained with the transjugular approach using contemporary methods [5,8]. This approach allows for measurement of the hepatic venous wedge pressure. A hepatic venous pressure gradient of more than 10 mmHg has 91% specificity and 60% sensitivity for SOS, with higher pressure gradients conferring a worse outcome [5]. Percutaneous liver biopsy may not be feasible due to bleeding risk from thrombocytopenia, and laparoscopy carries the risk of a false-negative biopsy due to the patchy nature of liver involvement with SOS in early stages [8].

Biochemical evidence of SOS includes elevated levels of plasminogen activator inhibitor-1 (PAI-1) [29], *N*-terminal peptide of type III procollagen [5], and reduced levels of ATIII and protein C [30].

Hepatic Graft-versus-Host Disease

Acute HGVHD is typically accompanied by GVHD of the gastrointestinal tract and skin. HGVHD can be the presenting feature of systemic GVHD, but isolated liver dysfunction without skin or gut involvement should call into question a diagnosis of acute HGVHD [5,16]. The staging and grading of GVHD is presented in Table 27.4. Acute HGVHD is suggested by elevated serum AST, ALT, and AP, hyperbilirubinemia, and mild hepatomegaly. As HGVHD progresses, severe hepatic dysfunction with ascites, coagulopathy, and encephalopathy is observed.

A diagnosis of acute HGVHD is based most commonly on clinical suspicion (i.e., the presence of liver biochemical abnormalities with skin and gastrointestinal symptoms). Liver biopsy via the transjugular approach can be used to confirm the diagnosis, but often is not necessary. In one series from Mayo Clinic, only 61 of 1700 patients receiving bone marrow transplant over a 20-year period underwent liver biopsy to evaluate hepatic dysfunction. Of those found to have HGVHD histologically, all but one had evidence of skin or gut GVHD [31]. Thrombocytopenia in the post-HSCT setting may preclude the ability to obtain a liver biopsy. Therefore, a liver biopsy is reserved for the following situations [32]:

- Rule out other causes of hepatic dysfunction (e.g., SOS, DIH, infection);
- Suspicion of isolated acute HGVHD;
- No improvement in hepatic dysfunction with changes to immunosuppression.

Table 27.4a Stage of acute graft-versus-host disease.

Stage	Skin findings	Liver findings [bilirubin level, (mg/dL)]	Gastrointestinal findings
+	Maculopapular rash on <25% of body surface	2–3	Diarrhea 500–1000 mL/day or persistent nausea
++	Maculopapular rash on 25–50% of body surface	3–6	Diarrhea 1000–1500 mL/day
+++	Generalized erythroderma	6–15	Diarrhea > 1500 mL/day
++++	Desquamation and bullae	> 15	Pain with or without ileus

Table 27.4b Grade of acute graft-versus-host disease.

Overall grade	Skin	Liver	Gastrointestinal	Functional impairment
0 (None)	0	0	0	0
I (Mild)	+ to ++	0	0	0
II (Moderate)	+ to +++	+	+	+
III (Severe)	++ to +++	++ to +++	++ to +++	++
IV (Life-threatening)	++ to ++++	++ to ++++	++ to ++++	+++

Table 27.5 Classification of chronic graft-versus-host disease.

Classification	Clinical/histopathologic findings
Limited	Localized skin involvement and/or hepatic dysfunction due to chronic GVHD
Extensive	Generalized skin involvement or localized skin involvement and/or hepatic dysfunction due to chronic GVHD, plus one of the following: • Liver histology showing chronic aggressive hepatitis, bridging necrosis, or cirrhosis • Involvement of the eye • Involvement of minor salivary glands or oral mucosa demonstrated on labial biopsy • Involvement of any other target organ

GVHD, graft-versus-host disease.

Chronic HGVHD is usually accompanied by chronic GVHD of other organs. A diagnosis of chronic GVHD requires at least one clinical manifestation, with abnormalities of serum markers and/or findings on biopsy of an affected organ [33]. Thus, liver biopsy may be more helpful in establishing a diagnosis of chronic HGVHD than in the acute setting. Table 27.5 shows the classification of chronic GVHD.

Infection

Hepatic infection following HSCT is suspected in the setting of fever, liver biochemical abnormalities, and possibly painful hepatomegaly (as in fungal infection). Fungal infections involving the liver may be evident on CT, MRI, or ultrasound, but miliary involvement may be missed with imaging [5]. Positive fungal blood cultures are helpful in establishing the diagnosis, but occasionally liver biopsy with fungal stains and cultures is required to identify an organism. Similarly, blood cultures for bacteria, including mycobacterial cultures, along with liver biopsy, staining, and cultures, can solidify a diagnosis of bacterial infection in the liver. Viral cultures and polymerase chain reaction (PCR) testing for herpesviruses can be performed when viral infection of the liver is suspected.

Drug Toxicity

A diagnosis of DIH can be challenging, especially in the setting of HSCT, where multiple factors may be contributing to liver dysfunction. As proposed by Navarro and Senior, a diagnosis of DIH can be made if exposure to the implicated drug preceded the first signs of liver dysfunction, other causes of liver injury are excluded, liver function improves when the suspected drug is withheld, and liver dysfunction returns (often more rapidly and severely) on readministration of the drug [34]. Liver biopsy may be necessary if the diagnosis remains unclear. In such cases, liver histology may reveal a signature pattern easily ascribed to a particular drug.

Case continued

The differential diagnosis for the patient's disorder includes SOS, acute HGVHD, infection, and DIH. The patient has no other features to suggest acute GHVD, such as diarrhea or rash. Hepatitis B and C serologies, and serologies for HSV-1 and -2, CMV, and human immunodeficiency virus (HIV) are negative. She has been maintained on prophylactic doses of acyclovir and fluconazole during the hospital course. Therefore, acute hepatic GVHD and infection are less likely.

Several factors raise the possibility of SOS, including:

- Severe abdominal pain;
- Ascites;
- Generalized tenderness to palpation;
- Increase in weight from 55.6 kg on admission to 61.6 kg;
- Elevated serum AST, ALT, AP, total and direct bilirubin.

Although the patient's ultrasound revealed hepatosplenomegaly and ascites (consistent with a diagnosis of SOS), the patient was known to have ascites and a portal vein thrombosis prior to HSCT, making the diagnosis of SOS challenging. Additionally, the patient has been maintained on UDCA and enoxaparin for SOS prophylaxis.

To aid in making the diagnosis, serum protein C level and PAI-1 activity are obtained, but are found to be normal. [Serum protein C, 52% (RR: 0–150%); PAI-1 activity 8.1 IU/mL (RR: < 31.1 IU/mL).] Due to severe thrombocytopenia (10 x 10^9/L), a liver biopsy is not attempted.

With other causes deemed less likely, a tentative diagnosis of SOS is made.

Therapy

Sinusoidal Obstruction Syndrome

The most commonly used treatments for SOS are recombinant tPA with heparin, defibrotide, and antithrombin III. In the USA, defibrotide is currently available under compassionate use approval from the Food and Drug Administration.

tPA with heparin is used in SOS based on the presence of coagulation proteins on IHC stains of liver biopsies. In a retrospective review, 10 of 42 patients treated with a median tPA dose of 60 mg over 2–4 days with a 1000 IU intravenous bolus of heparin followed by 150 IU/kg/day continuous heparin infusion, experienced severe bleeding, with death from bleeding in three cases. The authors concluded that tPA with heparin should not be given to patients with severe SOS and multiorgan failure [35].

Defibrotide, a polydeoxyribonucleotide extracted from mammalian tissue, is approved in Europe for the treatment and prevention of SOS. Defibrotide has multiple anticoagulant effects, but does not lead to systemic anticoagulation. Thus, it is not associated with a bleeding risk. In study of 88 HSCT patients with severe SOS and multiorgan failure, 36% experienced complete resolution, with 35% surviving until day +100. A decrease in serum creatinine and PAI-1 levels during therapy, younger age, autologous HSCT, and the presence of abnormal portal flow predicted better survival; busulfan conditioning or encephalopathy predicted worse survival [36]. In a phase II trial of 40 patients, 55% showed complete remission (defined as a decrease in serum total bilirubin to <34.2 μmol/L, with resolution of signs and symptoms of SOS and multiorgan failure), with 43% alive at day +100 [37]. The recommended defibrotide dose for SOS treatment is 10–40 mg/kg/day divided in four doses, with a maximum dose of 60 mg/kg/day divided in four doses.

At least two case series have evaluated ATIII concentrate for SOS treatment. In one series, all 10 patients studied experienced improvements in thrombocytopenia, abdominal pain, ascites, and/or weight gain [38]. Although ATIII concentrate has not been evaluated in large, prospective, randomized controlled studies, its use in the setting of SOS can be considered. ATIII concentrate is given with a loading dose of 50 IU/kg every 8 h for three doses followed by 50 IU/kg/day for 3–12 days.

Additional treatment options for SOS include transjugular intrahepatic portosystemic shunt (TIPS), charcoal hemofiltration, *N*-acetylcysteine, prostaglandin E_1, vitamin E, glutamine, and orthotopic liver transplantation. All have been reported in small numbers of patients with SOS [8]. Supportive care should include treatment of volume overload, therapeutic paracentesis, stopping hepatotoxic medications, treating underlying infections, and employing hemodialysis or continuous venous hemofiltration when necessary [8].

SOS prophylaxis strategies include UDCA, defibrotide, low molecular weight heparin (LMWH) and low-dose continuous infusion unfractionated heparin. Each has been evaluated in small studies. In a study of 67 patients undergoing allogeneic HSCT, patients randomized to receive UDCA had significantly lower rates of SOS compared to placebo ($p = 0.03$) [39]. In a study of defibrotide for SOS prophylaxis, 0 of 58 patients developed SOS [40]. A phase II study evaluated LMWH (dalteparin, 2500 anti-Xa IU daily from day −1 to day +30 or hospital discharge) for SOS prophylaxis in 40 patients undergoing either autologous or allogeneic HSCT; nine patients developed SOS [41]. The authors could not conclude if LMWH was superior to continuous infusion unfractionated heparin (100 IU/kg/day), which has been shown in a randomized trial of 161 patients to lower SOS incidence compared to placebo [42]. At these authors' institution, LMWH (enoxaparin, 30 mg s.c. every 12 h) is preferred for SOS prophylaxis. High-risk patients are given LMWH with UDCA.

Hepatic Graft-versus-Host Disease

For patients developing acute GVHD despite prophylaxis, corticosteroids remain first-line treatment. Based on a randomized trial of 95 patients developing acute GVHD, methylprednisolone 2 mg/kg/day is the standard starting dose, increased to 10 mg/kg/day if the patient has had no improvement after 5 days [43]. Corticosteroids should be tapered gradually once there is evidence of a response to therapy. If high-dose corticosteroids do not result in improvement, additional treatment options include tacrolimus, infliximab (a monoclonal antibody to tumor necrosis factor-α), daclizumab [a monoclonal antibody to the interleukin (IL)-2 receptor], mycophenolate mofetil, and antithymocyte globulin (ATG).

As with acute GHVD, chronic GVHD is managed with corticosteroids, usually at a dose of 1 mg/kg every other day. Prednisone with cyclosporine also has been given for patients at high risk of complications from chronic GVHD [5]. Tacrolimus, mycophenolate mofetil, and sirolimus are also used. Chronic GVHD involving the liver may respond to UDCA. Studies investigating UDCA in chronic GVHD report improvements in liver biochemistries, including normalization in some patients when given for 1 year [44].

Infection

Appropriate antiviral, antibacterial, and antifungal agents should be used for infections affecting the liver after HSCT. Prophylaxis with acyclovir (400 mg orally twice daily) and fluconazole (400 mg orally daily) has reduced the incidence of herpesvirus and fungal infections. Reactivation of HSV or VSV may be treated with acyclovir 500 mg/m^2 i.v. every 8 h for 7–10 days. Ganciclovir (5 mg/kg i.v. twice daily) should be given for CMV prophylaxis to CMV-seropositive recipients or those receiving stem cells from a CMV-seropositive donor; the same dose can be given to patients with CMV reactivation following HSCT. Lamivudine for prevention of HBV reactivation should be used for chronic HBV carriers. For patients with chronic HCV, interferon-α and ribavirin therapy can be considered once all immunosuppressive therapy has been discontinued for 6 months and no evidence of GVHD or myelosuppression is found. Such patients achieve similar response rates to chronic HCV therapy as patients not receiving HSCT [5].

Drug Toxicity

The main therapy for DIH is withdrawal of the drug. With the exception of *N*-acetylcysteine in acetaminophen liver toxicity, there are no drugs of proven benefit in reversing hepatotoxicity. Corticosteroids may be used in cases of hypersensitivity reactions. UDCA often is used in cholestatic patterns of liver injury, but has not been well-studied [45].

Case continued

As the decision is being made on a course of treatment for presumed SOS, the nurse reports that the patient has developed epistaxis. The bleeding is controlled with direct pressure.

The decision is made to initiate treatment with ATIII, since tPA with heparin is contraindicated in the setting of bleeding. Defibrotide is an option, but not readily available. The patient is given ATIII loading dose (three doses of 50 IU/kg at 8-h intervals) followed by 3225 IU/day. UDCA is continued. Enoxaparin is discontinued due to epistaxis. The possibility of liver transplantation is discussed, but deferred as the patient experiences stabilization of liver biochemistries and symptoms. After 7 days of treatment with ATIII, in addition to supportive care including aggressive diuresis, the patient's serum AST, ALT, and AP normalize. Serum total bilirubin also improves, but remains elevated at 2.2 mg/dL on the day of hospital discharge.

Prognosis

Sinusoidal Obstruction Syndrome

A majority of patients will experience resolution within 2–3 weeks. Death can occur in 20–50% of patients. The rate of bilirubin increase and the peak concentration are important predictors [8]. Death in SOS patients is usually caused by failure of other systems, such as kidney, respiratory, and cardiac failure, rather than hepatic failure. Long term sequelae are rare, with only a small percentage of patients developing fibrosis and portal hypertension [8].

Hepatic Graft-versus-Host Disease

HGVHD is present in 73–86% of patients with acute GVHD, and it may respond more slowly to treatment [16]. Acute HGVHD may develop to chronic HGVHD, and can portend a 20% survival at 6 years if present with chronic GVHD of skin and mucous membranes [46]. A retrospective review of 427 patients with acute GVHD not responding to primary therapy showed a complete and partial response rate of 40%. Just 25% of patients with HGVHD saw improvement or resolution with second-line therapies (corticosteroids, cyclosporinee, monoclonal antibodies, or ATG) [47]. A retrospective review of 197 patients with grade II–IV acute GVHD showed resolution in 41% after a median 21 days of treatment, with 70% of patients developing chronic GVHD [48]. Thus, ongoing immunosuppression is necessary in a majority of patients to limit chronic GVHD.

Drug Toxicity

Most patients experience recovery of normal liver function once the hepatotoxic drug is stopped. Recovery may be prolonged, as long as weeks to months in some cases [34]. The presence of jaundice with elevated aminotransferases has been associated with a 10–50% mortality rate in DIH [34].

Conclusions

Clinicians often must evaluate liver abnormalities following HSCT. An algorithm for assessment of patients status post HSCT with abdominal pain, liver biochemical abnormalities, hepatomegaly, and/or weight gain is depicted in Figure 27.3. The first step in diagnosis, after

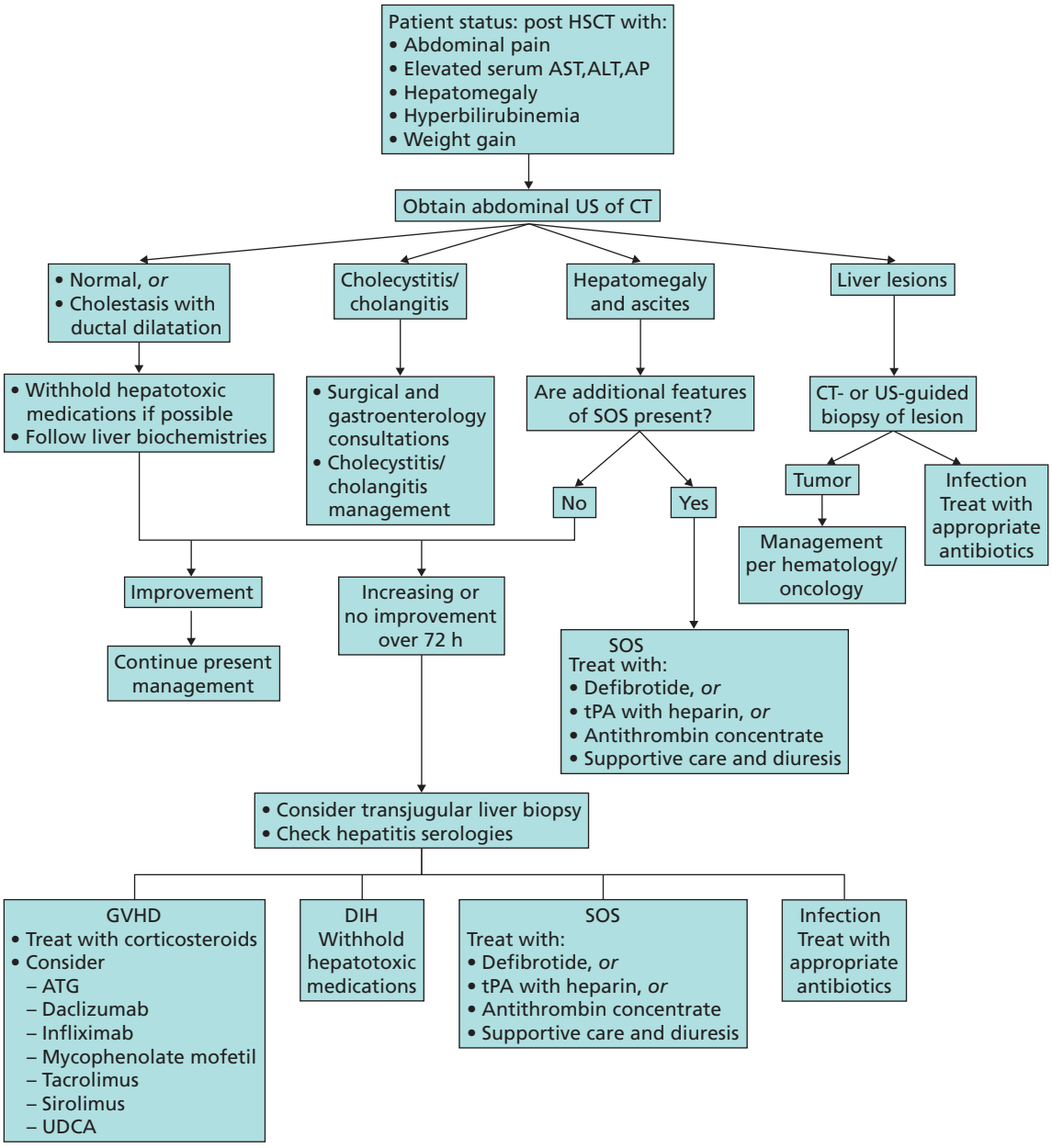

Figure 27.3 Algorithm to assess patients with abdominal pain, liver biochemical abnormalities, hepatomegaly, and/or weight gain following hematopoietic stem cell transplantation (HSCT). AST, aspartate aminotransferase; ALT, alanine aminotransferase; AP, alkaline phosphatase; CT, computed tomography; US, ultrasound; GVHD, graft-versus-host disease; DIH, drug-induced hepatotoxicity; SOS, sinusoidal obstructive syndrome; ATG, antithymocyte globulin; UDCA, ursodeoxycholic acid; tPA, tissue plasminogen activator.

history and physical examination, is to obtain an abdominal ultrasound or CT scan. Management depends on ultrasound/CT scan findings. Many patients may have no abnormal findings, in which case hepatotoxic medications should be withheld where possible, and the patient should be followed for 72 h. If no improvement is seen within that time frame, a hepatology consultation is appropriate, to consider transjugular liver biopsy for further evaluation.

Hepatic dysfunction after HSCT is both an acute and a long term problem, and coordination of care among multidisciplinary teams is necessary to ensure favorable outcomes for such patients. Fortunately, many treatment options exist for HGHVD, SOS, and infection. Continued research into hepatic disease processes following HSCT will undoubtedly lead to more effective therapies, ultimately lessening the morbidity and mortality of hepatic dysfunction in this setting.

Take-home points

- SOS, acute/chronic HGVHD, infection, and DIH are the most common reasons for liver abnormalities following HSCT.
- SOS is characterized by rapid weight gain due to fluid retention, hyperbilirubinemia, and hepatomegaly with right upper quadrant pain.
- Liver biopsy is the gold standard for SOS diagnosis.
- SOS treatment options include t-PA with heparin, defibrotide, and ATIII.
- Acute HGVHD generally occurs with skin and gastrointestinal tract GVHD.
- Chronic HGVHD presents with other manifestations of chronic GVHD, and resembles an autoimmune disorder much like scleroderma.
- Treatment of infection with appropriate antibiotics, or withholding liver-toxic medications for DIH, results in liver function improvement for most patients.

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28

CHAPTER 28
Hepatic Manifestations of Systemic Diseases

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Summary
A wide variety of systemic diseases can affect the liver and biliary system. This chapter will discuss these disorders. Selected disorders presented in depth in other chapters, such as the porphyrias, non-alcoholic fatty liver disease, organ transplantation, and drug-induced hepatic toxicity will not be discussed. Many of these disorders, such as systemic congestive heart failure and rheumatologic disorders, commonly alter liver function tests but rarely result in liver disease.

Cardiovascular Disorders

The liver receives nearly 30% of the total cardiac output, 65–75% via the portal venous system and 25–35% via the hepatic arterial system. More than half the oxygen supply to the liver is delivered by hepatic arterial blood. The hepatic artery also supplies the gall bladder and bile ducts. Thus, any process that substantially reduces arterial blood flow or arterial oxygen content to the liver can result in *ischemic hepatitis*. The most common *cardiac* disorders responsible for ischemic hepatitis are *acute myocardial infarction* and *arrhythmias*. Valvular heart disease, cardiomyopathy, and pericardial tamponade also can result in arterial hypotension complicated by ischemic hepatitis. Non-cardiac conditions, such as sepsis, burns, trauma, dehydration, heat stroke, hemorrhage, and peritonitis also can cause hypotensive ischemic hepatitis. Postoperative ischemic hepatitis may occur secondary to transient perioperative ischemia, hypoxia, and other factors. Hypoxia from acute respiratory failure, pulmonary embolus, and obstructive sleep apnea, likewise, can result in ischemic hepatitis. Altered (diminished) portal venous blood flow, such as portal hypertension in patients with cirrhosis, increases susceptibility to ischemic hepatitis during episodes of arterial hypotension or hypoxia. Furthermore, altered (diminished) hepatic venous outflow (i.e., congestive heart failure, Budd–Chiari syndrome) and biliary obstruction also increase an individual's risk for ischemic hepatitis with hypotension or hypoxia.

Ischemic hepatitis usually is secondary to an acute event, which may or may not be evident. By definition, ongoing hypotension, or shock, would result in multiple end-organ failure or death. Patients who recover from acute ischemia subsequently may be asymptomatic, or may develop right upper quadrant pain, nausea, and vomiting. Many patients are severely ill from other consequences of hypotension or hypoxia, including, in particular, renal failure. Typically, there is a rapid rise in serum aminotransferases within 24–48 h of the ischemic event, often to several thousand international units per liter, with a rapid decline (40–60% per 24 h) over the next 3–7 days back towards baseline or normal. This aminotransferase pattern also can be seen in persons with acute choledocholithiasis, but the maximal levels of alanine

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transaminase (ALT) and aspartate transaminase (AST) more often peak in the hundreds or low thousands. Serum lactate dehydrogenase (LDH) also is elevated, often to levels greater than ALT. Serum bilirubin, alkaline phosphatase, and international normalized ratio (INR) may be modestly elevated. Mental status changes may occur, but are due to cerebral hypotension and not hepatic encephalopathy. Liver biopsy, generally not needed to make the diagnosis, demonstrates centrilobular zone 3 necrosis and congestion with sinusoidal dilatation, rupture, and extravasation of red blood cells. Significant inflammation and fibrosis are not present. Fulminant liver failure is rare, often fatal, and usually occurs in patients with concomitant cirrhosis or chronic congestive heart failure complicated by acute ischemic hepatitis. Prognosis is related to recovery from the acute event, with restoration of arterial blood pressure and oxygenation. There is no specific therapy for the ischemic hepatitis itself. Elective surgery and anesthesia should be avoided during episodes of ischemic hepatitis.

Congestive hepatopathy, in contrast to ischemic hepatitis, is due to elevated right atrial pressure resulting in passive venous outflow congestion of the liver. In adults, congestive hepatopathy is one of the most common causes of mild abnormal results of liver tests. The most common cardiac causes for this condition are *ischemic cardiovascular disease* and *hypertensive heart disease*. Valvular heart disease, cor pulmonale, and constrictive pericarditis also commonly are complicated by congestive hepatopathy. Patients may be asymptomatic, or suffer from right upper quadrant pain (hepatomegaly with stretching of the capsule), anorexia, nausea, vomiting, or diarrhea. Hepatomegaly is common (around 95%) on physical exam, along with jugular venous distension, hepatojugular reflux, splenomegaly, pleural effusion, ascites, and lower extremity edema. Mild unconjugated hyperbilirubinemia, mild increased transaminases, mild elevation of the INR, and, less often, a mild increase in alkaline phosphatase and a mild decrease in serum albumin may be seen. In patients with ascites, the serum to ascites albumin gradient is greater than 1.1, and the ascitic fluid protein is high (>2.5 g/dL). Histology demonstrates the classic nutmeg liver, with centrilobular zone 3 necrosis, congestion, and hemorrhage. Because this condition often is chronic, central vein fibrosis (phlebosclerosis) with extension of fibrosis into the sinusoids can occur, rarely resulting in cardiac cirrhosis. When seen, this is often secondary to chronic constrictive pericarditis or valvular heart disease (especially mitral valve disease with severe secondary tricuspid regurgitation). Zone 1 non-cirrhotic regenerative nodular hyperplasia also may be found. Even with cirrhosis, esophageal varices and other stigmata of chronic liver disease are rarely found, and the prognosis is directly related to the cardiac condition. Metabolism of certain medications, such as warfarin, may be significantly diminished in patients with congestive hepatopathy. Treatment of the underlying cardiac condition determines the prognosis.

Vascular disorders affecting the hepatic artery, portal vein, or hepatic veins can affect the liver. *Hepatic infarction* can occur when hepatic arterial blood flow is compromised due to conditions acutely affecting the hepatic artery or its branches. Hepatic artery thrombosis can occur as a complication of *liver transplantation*, *hepatobiliary surgery*, *aortic or hepatic artery aneurysm*, *intraarterial chemotherapy* and *chemoembolization*, *radiofrequency ablation of hepatocellular carcinoma*, *infective endocarditis*, *trauma*, or *transjugular intrahepatic portosystemic shunt*. *Hypercoagulable states*, *vasculitis* (especially polyarteritis nodosa and systemic lupus erythematosus), tumor emboli, sickle cell crisis, toxemia of pregnancy, and cocaine also are risk factors for hepatic infarction. Ischemic damage to the biliary system also can occur, with biliary sepsis. The most severe cases can be complicated by fulminant liver failure. Mild cases may be asymptomatic, with transient elevations in serum aminotransferase levels. Symptomatic patients may complain of nausea, vomiting, right upper quadrant pain, and fever. Serum leukocytosis and abdominal radiographic studies help make the diagnosis. Sepsis, liver abscess formation, and bile duct strictures may occur. Treatment is directed towards the underlying cause and complications.

Portal vein thrombosis as a consequence of *hypercoagulable states*, *intra-abdominal inflammation* (i.e., pancreatitis, cholecystitis, appendicitis, inflammatory bowel disease), *infection* (pylephlebitis, omphalitis in children), *trauma* (including surgery), and *stasis* (cirrhosis) often results in portal hypertension, splenomegaly, and variceal bleeding. Combinations of these risk factors, especially more than one hypercoagulable state, or cirrhosis plus a hypercoagulable state, greatly increase the risk of portal vein thrombosis. Hepatic encephalopathy and clinically significant ascites are much less common in contrast to patients with cirrhosis. Uncommonly, portal

biliopathy with strictures, cholangitis and cholecystitis may occur. Extension of the thrombotic process into the superior mesenteric venous system can result in mesenteric ischemia. *Hepatic artery–portal vein fistulae* as a result of *trauma* (i.e., liver biopsy) or in patients with *Osler–Weber–Rendu syndrome* can cause complicated portal hypertension, biliary strictures, and hepatobiliary infection, as well as cardiac failure. Patients with Osler–Weber–Rendu syndrome also can develop *hepatic artery–hepatic vein fistulae* complicated by cardiac failure and *portal vein–hepatic vein fistulae* complicated by hepatic encephalopathy.

Disorders of *hepatic venous outflow* such as *Budd–Chiari syndrome* (secondary to *hypercoagulable states*, *malignancies*, *space-occupying lesions* of the liver, *infections*, and miscellaneous causes), *membranous webs* occluding the suprahepatic inferior vena cava, and *sinusoidal obstruction syndrome* (due to preconditioning for *bone marrow transplantation*, plant *pyrrolizidine alkaloid poisoning*, *hepatic radiation*, and selected *medications* such as azathioprine) all can result in pressure-induced hepatic necrosis and cirrhosis.

Pulmonary Disorders

Hypoxia from *respiratory failure* of any cause can result in ischemic hepatitis. *Obstructive sleep apnea* and *pulmonary embolus* also can be complicated by ischemic hepatitis due to hypoxia as well as cardiac dysfunction. *α_1-Antitrypsin deficiency* due to the inability of the liver to export an abnormal gene product (usually the ZZ protease inhibitor type, often but not always with low serum α_1-antitrypsin levels) can present in the neonate (about 10%) as hepatitis or cholestasis, both of which often resolve. Later in life, it can present as *chronic hepatitis*, *cirrhosis*, *cholangiocarcinoma*, or *hepatocellular carcinoma* [1]. Liver biopsy should demonstrate portal and periportal diastase-resistant periodic acid–Schiff positive inclusion bodies. Interestingly, only about 10–15% of persons with the ZZ protease inhibitor type develop clinically significant liver disease. Some patients, especially children, may require liver transplantation. Although serum α_1-antitrypsin levels normalize, it is unclear if this benefits pulmonary disease. Up to 30% of persons with *cystic fibrosis* develop liver disease, which can be severe in up to 5% of patients [2]. Many, however, are asymptomatic with hepatomegaly or elevated liver function tests. Some patients have *hepatic steatosis* due to their cystic fibrosis as well as malnutrition and other factors. *Neonatal hepatitis*, *neonatal cholestasis*, and by childhood and early adulthood, *biliary cirrhosis* secondary to inspissated material in small bile ducts may occur. A focal biliary cirrhosis is typical, which can progress to a generalized cirrhosis with complicated portal hypertension. This often happens before puberty. Liver biopsy can demonstrate steatosis, dilated cholangioles filled with inspissated material, and fibrosis, even in asymptomatic persons. Ultrasound, magnetic resonance cholangiography, and endoscopic retrograde cholangiopancreatography may help make the diagnosis. Patients with cystic fibrosis also may develop *gallstones* (up to 12%).

Renal Disorders

Autosomal dominant polycystic kidney disease (ADPKD) is associated with numerous fibrocystic disorders of the liver, including *congenital hepatic fibrosis*, *Caroli disease*, *choledochal cysts*, and, more often, *polycystic liver disease*. Pregnancy and administration of estrogen can hasten liver cyst growth in women with ADPKD. The less common *autosomal recessive polycystic kidney disease* also can be associated with *congenital hepatic fibrosis*, *Caroli disease*, and *choledochal cysts*. There are rare reports of bladder infections with urease-producing *Proteus* or *Escherichia coli* infections resulting in hyperammonemia and encephalopathy, mimicking hepatic encephalopathy in persons without liver disease or portal hypertension. *Stauffer syndrome* or paraneoplastic intrahepatic cholestasis with jaundice and without hepatic involvement can be seen in patients with *renal cell carcinoma*.

Endocrine Disorders

The liver plays a central role in the metabolism of hormones, such as thyroid and adrenal hormones. Mild abnormalities of liver tests are common in patient with *hyperthyroidism*, especially elevated serum alkaline phosphatase and aminotransferase levels. More than mild abnormalities and even severe jaundice can be seen in persons with *thyroid storm* [3]. Increased hepatic oxygen consumption as well as congestive heart failure may

account for centrilobular findings of necrosis or cholestasis on liver histopathology. Hyperthyroidism (usually Graves disease) is associated with *primary biliary cirrhosis* as well as *autoimmune hepatitis*. Persons with *hypothyroidism* often have mild hepatomegaly and mild abnormalities of liver function tests, especially elevated serum transaminases. Fatty liver secondary to altered lipid metabolism, mild congestive heart failure, and myopathy (creatine kinase elevation greater than AST and greater than ALT) may cause these biochemical abnormalities. Cholestasis and jaundice may be found in more severe hypothyroidism. Protein-rich ascites (>4 g/dL) in the absence of liver disease can occur, probably due to altered permeability of the peritoneum or congestive heart failure [4]. Liver histopathology may reveal centrilobular congestion and rarely, fibrosis. Chronic autoimmune thyroiditis is associated with *primary biliary cirrhosis* as well as *autoimmune hepatitis*. *Hypoparathyroidism* also can be associated with *autoimmune hepatitis*.

Cushing disease, due to its association with *obesity*, can be complicated by *fatty liver* or *steatohepatitis*, with mild elevation of liver function tests, especially serum aminotransferases. *Addison disease* may present with mild elevation of serum aminotransferases. *Hepatomegaly* may be detected in patients with *acromegaly*. *Diabetes mellitus*, especially type II diabetes with insulin resistance, increasingly is found, along with obesity and hyperlipidemia, as a cause of *non-alcoholic fatty liver disease (NAFLD)*, including fatty liver, steatohepatitis, and cirrhosis. Asymptomatic elevations in serum aminotransferases and mild elevation in serum alkaline phosphatase are common in diabetic patients with NAFLD.

Rheumatologic Disorders

Many rheumatologic diseases are complicated by or associated with liver disease. In many cases, the systemic inflammation of active rheumatologic disorders is accompanied by mild, non-specific liver test abnormalities that resolve as the joint and systemic disease resolve. Liver biopsy findings in these patients are mild and non-specific. Medications used to treat rheumatologic diseases by themselves often result in mild elevation of liver tests (i.e., non-steroidal anti-inflammatory drugs). Patients with active *rheumatoid arthritis* often develop mild elevation of serum alkaline phosphatase and serum aminotransferases, and may have mild hepatomegaly. Liver biopsy usually demonstrates minor non-specific findings or steatosis. *Autoimmune hepatitis* and *primary biliary cirrhosis* are found in some rheumatoid arthritis patients. *Nodular regenerative hyperplasia* also can be seen in these patients but is more commonly seen in the subset of more ill rheumatoid arthritis patients with *Felty syndrome* (severe seropositive rheumatoid arthritis, neutropenia, and splenomegaly). Portal hypertension often occurs with complications, especially variceal bleeding, secondary to nodular regenerative hyperplasia as well as splenomegaly. *Secondary amyloidosis* can be found in patients with either rheumatoid arthritis or Felty syndrome. Similar to rheumatoid arthritis, patients with active *systemic lupus erythematosus* often develop mild aminotransferase elevation. Liver disease is rare in these patients, with the exceptions of associated *autoimmune hepatitis*, *primary biliary cirrhosis*, and *nodular regenerative hyperplasia*, as well as systemic lupus erythematosus patients with *antiphospholipid syndrome* [5]. These patients may have anticardiolipin antibodies or lupus anticoagulant, and develop arterial vasculitis with thrombosis, resulting in *hepatic infarction* or *Budd–Chiari syndrome*, as well as *portal vein thrombosis* or *sinusoidal obstruction syndrome*. Active *adult Still disease* patients may have mild to moderate elevation in serum transaminases, and in rare cases, develop liver failure. *Polymyalgia rheumatica* is associated with *primary biliary cirrhosis* and *nodular regenerative hyperplasia*. *Sjögren syndrome* not infrequently is associated with *autoimmune hepatitis* and *primary biliary cirrhosis*. *Scleroderma* rarely is complicated by liver disease, but is associated with *autoimmune hepatitis*, *primary biliary hepatitis*, and *nodular regenerative hyperplasia*. The *CREST syndrome* also is associated with *primary biliary cirrhosis* and *nodular regenerative hyperplasia*. Liver disease rarely is seen in patients with *mixed connective tissue disease*, but there are reports of *Budd–Chiari syndrome*. *Polymyositis/dermatomyositis* is associated with *primary biliary cirrhosis*.

Vasculitis in disorders such as *Behçet syndrome* often is associated with *nodular regenerative hyperplasia*. Patients with Behçet syndrome can develop *Budd–Chiari syndrome* as well. Vasculitis due to *polyarteritis nodosa*, whether associated with *hepatitis B virus* infection (<10%) or not, can be complicated by *liver infarction*, *nodular regenerative hyperplasia*, *biliary strictures*, or *acalculous cholecystitis* [6]. A host of other conditions with vascular

involvement, such as *Churg–Straus syndrome*, *temporal arteritis*, *Takayasu arteritis*, and *systemic lupus erythematosus*, can result in *liver infarction*, *gall-bladder necrosis*, and *biliary disease*. The *antiphospholipid syndrome*, which may or may not be associated with systemic lupus erythematosus, is a hypercoagulable disorder resulting in arterial or venous thrombosis, including *portal vein thrombosis* and *Budd–Chiari syndrome*.

Gastroenterologic Disorders

Celiac disease often is associated with liver disease and in most cases, simply elevated liver function tests [7]. Nearly half of all patients with celiac disease will have mild to moderate aminotransferase elevations. Liver biopsy in those patients usually demonstrates non-specific changes. Fatty liver may be found, but it is not clear if this is related to the elevated aminotransferases or a coincidental association. Treatment of these patients with a gluten-free diet usually results in normalization of the aminotransferases. It is useful to know that up to 9% of persons with otherwise unexplained elevated aminotransferases are found to have celiac disease. Patients with celiac disease are more likely to have *primary biliary cirrhosis*, as well as *primary sclerosing cholangitis*, *autoimmune hepatitis* and *nodular regenerative hyperplasia*. Rare patients with celiac disease can present with severe liver disease and may improve with institution of a gluten-free diet.

Liver disease is commonly associated with *inflammatory bowel diseases*. Nearly 80% of all patients with *primary sclerosing cholangitis* have *ulcerative colitis* (most of the group) or colonic *Crohn disease* (far fewer patients). Between 2% and 7% of ulcerative colitis patients develop primary sclerosing cholangitis. Similar to celiac disease, patients with active inflammatory bowel disease often have mild elevated aminotransferases which may normalize with resolution of active bowel inflammation. Fatty liver, *autoimmune hepatitis*, *primary biliary cirrhosis*, *cholelithiasis* (usually in patients with Crohn disease or resection of the terminal ileum), *secondary amyloidosis* (more often in Crohn disease than ulcerative colitis), as well as *Budd–Chiari syndrome* or *portal vein thrombosis* (hypercoagulable state) can occur in these patients. *Cholangiocarcinoma* complicates primary sclerosing cholangitis in patients with inflammatory bowel disease more often than in patients with primary sclerosing cholangitis alone.

Liver disease is rare in patients with *Whipple disease*. Mild liver test abnormalities, upper abdominal pain, and hepatomegaly may be found. Liver biopsy may reveal periodic acid–Schiff positive macrophages and granulomas.

Hematologic Disorders

Liver involvement is common in persons with hemolytic anemias. In persons with *sickle cell anemia*, erythrocytes can sickle within the sinusoids, resulting in Kupffer cell erythrophagocytosis, dilated sinusoids, and eventually hepatic fibrosis and cirrhosis in some. Concomitant iron loading, viral hepatitis, and medications can contribute to the liver injury. Painful, thrombotic veno-occlusive crises often are accompanied by hepatomegaly and moderate elevations of serum aminotransferases and bilirubin. In a small percentage of these cases, the crisis persists and worsens with aminotransferases over 1000 IU/L and bilirubin over 15 g/dL, with *hepatic infarction*, liver failure coagulopathy, encephalopathy, and other end-organ failure (i.e., renal failure). In some instances, severe degrees of hepatic sequestration result in severe painful hepatomegaly and a dramatic fall in the hematocrit. Persons with sickle cell anemia and other hemolytic anemias also are at risk for *cholelithiasis*, *cholecystitis*, and *cholangitis*. Asymptomatic patients with sickle cell anemia may have mild elevations of serum transaminases for multiple reasons, including hepatic sickling, congestive heart failure, hypoxia, medications, and viral hepatitis. Patients with hemolysis and anemia due to *paroxysmal nocturnal hemoglobinuria* are at risk for venous and arterial thrombosis, including *Budd–Chiari syndrome*, *portal vein thrombosis*, and *splenic vein thrombosis*.

Leukemias and lymphomas commonly involve the liver with or without symptoms. Infiltration of the liver occurs in up to 50% of patients with *Hodgkin disease*. Virtually all of these patients also have splenic involvement. Mild to moderate elevations of serum alkaline phosphatase and aminotransferases are more common in more advanced stages of Hodgkin disease. Portal tract infiltration with a non-specific infiltrate often is found on liver biopsy. Reed–Sternberg cells are seen in up to 8% of cases. Surgical or laparoscopic liver biopsies are

more likely than percutaneous biopsies to make the diagnosis. Patients can develop extrahepatic obstruction due to extrahepatic bile duct involvement or secondary to infiltration of porta hepatis lymph nodes. *Intrahepatic cholestasis* without hepatobiliary involvement (*Stauffer syndrome*) may be due to a metabolic or paraneoplastic phenomenon or vanishing bile duct syndrome, and may improve with successful treatment of the Hodgkin disease outside of the hepatobiliary system. *Non-Hodgkin lymphoma*, similar to Hodgkin disease, can be found in the liver in up to 50% of patients. In contrast to primary hepatic lymphoma, secondary involvement far less often is detectable as a mass lesion on imaging studies. Mild to moderate elevation of alkaline phosphatase and aminotransferases are not unusual. Less common presentations include extrahepatic obstruction secondary to porta hepatis nodal involvement and *acute liver failure* due to diffuse hepatic infiltration. *Multiple myeloma* and *Waldenström macroglobulinemia* also can involve the liver and spleen with abnormal liver function tests. Some of these patients can develop *portal hypertension* with ascites and varices. *Extramedullary hematopoiesis* can contribute to the portal hypertension. Liver biopsy can reveal malignant infiltration of the sinusoids and portal tracts. Nearly 10% of patients with multiple myeloma also develop *amyloidosis*.

The majority of patients with *acute leukemia* have involvement of the liver. Hepatomegaly, splenomegaly, and portal hypertension are common. *Acute liver failure* can be a presentation of extensive hepatic infiltration. Bone marrow transplantation can be complicated by *sinusoidal obstruction syndrome*, *graft-versus-host disease*, as well as numerous systemic infections that can affect the liver. Chronic leukemias also commonly involve the liver. Patients with *chronic lymphocytic leukemia* can develop *extrahepatic obstruction* due to portal hepatitis nodal involvement.

Myeloproliferative syndromes can be complicated by *portal hypertension* due to extramedullary hematopoiesis as well as splenomegaly and increased portal blood flow. *Portal vein thrombosis* and *Budd–Chiari syndrome* often are due to myeloproliferative syndromes, which may be difficult to diagnose in their early stages in some patients. Testing for the *JAK2 V617F* mutation may help diagnose the myeloproliferative syndrome. *Nodular regenerative hyperplasia* can complicate many of these conditions, including myeloproliferative syndromes, Hodgkin disease, non-Hodgkin lymphoma, and *systemic mastocytosis*, all of which can infiltrate the liver.

Infiltrative Systemic Disorders

Sarcoidosis is a systemic granulomatous disorder which in the US is much more common in African American than Caucasian persons. By definition, multiple organ systems are involved. Pathologic involvement of the liver is frequent, in over two-thirds of patients, with non-caseating granulomas, especially in the portal and periportal areas. Most patients are asymptomatic, with hepatomegaly in about 25% on physical examination. A similar percentage of patients will be found to have a mildly elevated serum alkaline phosphatase level and, in some, mildly elevated transaminases. Rarely, patients with sarcoidosis can develop *cholestatic jaundice*, which can be *intrahepatic* with loss of intralobular bile ducts, fibrosis and cirrhosis in a pattern similar to primary biliary cirrhosis, or *extrahepatic* with cholangiographic features similar to primary sclerosing cholangitis or secondary to hilar lymphadenopathy [8]. Granulomatous obliteration of hepatic veins (*Budd–Chiari syndrome*), as well as involvement of portal vein branches, has been described. Portal hypertension can be multifactorial, due to prehepatic (*portal venous disease*, *nodular regenerative hyperplasia*) or hepatic (cirrhosis) causes. Clinically significant hepatic sarcoidosis can occur without respiratory involvement. Corticosteroid or other immunosuppressive therapy may or may not benefit those patients with diverse causes of cholestatic jaundice. Some may require liver transplantation [9]. Post-transplant recurrence of sarcoidosis has been reported. More controversial is the entity of isolated hepatic sarcoidosis, without involvement of other organs, versus *idiopathic granulomatous hepatitis*. These patients present with fever, weight loss, and severe cholestasis (elevated alkaline phosphatase), without jaundice or complications of liver disease. Thorough evaluation to exclude other causes of granulomatous involvement of the liver, especially tuberculosis, other infections and adverse drug reactions are important.

Amyloidosis is a systemic condition which when present usually involves the liver histologically, but causes symptoms related to the liver very infrequently. *Primary amyloidosis* secondary to immunoglobulin light chain or light chain fragment deposition (AL amyloid) in

the liver and other organs occurs in patients with plasma cell dyscrasias such as multiple myeloma, Waldenström macroglobulinemia, and some B-cell malignancies. *Secondary amyloidosis*, due to serum amyloid disposition (AA amyloid), is seen in patients with chronic inflammatory and infectious disorders, such as rheumatoid arthritis, ankylosing spondylitis, bronchiectasis, familial Mediterranean fever, osteomyelitis, and Crohn disease. It also has been described in Hodgkin disease, gastric cancer, and hypernephroma. The relative organ distribution and histologic patterns in the liver of primary and secondary amyloidosis overlap greatly. Hepatomegaly may occur in up to 80% of these patients, often with elevated serum alkaline phosphatase and, less often, elevated transaminases or bilirubin. Liver biopsy, even without abnormal liver tests, usually demonstrates amyloid protein deposition in the parenchyma (sinusoidal and perisinusoidal) or in a vascular pattern (blood vessels and periportal distribution). Immunohistochemistry to diagnose different types of amyloid is available. There have been reports of hemorrhage and even hepatic rupture after liver biopsy in patients with systemic amyloidosis. Some patients with amyloid will have a coagulopathy. Because amyloidosis involves multiple organs, abdominal fat-pad biopsy, rectal biopsy, or gastric biopsy usually makes the diagnosis. Morbidity and mortality due to amyloidosis is usually related to non-hepatic involvement. Complications of chronic liver disease such as portal hypertension are rare. Besides primary and secondary, there are other types of amyloidosis, including *familial amyloidosis*. The ATTR or *Type I familial amyloidosis* results in systemic disease due to deposition of a liver-produced mutant transthyretin protein (prealbumin). Liver transplantation is useful in these patients before the occurrence of advanced disease of other organs, especially neurologic dysfunction. Often, the native liver can then be transplanted into an older recipient, as systemic disease in the recipient due to the transplanted liver's production of mutant transthyretin would take many years to develop.

Miscellaneous Disorders

Liver function test abnormalities are common in persons with systemic infections [10]. A wide spectrum of extrahepatic, extrabiliary infections with diverse bacteria, fungi, and other infectious organisms release endotoxin and other bacterial cell wall compounds that enhance the release of inflammatory cytokines. These compounds then can decrease basolateral and canalicular bile acid and organic anion transport, with mild to modest elevations in serum aminotransferases as well as serum alkaline phosphatase. Mild to moderate to severe (up to 50 mg/dL) elevations of serum bilirubin may occur. Survival is dependent on the underlying disorder rather than the liver test abnormalities or liver failure, which is uncommon. Coagulopathy and pruritus are uncommon. Imaging studies to exclude structural hepatobiliary disease and to look for an extrahepatic, extrabiliary source of infection are important. Once the source of infection is identified and treated, liver test abnormalities should improve. Severe cholestasis may take weeks or even months to resolve.

A number of systemic disorders are associated with *nodular regenerative hyperplasia* of the liver, including many conditions associated with vasculitis, hypercoagulability, and autoimmune phenomena, as well as myeloproliferative and lymphoproliferative disorders (Table 28.1). Treatment of the underlying condition and withdrawal of offending medications (azathioprine and other chemotherapeutic agents) are critical in addition to the therapeutics directed towards portal hypertension.

Table 28.1 Systemic disorders associated with nodular regenerative hyperplasia.

- Myeloproliferative disorders
- Lymphoproliferative disorders
- Sickle cell disease
- Multiple myeloma
- Hypercoagulable states
- Rheumatoid arthritis
- Felty syndrome
- Systemic lupus erythematosis
- Adult Still disease
- Polymyalgia rheumatica
- Sjögren syndrome
- Scleroderma
- CREST syndrome
- Polymyositis
- Behçet syndrome
- Polyarteritis nodosa
- Celiac disease
- Myasthenia gravis
- Sarcoidosis

Take-home points

- Ischemic hepatitis occurs as a result of impaired arterial blood flow or reduced arterial oxygen content to the liver.
- Congestive hepatopathy secondary to passive venous outflow congestion of the liver is one of the most common causes of mild abnormal results of liver tests.
- Mild abnormalities of liver tests are common in patients with thyroid disease, adrenal disease, diabetes mellitus, rheumatologic diseases, systemic infections, and inflammatory disorders of the gastrointestinal tract.

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VI

PART 6

Liver Transplantation

29

CHAPTER 29

Indications and Selection of Patients for Liver Transplantation

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Summary

Successful transplantation outcomes require optimal patient selection and timing. Currently the major limitation facing liver transplantation centers is the shortage of organs. The limited availability of organs has led to long waiting periods for liver transplantation and consequently many patients become seriously ill or die while on the waiting list. This has major implications for the selection of patients, as well as the timing of transplantation and optimal use of these scarce organs. Indications and contraindications have changed slightly over the years and will be reviewed in this chapter. Timing for transplantation has changed more dramatically in recent years since major changes to organ allocation systems have been undertaken to provide clinicians with a better way to prioritize patients for liver transplantation.

Case

A 66-year-old male with alcohol-related liver disease is seen for increased abdominal girth and is noted to have ascites on clinical exam. He is known to have had cirrhosis for approximately 4 years, and has had no previous decompensation. He quit drinking alcohol 8 years ago and continues to attend Alcoholics Anonymous. Abdominal ultrasound reveals a 2.8 cm lesion in the left lobe. Laboratory studies reveal a bilirubin of 1.5 mg/dL, albumin of 3.4 g/dL, INR 1.4, and creatinine 1.1 mg/dL. Other medical problems include well-controlled hypertension on metoprolol and benign prostatic hypertrophy. His model for end-stage liver disease (MELD) score is 13, and Child–Turcotte–Pugh (CTP) score is 6. Subsequent computed tomography (CT) scan confirms the 2.8 cm lesion in the left lobe suspicious for hepatocellular carcinoma, as well as a small 0.9 cm indeterminate lesion in his right lobe. He asks you if liver transplantation is an option for him.

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Introduction

Liver transplantation has been proven to be effective treatment of patients with end-stage liver disease and fulminant hepatic failure. Over the last several decades there have been many improvements in the selection and management of patient undergoing liver transplantation.

Successful transplantation outcomes require optimal patient selection and timing. Currently the major limitation facing liver transplantation centers is the shortage of organs. The limited availability of organs has lead to long waiting periods for liver transplantation, and consequently, many patients become seriously ill or die while on the waiting lists. This has major implications in the selection of patients, as well as the timing of transplantation for optimal use of these scarce organs. Indications and contraindications have changed slightly over the years and will be reviewed in this chapter. Timing for transplantation has changed more dramatically in recent years since major changes to organ allocation systems

have been undertaken to provide clinicians with a better way to prioritize patients for liver transplantation. Since 2002, all transplant centers in the US have implemented the model for end-stage liver disease (MELD) scoring system in an effort to more objectively allocate organs.

Indications for Liver Transplantation (Table 29.1)

There are two major goals of liver transplantation: to prolong survival and to improve the quality of life for patients. Therefore, transplantation should be considered for any patients in whom it will extend life expectancy beyond what the natural history of their liver disease predicts and/or in whom it will likely improve the quality of life.

Chronic or End-stage Liver Disease

In general, patients with significant complications from their chronic liver disease and/or portal hypertension, such as hepatic encephalopathy, ascites, variceal bleeding, portopulmonary hypertension, hepatopulmonary syndrome, hepatocellular carcinoma, or cholangiocarcinoma, should be referred to a transplant center for evaluation for liver transplantation. Fulminant liver failure of any cause is an indication for transplantation if the patient is neurologically intact and otherwise healthy enough to undergo surgery. Another group of patients to consider for transplantation are those without end-stage liver disease, but with recurrent life-threatening complications relating to liver disease (e.g., recurrent cholangitis). These patients are disadvantaged by the organ allocation scoring system (requiring significant liver and renal dysfunction), but may have the option of living donor liver transplantation.

Hepatocellular Carcinoma

Liver transplantation is indicated in patients with hepatocellular carcinoma (HCC) who fit within the Milan criteria. These criteria include lesions less than 5 cm in diameter or three or fewer lesions, the largest of which is less than 3 cm in diameter [1]. Those patients have 4-year survival rates in excess of 80%, which is comparable to other liver transplantation recipients. Some centers may consider liver transplantation for patients with HCC if they have a single lesion of up to 6.5 cm, or up to three lesions, the largest of which is 4.5 cm or smaller and the cumulative tumor size is 8 cm or smaller, deemed the University of California at San Francisco (UCSF) criteria [2]. Discussions with the referral center are warranted before excluding transplantation as an option for patients with HCC, as those with tumors that have been reduced in size by chemoembolization or radiofrequency ablation ("downstaging") to fit within these criteria may now also be acceptable candidates.

Table 29.1 Indications for liver transplantation.

Complications of end-stage liver disease of any etiology:
- Refractory ascites
- Hepatorenal syndrome
- Encephalopathy
- Gastrointestinal bleeding due to portal hypertension
- Portopulmonary hypertension
- Hepatopulmonary syndrome
- Hepatocellular carcinoma
- Cholangiocarcinoma

Fulminant hepatic failure

Metabolic or genetic diseases:
- Hyperoxaluria
- Familial amyloidosis
- Polycystic liver disease
- Caroli disease
- Glycogen storage disease I, IV
- Hemophilia A, B
- Byler disease
- Crigler–Najjar syndrome
- Alagille syndrome

Miscellaneous diseases:
- Budd-Chiari syndrome
- Sinusoidal obstruction syndrome (veno-occlusive disease)
- Graft-versus-host disease
- Nodular regenerative hyperplasia
- Hepatic tumors (adenoma, carcinoid, pancreatic islet cell tumors, epithelioid hemangioendothelioma, fibrolamellar carcinoma, hepatoblastoma)
- Hepatic trauma

Cholangiocarcinoma

Patients with cholangiocarcinoma (CCA) were once thought to be poor candidates for transplantation due to recurrent disease and poor survival overall. The Mayo Clinic developed a novel therapeutic protocol combining neoadjuvant chemoradiation and liver transplantation in

1993 to treat patients with unresectable hilar CCA or CCA arising in the setting of primary sclerosing cholangitis, and has had 1-year survival rates of 82% [3]. Patients with hilar CCA treated with this protocol and a negative staging laparotomy are acceptable liver transplantation candidates only at highly specialized institutions.

Other Liver Tumors

Neuroendocrine tumors are slow growing neoplasms, frequently presenting with multifocal liver metastases. Liver transplantation should be considered in select patients with no evidence of extrahepatic tumor spread, although the timing of transplantation in these individuals is controversial. If performed early enough in the course of disease, a chance to cure the malignancy is possible. In general, however, transplantation may only offer a chance to "reset the clock" in this slow growing tumor, as most studies suggest a 5-year survival rate of 30–60% [4]. Patients with other liver tumors, such as large or multifocal adenomas, epithelioid hemangioendothelioma (EH), or very select cases of fibrolamellar carcinoma (if the tumor is localized to the liver) may be considered to be transplantation candidates. In the case of EH, 5-year survival rates of 75% can be expected and unlike for other primary liver neoplasms, the presence of extrahepatic metastases does not correlate with survival, so this finding is not necessarily a contraindication to the liver transplantation [4].

Other Indications

Other indications for liver transplantation are summarized in Table 29.1. These include less common indications such as systemic metabolic diseases (e.g., oxalosis and familial amyloidosis), where the metabolic defect is localized to the liver. End-organ damage relating to the metabolic derangement is likely to improve after liver transplantation in these individuals. Patients with polycystic liver disease have normal liver function and their indication for transplantation is usually cachexia and early satiety relating to hepatomegaly. Occasionally they may develop complications of portal hypertension. Patients with nodular regenerative hyperplasia rarely have synthetic liver dysfunction, but can have significant complications relating to portal hypertension, thus occasionally requiring liver transplantation. Special circumstances such as sinusoidal obstruction syndrome (previously known as veno-occlusive disease) or graft-versus-host disease would be extremely rare indications for transplantation as these entities are usually associated with underlying diseases with a very poor prognosis (i.e., bone marrow transplant patients). Patients would have to be assessed on an individual basis with multidisciplinary interaction.

Quality of Life

The majority of patients with advanced liver disease typically have poor quality of life from fatigue, cachexia, pruritus, ascites, encephalopathy, and gastrointestinal bleeding. These conditions are not accounted for in the current organ allocation system and are unable to contribute to the listing priority, but remain valid indications for liver transplantation. The majority of patients report improvement in their quality of life, both in physical health and psychological functioning, after transplantation [5].

Contraindications to Liver Transplant

With improvement in medical management and surgical techniques over the years, conditions which preclude liver transplantation are few (Table 29.2). Conditions that were thought to preclude transplantation 10–20 years ago are no longer considered even relative contraindications for transplantation. For example, the initial experiences with poor outcome of liver transplantation for patients with hepatitis B led most centers to stop transplanting these patients. However, the development of hepatitis B immunoglobulin and antiviral therapy dramatically changed the outcome to one of the best patient survival rates post liver transplantation. Another example is CCA; while this was once thought to be an absolute contraindication to transplantation, this is now possible in a select group of patients in a few centers. It is extremely important for referring physicians to know that contraindications to transplantation are dynamic and may differ between centers, reflecting local expertise.

Absolute Contraindications

Uncontrolled Infection

Frequently the sickest patients on the waiting list are in hospital, often with a serious infection. This infection is

Table 29.2 Contraindications to liver transplantation.

Absolute:
• Active extrahepatic malignancy (except superficial skin cancer)
• Hepatocellular cancer beyond accepted transplantation criteria
• Active substance abuse (alcohol, street drugs)
• Severe cardiopulmonary disease
• Advanced HIV or AIDS
• Medical non-compliance
• Brain death
Relative:
• Advanced age
• Severe obesity
• HIV (center dependent)
• Previous non-hepatic malignancy within 2–5 years
• Active psychiatric illness
• Poor social support

frequently related to their liver disease (e.g., cholangitis, bacterial peritonitis) or their immune compromised state secondary to their end-stage liver disease. The decision to pursue liver transplantation in this setting is usually made in collaboration with the infectious disease team and is dependent on the organism involved and the control of the infection with appropriate antibiotics.

Severe Co-morbid Disease

Liver transplantation is a major surgery and thus patients must have minimal or well-controlled co-morbid conditions. Most centers require cardiorespiratory investigations on all patients prior to listing for liver transplantation. Well-controlled human immunodeficiency virus infection (negative viral load and CD4 counts > 250) is not a contraindication, but advanced disease or acquired immune deficiency syndrome (AIDS) preclude transplantation in these individuals.

Malignancy

Immunosuppression impairs innate tumor surveillance mechanisms; therefore, extrahepatic malignancies typically exhibit an accelerated course following transplantation. For this reason, it is important to evaluate liver transplant candidates for common cancers. Most programs require a less than 10% risk of tumor recurrence within 5 years prior to accepting patients for liver transplantation. Some centers may reject patients with a history of malignancy within an arbitrarily set period of time ranging from 2 to 5 years, depending on the underlying malignancy. Patients with HCC outside of the Milan [1] or UCSF [2] criteria are not candidates for liver transplantation due to the high risk of recurrent disease and poor survival rates after transplant. CCA with spread within or outside the liver is a contraindication to transplantation.

Active Substance Abuse

Active substance abuse, including the use of alcohol, is generally considered to be a contraindication to transplantation. The reasons for this are many, including the risk of recidivism, non-compliance with medications or medical follow-up and consequently graft failure. It is common practice for transplant centers to require a period of absolute abstinence of 3–6 months in addition to successful completion of an alcohol rehabilitation program [6]. Each center has different requirements, but generally these patients are evaluated by addiction psychiatry specialists as well as social workers, as many of these patients lack family support, complicating the situation.

Medical Non-compliance

Patients after liver transplantation are committed to continue life-long medical care, including immunosuppressive drugs, routine laboratory tests, and frequent clinical follow-up; thus, a history of non-compliance with medical care is a contraindication to liver transplantation. Active psychiatric issues may impact patient compliance and need to be well controlled before pursuing transplantation.

Irreversible Brain Injury

This issue is more often encountered in patients with fulminant hepatic failure, and typically occurs as a result of cerebral edema and brainstem herniation. Those patients need frequent evaluation by careful neurological examination, with a low threshold for imaging the brain.

Relative Contraindications

The list of relative contraindications varies between centers and is actively evolving. Although old age is not a contraindication for liver transplantation, most transplant centers require older candidates to have more rigorous assessment of their general health [7]. Most centers

have a relative age limit between 65 and 70, although generally there is no concrete limit if the patient is otherwise in good health.

Obesity is a problem in our society including among patients with liver disease who need liver transplantation. Many centers have a specific body mass index (BMI) above which patients are not candidates for transplantation surgery for technical reasons. Each center is different with most having a cut-off of a BMI of greater than 40 as prohibitive, and many centers may consider a BMI greater than 35 as a relative contraindication, depending on the distribution of adipose tissue and the medical condition of the patient. All efforts should be made to identify these patients early and to enroll them into a weight loss program prior to transplantation.

Although not contraindications to transplantation, due to center-specific expertise, patients with well-controlled HIV or Jehovah's Witness patients are only offered liver transplantation in a few specialized centers.

Timing of Liver Transplantation

In the past, organ allocation systems used both waiting time and severity of liver disease to prioritize patients on the waiting list. Severity of liver diseases can be assessed by the Child–Turcotte–Pugh criteria (CTP) (Table 29.3). The estimated 1-year survival for a patient with a Child score of 7 is approximately 80–90% and after liver transplantation it is 85–90%; thus, in most centers a patient is not considered for listing for liver transplantation until the Child score is a minimum of 7. There is no role for the CTP score in organ allocation in the current system.

Table 29.3 Child–Turcotte–Pugh scoring system.

Parameter	Points assigned		
	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2–3	>3
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
INR	<1.7	1.7–2.3	>2.3
Encephalopathy	None	Grade 1–2	Grade 3–4

Scores of 5–6 = Child A, 7–9 = Child B and 10–15 = Child C.
1-year patient survival: A—100%, B—80%, C—45%.

Subjective variables in the CTP scoring system, such as the degree of ascites and the grade of encephalopathy, were used to manipulate scores in the previous organ allocation system and thus led to investigations for a more accurate and less easily manipulated method of predicting mortality in patients with liver disease. Malinchoc *et al* defined a mathematical model utilizing patient laboratory data, including bilirubin, creatinine, and INR, to predict mortality risk in any patient with portal hypertensive complications undergoing a transjugular intrahepatic portosystemic shunt (TIPS) procedure regardless of the underlying chronic liver disease [8]. This MELD score (ranging from 6 to 40 in order of severity) has subsequently been shown to be highly predictive of 3-month mortality for patients awaiting liver transplantation. The MELD score has been widely accepted as a measure of chronic liver disease severity and was adapted and incorporated into US liver allocation policy in 2002 for determination of priority on the waiting list. Many other countries are now incorporating the MELD score into their organ allocation system [9]. A MELD score of 10 is thought to be equivalent to the CTP score of 7, the minimal listing criteria.

$$\text{MELD} = 3.8[\text{Ln serum bilirubin (mg/dL)}] + 11.2[\text{Ln INR}] + 9.6[\text{Ln serum creatinine (mg/dL)}] + 6.4)$$

or online calculator (www.unos.org/resources/MeldPeldCalculator.asp?index=98).

Liver Transplantation Evaluation

Once a patient is referred for liver transplantation evaluation, an extensive evaluation is done to determine whether or not transplantation is indicated for that patient and whether any co-morbidity will preclude that patient as a candidate. As liver transplantation surgery is a major operation, all patients will undergo cardiac and pulmonary testing. Other components of the evaluation include assessment of medical and surgical risks, psychological evaluation, and continued patient education [10,11]. The decision on transplantation candidacy is made by multidisciplinary committee members, including transplant hepatologists, surgeons, nurses, psychiatrists, social workers, and other center-specific team members.

Conclusion

Liver transplantation evaluation is warranted in any patient with an appropriate indication and no obvious contraindication. Early referral of patients to a transplant center is preferable to allow adequate time for work-up and stabilization of the patient to maximize their likelihood of a good outcome. If in doubt, always call the local referral center before deeming the patient a poor candidate.

Case continued

The patient is in otherwise good health, is abstinent and is attending Alcoholics Anonymous. He fits within the Milan criteria for transplantation for HCC and would be a transplant candidate if his medical (cardiac) work-up proves negative.

Take home points

- Successful liver transplantation requires optimal patient selection and timing of transplantation.
- Indications and patient selection for transplantation are similar across most transplant centers and have changed only slightly in recent years.
- Contraindications to transplantation are dynamic and may differ between centers, reflecting local expertise.
- MELD scores are a more accurate and less manipulated method of predicting mortality in patients with liver disease and are currently used to prioritize organ allocation.
- Early referral of patients to a transplantation center is preferable to allow adequate time for work-up and stabilization of the patient to maximize their likelihood of a good outcome. If in doubt, always call the local referral center before deeming the patient a poor candidate.

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CHAPTER 30

What Hepatologists Should Know About Liver Transplant Surgery

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Summary

The techniques of liver transplantation have evolved significantly over the last few decades, and the development of collaborative, multidisciplinary care has become a cornerstone of successful outcome in these patients. Fundamental comfort with the hepatic anatomy coupled with an understanding of the process that takes place during the hepatectomy and implantation of the new donor allograft can be a key for the hepatologist to understand the risks and complications the patient must endure. Each phase of the transplant operation has unique physiologic events that can play a significant role in surgical outcome. Biliary complications are most common, followed by hepatic arterial, portal venous, and hepatic venous complications, and their diagnosis and management strategies are discussed. Finally, new techniques, especially the introduction of living donor liver transplantation (LDLT), have been used to further expand the donor pool and provide excellent long term patient outcomes.

Introduction

Orthotopic liver transplantation remains the only successful treatment for end-stage liver disease. The first liver transplant was performed in 1963 by Dr Thomas Starzl [1], and the first time a recipient survived beyond 1 year was in 1967. Although techniques have been refined and patient and graft survival have improved since 1963, liver transplantation remains a formidable surgical challenge. The technical complexities of the procedure can result in multiple early and late postoperative complications. Transplant hepatologists need to be familiar with the operation of both deceased and LDLT, as well as the potential complications, so they can be recognized and treated in the postoperative period. The hepatologist must recognize the source of post-transplantation complications in order to attend to the needs of the patient and keep team cohesiveness at maximal levels.

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Anatomy

A thorough knowledge of hepatic anatomy, in particular the blood vessels and their relationship to the liver parenchyma, is important to understand the nuances of liver transplantation. The liver lies in the right upper quadrant of the abdomen, suspended from the diaphragm by the triangular and coronary ligaments. The liver can be divided into eight segments based upon the portal venous vascular supply and hepatic venous drainage. These segments are unique in that each has its own arterial and venous blood supply and venous and biliary drainage, rendering each segment capable of functioning independently of the others. A central vertical division plane, called the median scissura or Cantlie's line, divides the liver into left and right lobes (Figure 30.1). The caudate

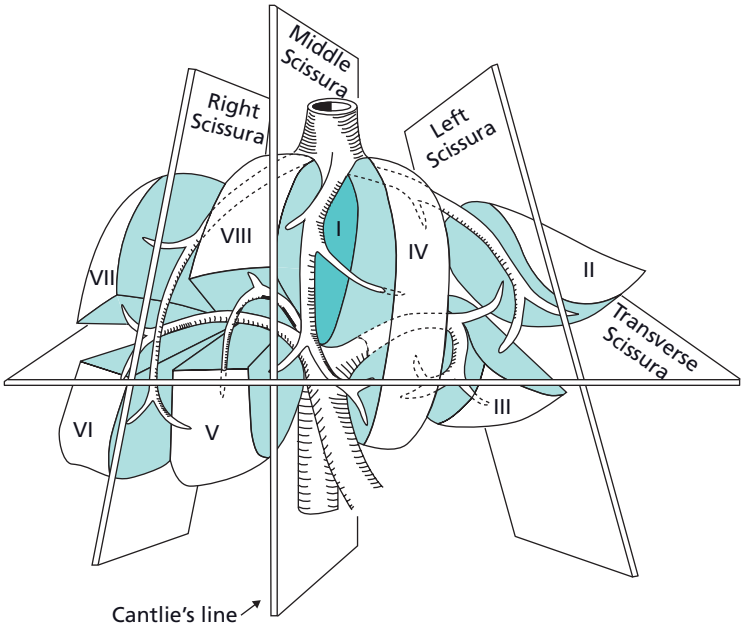


Figure 30.1 Hepatic segmental anatomy.

lobe (segment 1) encircles the inferior vena cava (IVC). It is often disproportionally large in patients with cirrhosis, especially in conditions like Budd–Chiari syndrome, as the outflow from the caudate lobe is separate from the right, middle, and left hepatic venous drainage utilized by the rest of the liver. The liver is the only organ in the body that has dual inflow; the portal vein and hepatic artery.

The portal vein is formed at the confluence of the superior mesenteric vein (SMV) and splenic vein, and tracks behind the neck of the pancreas *en route* to the liver. Unlike the hepatic artery, there are fewer anatomic anomalies of the portal vein, the most common being the trifurcation of the portal vein into the right and left lobes. Pediatric patients can have congenital agenesis of the portal vein, or direct drainage of the portal vein into the IVC. Adult patients with cirrhosis are prone to developing thrombus in the portal vein due to stagnant venous flow. Patients with chronic thrombus may develop cavernous transformation as well. At the time of transplantation, portal venous thrombus can be carefully extracted from the portal vein in most cases [2]. However, if the thrombus cannot be extracted, then a graft (iliac vein harvested at the time of donation) is usually connected between the SMV and the donor graft portal vein. It is imperative that potential recipients with portal vein thrombosis have a patent SMV in case a graft is necessary. The surgical techniques to deal with this condition are quite harrowing and may lead to a greater risk of post-transplant complications and intraoperative blood loss. In patients undergoing LDLT, portal venous thrombosis may prevent successful transplantation and thrombosis rates of SMV–portal vein conduits can be as high as 20%. Patients with thrombosis of the portal–superior mesenteric–splenic confluence into the SMV are not candidates for transplantation. Portal venous thrombosis in the setting of hepatocellular carcinoma is also a contraindication to transplant.

The hepatic artery can have multiple variations. Typically, the common hepatic artery arises as a branch off of the celiac artery. The common hepatic artery usually gives rise to two branches, the right gastric artery and gastroduodenal artery (GDA), and then proceeds as the proper hepatic artery. The proper hepatic artery divides to form the right and left hepatic arteries in the porta hepatis. The major hepatic arterial anomalies are a replaced or accessory right hepatic artery, which arises from the superior mesenteric artery (SMA) in 25% of patients, and the replaced left hepatic artery, which arises from the left gastric artery in 11%. Other anomalies include a completely replaced hepatic arterial system arising from the SMA, a right hepatic artery arising from

the GDA, and an independent common hepatic artery arising from the aorta. In less than 1% of people, a triple artery configuration exists, namely a replaced or accessory right, left, and main hepatic arterial system simultaneously. These anomalies are more important to recognize in the donor than in the recipient, as failure to notice and properly reconstruct the arterial inflow during a liver transplant can result in significant ischemia, especially to the biliary tree. If there is decreased inflow arising from the recipient's native arterial system, whether due to vascular disease, arcuate ligament tethering of the celiac artery, or small native vasculature, alternative sources of improved arterial flow need to be investigated. In those cases, a graft (usually the iliac artery from a deceased donor) can be anastomosed from the aorta to the donor hepatic artery. As transplant specialists become more aggressive with preoperative chemoembolization of hepatic lesions, the hepatic artery can be injured, especially with repeat treatments. In those cases or when an artery is injured intraoperatively, a "jump graft" or "iliac artery conduit" may be necessary.

Techniques of Liver Transplantation

Orthotopic deceased donor liver transplantation can be completed with either complete replacement of the retrohepatic IVC (conventional) or a caval sparing (Barcelona or piggyback) technique (Figure 30.2). Up until the late 1990s, liver transplantation was almost always completed by completely replacing the IVC and placing the patient on veno-venous bypass. Bypass cannulae were placed in the recipient's femoral vein and portal vein, and bypassed through a machine that acts as an extracorporeal pump, similar to cardiopulmonary bypass, and pumps the blood from below the diaphragm into the subclavian or jugular vein. Veno-venous bypass allowed decompression of the portal system, giving time for the hepatectomy to be competed without bowel congestion, protecting renal function by decreasing renal venous hypertension, and also preventing hemodynamic instability associated with clamping the IVC (the decreased venous return to the right heart can cause severe hypotension). The complications of veno-venous bypass include hemorrhage, coagulopathy, air embolus, thrombotic events, and venous injury in 30% of patient [3]. It is also time consuming and increases the cost of the liver transplant procedure.

In 1968, Sir Roy Calne first described the caval sparing technique, where the retrohepatic IVC is spared by clamping the hepatic vein orifices [4]; however, it took several decades to become a routine practice [5–7]. The most significant benefit of the so-called *piggyback* technique was that veno-venous bypass was no longer needed,

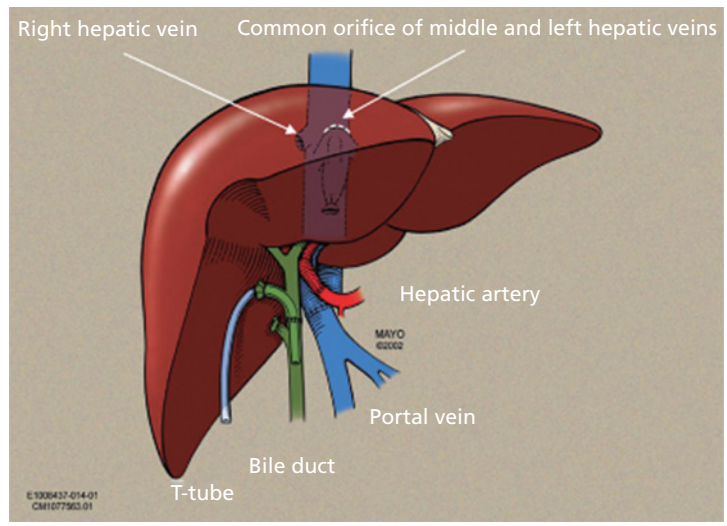


Figure 30.2 Classic "piggyback" technique. The Barcelona modification included the right hepatic vein to the outflow anastomosis avoiding hepatic congestion. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

although technically it can be more challenging to dissect the liver from the vena cava and there is an increased risk of outflow obstruction [3,8]. Originally, the technique utilized the middle and left hepatic vein orifices as a common cloaca or orifice, but the team from Barcelona demonstrated that frequently this created an outflow gradient for the liver allograft and adding the right hepatic vein to the middle/left combined orifice would ensure widely patent outflow with no gradient. This technique has been further modified by Belghiti *et al* who advocate a side-to-side vena cava anastomosis as an alternative to prevent outflow obstruction [9]. As the anesthetic techniques and comfort with liver transplantation have improved over time, even caval replacement can now be safely accomplished without veno-venous bypass. However, a few prominent centers still employ bypass as they consider it a safer procedure, especially when the ability to teach the surgical techniques to new trainees may require longer anastomotic times. Occasionally, veno-venous bypass may be indicated in patients with significant cardiac disease, large graft size or reduced space, retransplants requiring IVC replacement, and hemodynamic instability [10]. The development of piggyback techniques also facilitated the capability of split liver and LDLT. As the retrohepatic vena cava must stay with the donor, all living donor transplants (both right and left lobe grafts) are completed using piggyback techniques.

Phases of Liver Transplantation

Total Hepatectomy

The first phase of liver transplantation is the complete resection of the native diseased liver. Historically, heterotopic auxiliary liver transplantation has been attempted in animal models and human subjects, with limited success [11,12]. Many functions of the liver are dependent on its location in the abdomen, in particular biochemical functions related to the portal venous drainage and the drainage of the biliary system. In addition, the increased risk for hepatocellular carcinoma in any patient with cirrhosis mandates that the entire liver is resected. This is often the most difficult phase of a liver transplant due to coagulopathy and portal hypertension. In patients with cirrhosis, the ligaments that suspend the liver (triangular and coronary) often become thickened and lined with dilated venous collaterals. The venous collaterals are often present throughout the porta hepatis, falciform ligament, and even the abdominal wall, and can bleed excessively, especially in a coagulopathic patient. The liver is resected from its attachments and the portal triad is dissected free to isolate its constituents. Both the common bile duct and hepatic artery are ligated at this time, the bile duct at the junction of the cystic duct and the proper hepatic artery either at the junction of the right and left hepatic artery, or the right and left hepatic arteries are separately ligated. The portal vein is left intact until the hepatectomy is almost complete to reduce venous congestion and edema of the bowel, especially when veno-venous bypass is avoided.

The retrohepatic vena cava can present a major challenge during hepatectomy. The retrohepatic vena cava is surrounded by the caudate lobe and the posterior segments of the right lobe of the liver. The caudate lobe often has a small band of tissue that runs posterior to the vena cava. In patients with cirrhosis, the caudate lobe hypertrophies and this band of tissue can become a circumferential ring of liver parenchyma. In a piggyback operation as described above, there are multiple small hepatic veins that run from the retrohepatic vein cava to the caudate and right lobe of the liver that need to be carefully ligated for a caval sparing (piggyback) hepatectomy.

Hemodynamic instability is the hallmark of this stage of a liver transplant and careful volume regulation by the anesthesia team is mandatory. Excessive bleeding can lead to incredible management issues during the following phase of the operation, the anhepatic phase, which can in turn set the stage for significant patient compromise.

Anhepatic Phase

For a caval sparing liver transplant, a single vascular clamp is placed across a common cloacae or orifice created from the joining of the openings of the right, middle, and left hepatic veins, above their junction with the IVC, allowing the continuation of caval flow to the heart. For a conventional liver transplant, vascular clamps are placed on the supra- and infra-hepatic vena cava and the retrohepatic vena cava is removed with the liver. If the patient becomes hemodynamically unstable at the time of caval clamping, consideration for veno-venous bypass must be made. Even in a caval sparing

procedure, the vena cava may be partially occluded by the hepatic vein clamp and hemodynamic instability may be seen.

A second clamp is placed on the portal vein prior to completion of the hepatectomy. Prolonged clamping of the portal vein can result in significant venous congestion of the bowel, especially in patients who have not had time to develop venous collaterals (fulminant hepatic failure). The liver is then removed from the field. For a piggyback procedure, the common cloacae of the hepatic veins of the recipient are anastomosed in an end-to-end fashion to the suprahepatic vena cava of the donor, and the infrahepatic vena cava is then ligated, either with a tie or vascular stapler. This leaves a redundant segment of donor retrohepatic vena cava which thromboses over time in most patients. In conventional liver transplant, two separate end-to-end caval anastomoses are completed between the supra- and infra-hepatic vena cavae of the donor and recipient.

After the caval anastomoses are complete, most surgeons then complete the portal vein anastomosis also in an end-to-end fashion. Care must be taken to trim the portal vein to an appropriate length and prevent kinking, which could compromise portal flow to the liver graft. Between 2% and 26% of patients with cirrhosis have portal vein thrombosis at the time of transplantation, which carries an increased risk of perioperative complications and decreased long-term survival [13]. In most cases, the thrombus can be carefully separated from the intima of the portal vein and removed prior to anastomosis. However, in cases where it has become so organized or extensive that portal venous flow cannot be restored, an alternative inflow must be created. A segment of donor iliac vein or autologous vein (renal, saphenous, or jugular) can be used as a jump graft from the SMV to the donor portal vein. In cases where this cannot be done due to thrombosis or fragility of the SMV, the only choice is to anastomose the portal vein to the IVC (cavoportal hemitransposition), which usually results in a poor outcome [14,15].

If the team is able to make the appropriate vascular anastomoses in a reasonably short period of time and the hepatectomy was associated with a minimal blood loss, this phase can be relatively uneventful. However, there can be significant metabolic and electrolyte derangements during this phase that can alter cardiac physiology which, coupled with the blunted response of vasopressors in an acidic environment, can make management of the patient challenging.

Reperfusion

Standard practice is to reperfuse the liver after completion of the portal vein anastomosis to prevent a prolonged cold ischemic time, and complete the hepatic artery after reperfusion. Some surgical teams will not reperfuse until they complete the hepatic arterial anastomosis, in theory to decrease the risk of biliary ischemia. Similarly, there has been some evidence that initial arterial reperfusion may decrease hemodynamic instability at the time of reperfusion and may be indicated in patients with poor cardiac reserve [16,17], although this benefit may only be temporary until the portal vein is reperfused [18]. The order of vascular reperfusion in adult liver transplantation has not been proven to impart any significant clinical benefit.

At the time of procurement, most livers are preserved with University of Wisconsin (UW or Viaspan®) solution, although histidine–ketogluturate–tryptophan (HTK or Custodial®) solution is becoming more widely used. UW solution has a high concentration of potassium and the liver needs to be flushed with blood, albumin, or a plasmalyte solution prior to reperfusion to prevent severe hyperkalemia. HTK solution does not need to be flushed out unless there has been a prolonged cold ischemic time.

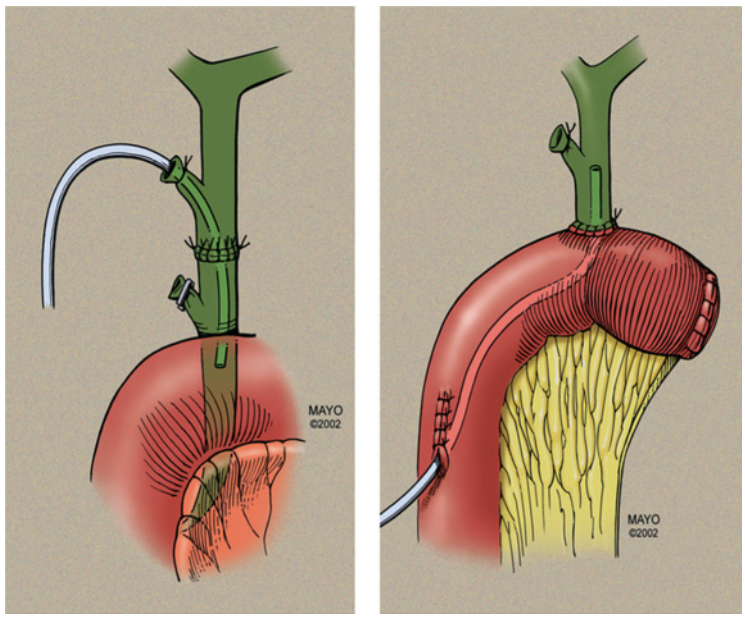
First the vena cava clamp or clamps are removed, and then the portal clamps, allowing blood to slowly flow through the liver, which is visible as the liver parenchyma becomes pinkish in color. Even with flushing, severe metabolic derangements and hemodynamic instability can occur, usually from cardiac arrhythmias. Hyperkalemia is the most common cause, usually from the build up of potassium in the bowel from congestion secondary to the portal vein occlusion. Arrhythmias can also occur from the cold preservation solution creating hypothermia in the myocardium. Competent, well-trained anesthesiologists with experience in liver transplantation are essential to anticipate and correct these derangements, and to get the patient safely through the reperfusion stage [19].

As soon as the patient is stable, the hepatic arterial anastomosis is completed. Most surgeons use a bifurcation of either the right and left or common hepatic artery and GDA as an end-to-end anastomosis to the common hepatic artery of the donor. If the donor has aberrant

hepatic arterial anatomy, reconstruction is completed at the back table prior to transplantation. If the recipient has variant arterial anatomy, the most substantial artery is used for the anastomosis. If the hepatic artery is damaged (not uncommon currently due to the increasing frequency of preoperative chemoembolization), it may be necessary to use a graft of iliac artery from the donor to connect from the donor hepatic artery to either the supraceliac or infrarenal abdominal aorta. These grafts do have a slightly decreased long-term patency rate compared to the native hepatic artery [20], although long term outcomes are similar [21]. In select cases, the recipient splenic artery, left gastric artery, or GDA may be used as a conduit.

Biliary Anastomosis

After blood flow is restored to the liver and adequate hemostasis is achieved, the biliary anastomosis is the last step. First, the donor gall bladder is removed and the donor cystic artery and duct are ligated. During both the donor and recipient hepatectomies, care must be taken not to strip the perivascular complex from the bile duct, which can compromise blood flow and lead to ischemic strictures. In most cases a choledochocholedochostomy (duct-to-duct anastomosis) is performed, in which the donor and recipient bile ducts are anastomosed together in an end-to-end fashion using absorbable suture. Historically, T-tubes were used in all biliary reconstructions, but this has fallen out of practice for most transplant programs because of a greater than 10–60% risk of biliary complications, especially at the time of removal [22,23] (Figure 30.3). Multiple studies have looked at running or interrupted sutures and perioperative biliary stents, without conclusive evidence that the risk of strictures and/or bile leaks is different, and this decision is most often surgeon specific [24,25]. Most surgeons complete this anastomosis in an end-to-end manner, but there is some evidence that a side-to-side anastomosis may decrease the risk of postoperative stenosis [26]. In patients with primary sclerosing cholangitis or an otherwise damaged native biliary system, a Roux-en-Y choledochojejunostomy is done to prevent further strictures resulting from native disease. Whenever a recipient common bile duct appears unfavorable, a hepaticojejunostomy will be performed. After completion of the transplant, three drains are placed to detect bleeding and bile leakage after transplant, usually under the right lobe, under the left lobe and behind the porta hepatis.



Duct-to-duct Roux-en-Y

Figure 30.3 Types of biliary reconstructions with T-tubes. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

Surgical Complications of Liver Transplantation

Surgical complications after liver transplantation affect over 10–25% of transplants and can have a significant impact on the long term outcome and cost of the transplant [27,28]. The risk of complication depends on multiple donor and recipient factors, as well as the ischemic time and technical issues during the case. Timely diagnosis is critical to long term graft and patient survival.

Hemorrhage

Postoperative hemorrhage is the most common complication after liver transplantation, occurring in 10–15% [27] of liver transplant recipients and requiring reoperation and hemorrhage control in 50% of cases. At the time of re-exploration, 80% will not have an identifiable cause of bleeding. Hemorrhage is the result of ongoing coagulopathy, which can be worsened by poor or delayed graft function and insufficient resuscitation of the recipient in the operating room. However, vascular anastomoses, injuries to the right adrenal gland, and liver lacerations can also result in postoperative bleeding. Patients who need re-exploration have an increased risk of intra-abdominal infection and there is significantly increased cost.

Hepatic Arterial Complications

Both hepatic artery stenosis and thrombosis are diagnosed initially by Doppler ultrasonography of the liver graft, which is readily available and cost-effective. The ultrasound may show an absence of arterial flow, or resistive indices of less than 0.5 with delayed upstroke of the arterial waveform. To confirm the ultrasound results, computed tomography angiography (CTA) is the best option. However, for patients with renal insufficiency, magnetic resonance angiography without gadolinium is another option. Conventional angiography may also be used, particularly in cases where stenosis is suspected with a therapeutic intent. Most interventional radiologists prefer not to intervene with angioplasty and/or stenting until at least 21 days post liver transplant.

Thrombosis

Hepatic artery thrombosis (HAT) can be divided into early (within 14 days) and late (after 14 days) occurrence. The risk of early HAT in adult cadaveric liver transplant is 3–10% [29,30], increasing to 6.5% in adult-to-adult LDLT [31] and over 20% in pediatric liver transplantation, secondary to smaller diameter arterial blood vessels. Other risk factors include arteriosclerosis, stenosis, aneurysm, splenic artery steal syndrome, and celiac stenosis or occlusion. Intraoperative arterial damage, including mural thrombus, intimal flap injury, and clamp injury can lead to HAT. Acute hepatic artery thrombosis can lead to massive liver necrosis with a mortality of greater than 80% without emergent revascularization or transplantation. With early recognition (within 24–48 h of thrombosis), revascularization, either by revising the initial anastomosis or using an iliac artery conduit from the aorta, can salvage over 80% of asymptomatic patients, but only 40% of symptomatic patients. Since the hepatic artery provides arterial supply to the biliary tree, late HAT often presents as bile leaks, bilomas, bile duct necrosis, and ischemic intrahepatic biliary strictures, which require retransplantation [32]. However, some patients (especially children) with late HAT will develop collateralization and graft function will remain stable without retransplantation.

Stenosis

Hepatic artery stenosis (HAS) is defined as angiographic evidence of greater than 50% reduction in the caliber of the arterial lumen, and has an incidence of 5–11%. The majority of HAS occurs at the anastomosis and is related to technical factors. Therapeutic angiography with balloon angioplasty and stenting is successful in greater than 90% of cases. If it occurs within the first 3 weeks after transplantation, it is best revised surgically, using donor iliac artery conduit if necessary.

Portal Vein Complications

Thrombosis

Portal vein thrombosis is a rare but life-threatening complication after liver transplantation. It is manifested by significant and rapid graft dysfunction, variceal bleeding, and massive ascites. It can be the result of technical factors (portal vein kinking or stenosis), recurrence or propagation of prior portal, splenic, or mesenteric vein thrombus, or poor mesenteric flow, often because large venous collaterals are stealing flow away from the liver. It requires immediate surgical thrombectomy and revascularization. Inspection and ligation of large collaterals

must be performed. A bypass graft may be necessary for rethrombosis. Retransplantation is necessary for cases that are recalcitrant to revascularization, although the outcomes are poor.

Stenosis

Portal vein stenosis (PVS) is a rare complication of liver transplantation, occurring in less than 3% of adults and 7% of pediatric recipients. Patients present with symptoms of portal hypertension. As with HAS, it is usually seen at the anastomosis. Intraoperatively it can be prevented by allowing a "growth factor" or "air knot" in the suture that allows for vein expansion with flow, preventing the anastomotic waist from occurring as a result of a too tight suturing technique. As with HAS, ultrasound and CTA are diagnostic. Early PVS should be revised surgically, and late PVS can undergo transluminal angioplasty and stenting.

Hepatic Vein and Inferior Vena Cava Complications (Outflow)

With conventional liver transplants, stenosis at the suprahepatic vena cava occurs in 1–2.5% of patients. The risk is increased to 6% with the caval sparing technique [33], and can be prevented intraoperatively by including all three hepatic veins in a broad orifice or a side-to-side cavoplasty. The risk of complete outflow obstruction is very low, but has a mortality of greater than 50%, and requires immediate operative intervention. Vena cava obstruction can be caused by too long a donor vena cava resulting in kinking, anastomotic narrowing, recurrence of Budd–Chiari syndrome, or anatomical anomalies of donor or recipient vena cavae [27]. Clinically, the patients present like Budd–Chiari syndrome, with liver dysfunction, ascites, and impaired renal function. Stenosis of the infrahepatic vena cava from a conventional liver transplant presents with lower body and extremity edema and impaired renal function. The first-line therapy is endovascular balloon angioplasty and stenting [34]. If that is not successful, the surgical options are limited. If the patient had a caval sparing approach, the retrohepatic donor vena cava can be anastomosed to the recipient vena cava to improve outflow [35]. Other surgical options for venoplasty [34] and/or revision are treacherous, and retransplantation may be the only option.

Biliary Complications

The overall incidence of postoperative biliary complications is 15–20%, increasing to up to 50% in split and reduced liver transplantation, and is the most frequent complication after liver transplant. Mortality related to persistent biliary complications is 10%. The diagnosis of both bile leak and stricture are non-specific, although elevated bilirubin and alkaline phosphatase are suggestive of problems. Biliary ductal dilation is often not seen in transplant recipients, and significant strictures can be present in the face of normal bile ducts. Diagnosis can be made with magnetic resonance or CT cholangiopancreatography. Endoscopic retrograde pancreatography (ERCP) or percutaneous transhepatic cholangiography (PTC) can be both diagnostic and therapeutic. Postoperative leakage is more common after choledochojejunostomy, and stenosis after choledochocholedochostomy.

Leak

Bile leaks occur in 10–15% of patients after liver transplantation and can cause significant morbidity. Risk factors for leaks include hepatic arterial insufficiency and technical factors that compromise the blood supply to the bile duct, including excessive bile duct dissection, excessive suturing, or increased bile duct length [27]. T-tube placement at the time of transplantation may increase the risk of postoperative biliary leak [36]. Leaks can easily become infected and inflame the surrounding structures, putting the vascular anastomoses at risk for the development of aneurysms and rupture. Initial treatment with antibiotics (including antifungal treatment) is mandatory, as is drainage and biliary stenting. If the leaks continue or are unable to be fixed with stenting, reexploration and conversion to a Roux-en-Y hepaticojejunostomy is necessary. At the time of diagnosis, it is imperative to rule out an HAT/HAS which can lead to biliary ischemia and leak.

Stenosis

Biliary strictures and stenosis are the most common biliary complications after liver transplantation, occurring in 2.5–20% of deceased donor transplantations and 18–32% of LDLTs [31,37]. They can result from a technical complication from the anastomosis, in particular a duct size mismatch or bile duct ischemia. They are usually at or proximal to the biliary anastomosis. ERCP

and PTC can be used to both balloon dilate and stent the anastomosis, and in almost all cases the strictures resolve over time, although it may take several treatments [38]. For recalcitrant strictures, revision to a Roux-en-Y hepaticojejunostomy is recommended. Prolonged stenosis can result in secondary intrahepatic biliary stricturing that may need retransplantation to be resolved.

Donor Related Complications

Primary Non-Function

Primary non-function (PNF) occurs in up to 6% of liver transplants; however, it is associated with a high risk of mortality [28]. The etiology of PNF remains unclear and it is difficult to predict. Donation after cardiac death, older donors, high donor sodium, graft steatosis, and prolonged ischemic time have all been identified as risk factors. It is often detected in the operating room or immediately postoperatively, presenting as significant coagulopathy, hemodynamic instability, and liver dysfunction. Intraoperatively the liver has abnormal color and turgor with coagulopathy, and may require immediate hepatectomy with a diverting portal caval shunt. The only option is retransplantation and patients should be listed status 1. While waiting for a liver, support with continuous dialysis, coagulation factors, plasma, and vasopressors is necessary. The mortality while waiting for retransplantation is over 50%.

Feng *et al* have developed a Donor Risk Index (DRI) scoring system that utilizes easily identifiable donor factors and recipient factors to assist transplant surgeons in selecting appropriate donor–recipient pairs with optimal outcomes. Both donor and recipient factors can lead to severe early graft dysfunction or PNF. Many times it is best to choose a donor graft with high risk factors such as long ischemia time, advanced age or significant (> 40% macro-) steatosis to implant into a recipient with a more stable hemodynamic profile and more normal renal function, such as a patient with advanced HCC, who may better tolerate the physiologic insult imparted with the transplant [39].

Small graft for size syndrome (SFSS) is defined as early graft dysfunction, in particular the triad of hyperbilirubinemia, coagulopathy, and ascites, in donors with less than 30–50% functional hepatic mass or a graft-to-recipient body weight ratio of less than 0.8 [28]. It is most common in adult-to-adult LDLT and adult split liver transplantation, and is thought to be related to portal hyperperfusion. Many patients recover function with time, but splenic artery ligation/embolization is also used to decrease portal flow [40]. Many surgeons advocate a temporary partial portosystemic shunt to alleviate this syndrome. Some patients may require retransplantation. Livers from donors with prolonged ischemic time, in particular from donation after cardiac death, can develop ischemic biliary structuring that may require retransplantation [41,42].

Living Donor Liver Transplantation

This is a chapter in itself; however, the same major principles exist as described for deceased donor liver transplantation. The additional special considerations to be aware of for LDLT recipients center around the much more complex and highly technically challenging operation of engraftment as well as the postoperative management. Due to the much smaller diameter and multiplicity of blood vessels and bile ducts, surgical complications are much more common, especially the biliary anastomotic issues (Figure 30.4; Video 4). As with deceased donors, HAT and HAS, PVT and PVS all occur, but at higher

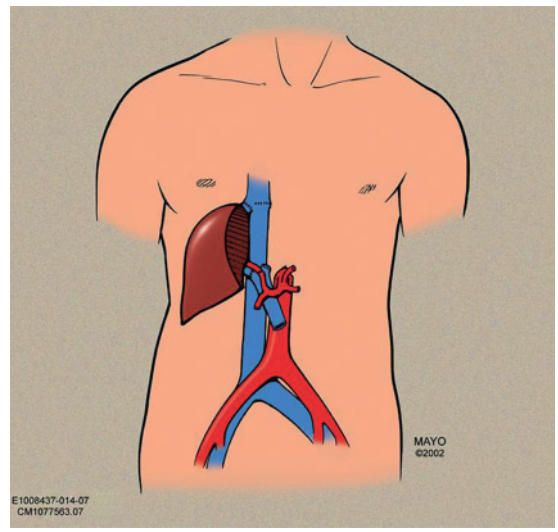


Figure 30.4 Right lobe living donor liver transplant. Smaller graft with much more complex anatomic reconstruction. (By permission of Mayo Foundation for Medical Education and Research. All rights reserved.)

rates (up to 20% incidence in some reports). The bile ducts have become the Achilles' heel of the LDLT, with complication rates of stenosis or leak of up to 50%. Reoperations for biliary complications seem to be less advantageous, while endoscopic or percutaneous management has a high success rate in over 80% of patients. Overall, the advantage for recipients of these life-saving grafts is a higher long term survival beyond 3 years according to the A2ALL study group reports as well as the experience at these authors' center. This is despite a higher early complication rate, which is predominant in the first 30 days post LDLT.

Conclusion

Liver transplantation remains the only treatment for end-stage liver disease. Although surgical techniques have improved significantly over the last 20 years, it remains a complex operation with multiple potential complications. Transplant recipients are more ill and donors less optimal than in the past. Transplant hepatologists need a thorough knowledge of the liver transplant operation to diagnose and treat these complications. There should be a high index of suspicion for both early and late complications to improve patient outcomes.

Take-home points

- Using the knowledge of hepatic anatomy, the surgical techniques and the complications that can occur at each phase during the entire transplant process can be understood.
- There are critical issues that can occur immediately after the liver transplant and should trigger a rapid diagnostic assessment to determine the appropriate treatment algorithm to employ.
- Donor and recipient selection can be key to a successful outcome.
- The most common early complication of liver transplantation is hemorrhage, which usually requires surgical intervention.
- The most common (surgical) complication overall is biliary stenosis or leak which can be managed with endoscopic and/or radiologic percutaneous interventions with high rates of success. Rarely is surgery required to treat biliary complications in this era.
- Living donor liver transplants are available to approximately 20% of potential recipients, and despite having a higher rate of early complications, especially of the biliary anastomoses, they enjoy a higher long term survival than patients receiving a deceased donor graft.

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31

CHAPTER 31

Immunosuppression in Liver Transplantation

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Summary

Liver transplantation has come a long way from the early days of immunosuppression with irradiation, 6-mercaptopurine, and corticosteroids. With the advent of calcineurin inhibitors, significant progress has been made over last 25+ years. Modern-day immunosuppression has become much more tailored for specific patient populations instead of one size fits all. The goal for future therapies will be maintaining the same excellent patient and graft survival while minimizing the toxicities that are common with many immunosuppressive medications.

Case

BS is at 59-year-old man with a past medical history significant for hepatitis C and hepatocellular carcinoma and post-liver transplantation approximately 1 month ago. His hospital course was uneventful and he was last seen 10 days ago. He presents to the clinic today for a routine follow-up.
His current list of medications include:
Tacrolimus 2 mg twice daily

Mycophenolate mofetil 1000 mg twice daily

Prednisone 10 mg daily

Omeprazole 20 mg daily

Bactrim 1 orally every Monday, Wednesday and Friday

Amoxicillin 500 mg orally three times daily

Metoprolol 25 mg orally twice daily

Phenytoin 200 mg orally twice daily
His labs are as follows:
Hemoglobin = 9.6 g/dL, sodium = 136 mmol/L, tacrolimus level = 2.5 ng/mL

Hematocrit = 31%, potassium = 4.1 mmol/L

WBC = 8.6 × 10^3/μL, CO_2 = 21 meq/L, platelets = 198 × 10^3/μL, chloride = 98 mmol/L, BUN = 33 mmol/L, creatinine = 1.4 mmol/dL, glucose = 134 mmol/dL, calcium = 7.4 meq/dL, magnesium = 1.8 meq/L, phosphorus = 3.0 meq/dL

AST = 300 IU/L, ALT = 386 IU/L, alkaline phosphatase = 300 IU/L, bilirubin = 6.8 mg/dL
A biopsy was ordered and the results were a rejection activity index (RAI) consistent with moderate rejection in four of nine instances. BS was questioned on what events had transpired over the last 10 days. He said that he had been to the emergency room for a episode of unresponsiveness. The doctor told him that it was a "seizure" of some kind and put him on phenytoin and he was going to be followed up by a neurologist next week.

Introduction

The term "transplant immunology" dates back to early 20th century. Early work done by JB Murphy between 1912 and 1914 helped to explain the term. Murphy

Practical Gastroenterology and Hepatology: Liver and Biliary Disease, 1st edition. Edited by Nicholas J. Talley, Keith D. Lindor and Hugo E. Vargas.

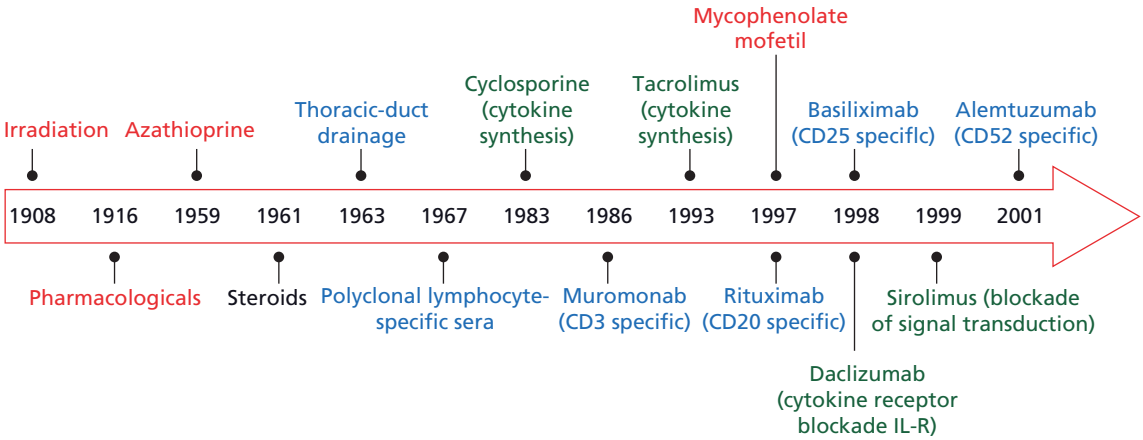

Figure 31.1 The development of immunosuppressive stages for transplantation. Timeline of four stages in the development of immunosuppressive strategies: stage 1—antiproliferative agents (red); stage 2—steroid therapy; stage 3—lymphocyte depletion/modulation (blue); stage 4—disruption of cytokines (green).

worked with experimental tumor and tissue transplantation and was convinced that tissue transplantation obeyed the same principles as tumor transplantation. He was able to show that the rejection reaction was due to "function which appeared secondarily in the organism at a certain period of life to eliminate foreign tissue." He also demonstrated that the reticuloendothelial system, particularly small lymphocytes, played a very important role in the rejection process [1].

This work led Medawar and Gibson to show that a second skin graft in the same animal was rejected more rapidly than the first and called this a "second stage phenomenon." This ultimately led to the discovery of humoral and cell-mediated immunity and the involvement in the rejection process [1].

Early immunosuppression was suboptimal at best. Corticosteroids and azathioprine were used in combination by Starzl *et al.* in his first five transplantations. The majority of the Colorado series from 1963 to 1976 received corticosteroids, azathioprine, and antilymphocyte globulin. A total of 170 patients were transplanted, and approximately 50% were children. Patients were divided into three time-based series: series 1 (1963–1976, 111 patients) had a 1-year survival rate of 28.8%; series 2 (1976–1978, 30 patients) had a 1-year survival rate of 50%; and series 3 (1978–1979, 29 patients) had a 1-year survival rate of 34.5%. Variations on these approaches included thoracic duct drainage or cyclophosphamide, although neither produced significant advantage. The Cambridge University group reported on a series from 1968 to 1980 with a total of 93 patients, with a 1-year survival rate of 23.7%. The lower survival rate may have been due to the lower rate of children transplanted by the Cambridge group [2,3]. This time frame has been referred to as the pre-cyclosporine (CyA) era (Figure 31.1).

Dawn of a New Era

The early 1970s saw the introduction of a new class of immunosuppressants, the so-called "calcineurin inhibitors" (CNIs). These compounds form the backbone of immunosuppression in liver transplant recipients. Currently, two CNIs are available: CyA and tacrolimus (TAC).

CyA was discovered by Jean-Francois Borel in 1973 from a soil fungus, *Tolypocladium inflatum*. The approval of the US Food and Drug Administration (FDA) was obtained in 1983 [4]. CyA causes selective suppression of cell-mediated immunity via inhibition of T-cell activation. After forming a complex with its cytoplasmic receptor protein (cyclophilin), CyA binds to and inhibits the calcium and calmodulin-dependent phosphatase calcineurin (Figure 31.2). It is believed that calcineurin plays a vital role in the transcriptional process by which interleukin (IL) 2 and other cytokines are activated. The pro-

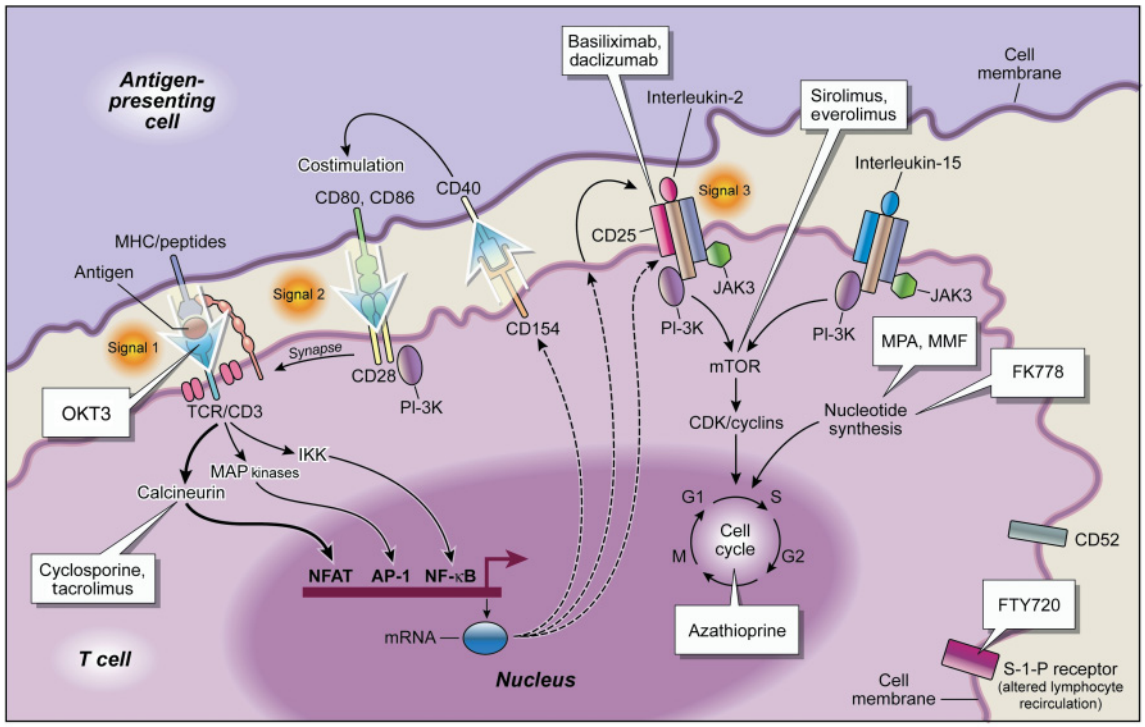

Figure 31.2 Depiction of immunologic engagement of T lymphocyte by antigen-presenting cell. MMF, mycophenolate mofetil; MPA, mycophenolic acid; TCR, T-cell receptor.

duction of these substances by T-helper cells is a vital component of the immune response and is central to the graft rejection process.

Two formulations of CyA are currently available. The standard formulation (Sandimmune) was the first to come to market and requires an emulsification step before digestion and subsequent release of the CyA. The step is heavily dependent on food intake, biliary flow, and gastrointestinal motility, and therefore subject to unpredictable bioavailability, with values ranging from 1% to 89% and a mean of 30%. The newer formulations are microemulsion preconcentrates (Neoral, Gengraf), which consist of the drug in a lipophilic solvent. These formulations produce more consistent bioavailability and are less dependent on biliary flow [5]. CyA is metabolized primarily in the liver via the cytochrome P4503A pathway. Drug interactions are common; the following are drugs that may increase CyA and TAC levels:

- Calcium channel blockers, e.g., diltiazem, nifedipine, nicardipine, verapamil
- Antifungal agents, e.g., clotrimazole, fluconazole, itraconazole, ketoconazole, voriconazole,
- Macrolide antibiotics, e.g., azithromycin, clarithromycin, erythromycin, troleandomycin, telithromycin
- Prokinetic agents, e.g., metoclopramide, omeprazole
- Miscellaneous agents, e.g., cisapride, amiodarone, cimetidine, methylprednisolone, protease inhibitors, nefazodone, ethinylestradiol.

The following are drugs that decrease the CyA and TAC levels:

- Anticonvulsants, e.g., carbamazepine, fosphenytoin, phenobarbital, phenytoin
- Antibiotics, e.g., rifabutin, rifampin, rifapentine,
- Herbal preparations, e.g., St John's wort
- Miscellaneous drugs, e.g., probucol, terbinafine.

Nephrotoxicity is one of the main side effects of CNI therapy. This can be both an acute and a long-term complication, inducing a post-orthotopic liver transplantation rate of renal failure of up to 20% [6]. Common metabolic abnormalities include hyperkalemia,

hypomagnesemia, hyperlipidemia, and to a lesser extent hyperglycemia. Gingival hyperplasia and hirsutism are also a common occurrence. Between 10% and 28% of patients have neurologic manifestations that range from mild tremor and peripheral neuropathy to psychoses, hallucinations, motor weakness, and seizures [7]. The common side effects of CyA are:

- Hypertension
- Renal dysfunction
- Hyperkalemia
- Gingival hyperplasia
- Hypomagnesemia.

The initial dosage of CyA ranges from 10 mg/kg per day to 15 mg/kg per day divided into two doses. Adjustment of the oral dose is based on trough level measurement, usually within 24 h of starting CyA. Target trough levels vary widely. Commonly used dose-targeted ranges in liver transplantation would be 250–350 ng/mL during weeks 1–2, 200–300 ng/mL during weeks 3–4, 150–250 ng/mL during weeks 5–24, and 100–200 ng/mL during weeks 25–52 [8,9]. More recently, dose adjustments based on blood concentration at 2 h after dose have been shown (C2 levels) to more closely correlate total exposure vs CO monitoring (trough). One example of this would be target blood concentration levels of 850–1400 ng/mL at 2 h after dose from 0 months to 3 months post-transplantation [10].

In 1984, a soil sample containing the fungus *Streptomyces tsukubaensis* was discovered close to Mt Tsukuba in Japan. Two years after this discovery, TAC was isolated [11]. TAC is 100 times more potent than CyA and exerts its action by binding to FK-binding protein (FKBP12). This complex then inhibits calcineurin, which is responsible for transcription of the interleukins IL-2, IL-3, IL-4, and IL-8, and various chemotactic factors.

TAC absorption occurs in the duodenum and jejunum. Unlike CyA, TAC absorption is not influenced by the presence of bile, which is advantageous in cholestatic patients or those with biliary diversion or ileus. Food reduces bioavailability, and TAC should be taken on an empty stomach. Metabolism occurs in the liver via the cytochrome P4503A. Coadministration of medications that inhibit or induce cytochrome P450 may significantly affect blood levels of TAC (see earlier). Side effects are similar to those of CyA, and include [12]:

- Post-transplantation diabetes mellitus
- Nausea, vomiting, and diarrhea
- Hyperkalemia
- Tremor
- Hypertension
- Hypomagnesemia
- Headache
- Renal dysfunction.

In general, the difference between the two CNIs can be summarized as follows: TAC has a higher rate of post-transplantation diabetes mellitus, whereas CyA predisposes to more hypertension, dyslipidemia, hirsutism, and gum hyperplasia (see above). Initial dose guidelines for TAC range from 0.1 mg/kg per day to 0.15 mg/kg per day orally. Dosages are modulated based on trough levels. Factors affecting adjustments are disease state, renal function, age of the patient, and other concomitant medications. Therapeutic goals for TAC early after surgery would be from 10 ng/mL to 15 ng/mL. Multicenter trials have shown that orthotopic liver transplant recipients treated with TAC-based immunosuppression compared with CyA have a lower rate of rejection within the first year, and patients infected with hepatitis C have longer graft survival [13]. A large percentage of orthotopic liver transplantation programs use TAC-based regimens.

Corticosteroids

As mentioned earlier, corticosteroids have been a mainstay since the early days of liver transplantation. They are by far the most heavily utilized non-calcineurin inhibitors in liver transplantation. Corticosteroids exert their most critical immunosuppressive effect by blocking T-cell-derived and antigen-presenting cell-derived cytokine expression. This includes IL-1, IL-2, IL-3, and IL-6 [14]. Corticosteroids continue to be used to reverse acute rejection and in maintenance therapy. Side effects are numerous and include hypertension, hyperglycemia, osteoporosis, hyperlipidemia, increased risk of gastric ulcers, risk of fungal and bacterial infections, and suppression of the hypothalamic–pituitary–adrenal (HPA) axis. The common side effects of corticosteroids include:

- Hypertension
- Mental status changes
- Lipid abnormalities
- Impaired wound healing
- Hyperglycemia

- Cushingoid syndrome
- Ulcers
- Myopathy
- Osteoporosis
- Fluid retention
- Cataracts.

Dosing varies widely but can be summarized as follows: a bolus dose of methylprednisolone just before surgery, i.e., 500–1000 mg, followed by a rapid taper over the next few weeks to a minimal dose, i.e., 2.5–5.0 mg/day. The vast majority of programs will try to wean patients off corticosteroids within the first year, except in cases of autoimmune hepatitis. The percentage of patients receiving corticosteroids before hospital discharge decreased from 91% in 2002 to 78% in 2006. In part this can be attributed to the rising concern over the negative impact of this class of medication on the recurrence of hepatitis C [15].

Antimetabolites

Azathioprine (AZA) was the first antimetabolite used in liver transplantation but its use has since decreased dramatically over time. Azathioprine is an imidazolyl derivative of mercaptopurine and antagonizes purine metabolism. The result is an inhibition in synthesis of DNA, RNA, and proteins. Current use stands at <1% of US transplant centers [15]. This has been primarily due to the side-effect profile, which includes significant myelosuppression and hepatotoxicity. The common side effects of antimetabolites include:

- Nausea, vomiting, and diarrhea
- Anemia
- Leukopenia
- Weight loss
- Thrombocytopenia.

Typical dosage is 1–2 mg/kg per day.

Mycophenolate mofetil (MMF) and mycophenolic acid (MPA) are the most recent additions to the antimetabolite arena, with MMF approval in 1995 and MPA in 2004. MPA is a delayed-release product in contrast to MMF, which is immediately released. Both formulations inhibit new purine nucleotide synthesis via abrogation of inosine monophosphate dehydrogenase and the production of guanosine nucleotides. This action leads to a blockage of DNA replication in T and B lymphocytes, which are unable to use alternate salvage pathways. Studies have shown a large variation in MMF pharmacokinetics in liver transplantation related to fluctuations in serum albumin concentrations, changes not seen in the renal transplant population. Liver dysfunction impairs MPA conjugation and prolongs MPA half-life. Furthermore, TAC has been shown to augment the bioavailability of MPA, resulting in higher exposure to MPA [16]. Drugs that decrease blood concentrations include antacids, cholestyramine, iron preparations, cyclosporine, proton pump inhibitors, and rifamycin derivatives and those that increase blood concentrations include allopurinol (AZA), probenecid (MMF), angiotensin-converting enzyme (ACE) inhibitors (AZA), methotrexate (AZA), and TAC (MMF). The incidence of adverse effects (nausea, gastritis abdominal pain, diarrhea, and neutropenia) requiring dose reduction or withdrawal is high, ranging from 24% to 57% [17].

The most recent data on usage show a continuing trend upward with >65% of the US transplant centers reporting use within the first year of transplantation [15]. Initial dosage ranges from 2 g to 3 g daily for MMF and 1440 to 2160 mg daily for MPA, divided into two doses. To reiterate, dose reductions are common and in some patients removed completely, especially when combined with other myelosuppressive medications, such as sirolimus.

Antibody Induction

Antibody therapy has been used as a means of delaying the introduction of maintenance therapy and/or helps facilitate the removal of an immunosuppressive agent, particularly corticosteroids. Antibody therapy can be seen as depleting or receptor modulating or both.

Antithymocyte Globulin

Polyclonal antilymphocyte antibody preparations are heterologous preparations. Animals (rabbits and horses) are immunized with human T cells and thymocytes. Antisera are then collected. A purified γ-globulin fraction (ATG) is used to reduce the likelihood of serum sickness. The ATG preparations approved by the FDA are ATGAM (of equine origin) and thymoglobulin (of rabbit origin). These polyclonal preparations are directed at multiple different epitopes on the T cell (CD2, CD3, CD4, CD8, CD28, and the T-cell receptor) as well as CD16 found on

natural killer (NK) cells and macrophages. These antibodies cause depletion of T cells by apoptosis, antibody-mediated cytolysis, and internalization of the cell surface receptors. The biologic effects of the depleting antibodies are profound and last longer than the presence of heterologous antibody. Side effects can include a "first-dose" effect (cytokine release syndrome) and are related to the myriad of cytokines released by these lymphocytes upon their demise. The symptoms typically include fever, chills, tachycardia, gastrointestinal disturbances, bronchospasm, and fluctuations of blood pressure, which can all be ameliorated by pretreatment with corticosteroids, diphenhydramine, and acetaminophen [17]. Usage in the USA has tripled from 3% in 2002 to 9% in 2006, primarily due to new immunosuppressive strategies as outlined later [17]. Dosing ranges from 1.5 mg/kg to 5 mg/kg as a single infusion usually over 4–6 hours for 3–5 days, depending on the indication.

Monoclonal Anti-T-cell Antibodies

Muromonab-CD3 (OKT3) is a murine-derived antibody directed to a specific portion of T cells. It exerts its activity by binding to the CD3 antigen on the surface of T lymphocytes. This binding inactivates the adjacent T-cell receptor, which is critical for activation of T lymphocytes. The end result is a rapid fall in the number of mature lymphocytes. OKT3 was first used in liver transplantation in 1987 for prophylaxis against acute cellular rejection and later to reduce CNI exposure and treatment of steroid-resistant rejection [17]. More recent data have shown a significant drop-off in favor of IL-2 receptor antibodies and polyclonal preparations [15].

A cytokine release syndrome is more frequently associated with the first dose compared with the polyclonal antibody preparations, and starts 1–3 hours after administration. Reactions can be quite severe and can range from flu-like symptoms (pyrexia, chills, dyspnea, chest pain, and tightness) to severe and life-threatening shock-like reactions (pulmonary edema). These symptoms can be mitigated with the administration of a corticosteroid, diphenhydramine, and acetaminophen just before dose administration. Re-exposure to OKT3 may result in lower efficacy due to the formation of antimurine antibodies. In the early transplantation period, when the incidence of acute cellular rejection was as high as 71% and steroid-resistant rejection was more common, OKT3 was the mainstay in the treatment of steroid-resistant rejection with high salvage rates [18,19]. Currently, steroid-resistant rejection rates are much lower, thanks to improved immunosuppressive agents and strategies. OKT3 use today is much lower, with many centers preferring treatment regimens for acute cellular rejection based on increasing TAC blood levels and then adding corticosteroid boluses if rejection is still present [15,20].

The FDA approved dosage is 5 mg intravenously daily for 10–14 days. Dosage adjustment or drug discontinuation may be necessary if there is a reduced T-cell clearance (increase in CD3-positive T cells) or low plasma OKT3 plasma levels.

More recently, some centers have been using a non-FDA-approved monoclonal antibody, alemtuzumab, as an induction agent. This agent targets the CD52 epitope, which is located on the surface of T lymphocytes including monocytes, macrophages, B cells, and NK cells. A single center study uses alemtuzumab induction along with tacrolimus monotherapy vs a control group that consisted of tacrolimus and corticosteroids. The conclusion of the study was that the alemtuzumab arm was comparable to the control arm [21].

IL-2 Receptor Antibodies

Two products are currently marketed: basiliximab and daclizumab. Daclizumab is a humanized product whereas basiliximab shows chimeric properties. Both bind to the IL-2R α-chain, which is upregulated on the surface of activated T lymphocytes. Immunosuppression is achieved by competitive antagonism of IL-2-induced T-cell proliferation. Although the half-lives of both drugs are decreased in liver transplant recipients, when compared with kidney recipients the immunosuppressive effects extend well into the third week for basiliximab and up to 10 weeks for daclizumab [17].

Side effects are generally mild for both agents and comparable to placebo [22]. Although neither agent is FDA approved for use in liver transplantation, usage appears to be increasing. Typical dosing for basiliximab is 20 mg given intravenously on the day of surgery, before engraftment. A second dose of 20 mg is given 4 days later. Relevant dosage for daclizumab is 1 mg/kg every 14 days for a total of five doses. A number of variations to the daclizumab regimen has been reported in the literature over the last few years and is discussed later. Current

usage stands at about 12% of liver transplant recipients receiving an IL-2 receptor antibody [15].

Miscellaneous

The following agents are used at different stages in liver transplantation, from induction to conversion.

Rapamycin

Sirolimus (or rapamycin—RAP) is a macrocyclic triene antibiotic (structurally related to TAC) with immunosuppressive, antitumor, and antifungal properties, although the latter two are not clinically significant. RAP binds to the immunophilin FKBP12 and blocks the response of T- and B-cell activation by cytokines, which prevents cell-cycle progression and proliferation; in contrast, TAC and CyA inhibit the production of cytokines. Interestingly, although RAP binds to the same immunophilin (FKBP12) as TAC, it has a very different mechanism of action, i.e., blockage of cell-cycle progression at the juncture of G1 and S phase [23]. As a result of this, many refer to the binding site for RAP as the "target of RAP."

Early excitement in the liver transplant arena was generated from a single-center study out of Halifax, Nova Scotia. A small number of liver transplant recipients were given combination therapy of TAC and RAP with targeted levels of 7 ng/mL and 5 ng/mL, respectively. Acute cellular rejection rates were 14% with an average follow-up of 23 months [24,25]. Since that time, multiple serious side effects have limited its use early on in liver transplantation. This includes leukopenia, thrombocytopenia, elevated serum cholesterol and triglyceride levels, anemia, lymphocele, wound dehiscence, and oral ulcerations. The common side effects of rapamycin include:

- Anemia
- Hypercholesterolemia
- Hypertriglyceridemia
- Leukopenia
- Hyperlipidemia
- Interstitial lung disease
- Thrombocytopenia
- Peripheral edema
- Wound dehiscence.

The most serious side effect has been the issue of hepatic artery thrombosis and includes the following black box warning in liver transplantation: "The safety and efficacy of sirolimus (Rapamune) as immunosuppressive therapy have not been established in liver transplant patients, and therefore such use is not recommended." Drug interactions are common and can be profound. Drugs that increase blood concentrations include:

- Calcium channel blockers, e.g., diltiazem, nicardipine, nifedipine, verapamil
- Antifungal agents, e.g., clotrimazole, fluconazole, itraconazole, ketoconazole, voriconazole
- Macrolide antibiotics, e.g., azithromycin clarithromycin, erythromycin, telithromycin, troleandomycin
- Prokinetic agents, e.g., metoclopramide, omeprazole
- Miscellaneous agents, e.g., amiodarone, cimetidine, cisapride, cyclosporine, methylprednisolone, protease inhibitors.

Drugs that decrease blood concentrations include:

- Anticonvulsants, e.g., carbamazepine, fosphenytoin, phenobarbital, phenytoin
- Antibiotics, e.g., rifabutin, rifampin, rifapentine,
- Herbal preparations, e.g., St John's wort.

A report from Colorado compared 170 RAP-treated liver transplant recipients with 180 historical controls using RAP and low-dose CNIs in a corticosteroid avoidance protocol. All patients had a minimum 1-year follow-up. No significant difference was seen between the two groups in relationship to hepatic artery thrombosis [17]. If this potential hurdle can be cleared, the potential benefit of RAP with low nephrotoxicity is very appealing.

Current Therapeutic Strategies for Steroid Avoidance

Interests in corticosteroid abstention stems from the well-known side effects of osteoporosis, hyperglycemia, cushingoid features, and hypertension, as well as the deleterious effects on recurrence of hepatitis C.

The first randomized study concerning complete steroid avoidance was published by Eason *et al.* The first group of 36 patients received TAC, MMF, and a two-dose regimen of rabbit antithymocyte globulin (thymoglobulin, rabbit ATG) 1.5 mg/kg on day 0 and 1. The second group received TAC, MMF, and corticosteroids with no induction. Median follow-up was 1.5 years. Graft

survival rate in each group was 89%. The biopsy-confirmed rejection rate in the rabbit ATG group was 20.5% vs 32%. TAC blood levels were elevated and all patients in the thymoglobulin group responded; 64% in the other group required additional steroids for treatment, and that percentage was statistically significant ($p < 0.05$). The incidence of recurrent hepatitis C was 50% in the rabbit ATG group and 71% in the steroid group (p = not significant) [26]. Details about surveillance and recurrence of hepatitis C were not expounded on.

A similar study using daclizumab induction without MMF with both groups receiving TAC showed a reduction in biopsy-confirmed steroid resistant rejection in the induction group ($p < 0.027$). Although the overall adverse events were similar, the incidence of diabetes mellitus and cytomegalovirus infections were higher ($p < 0.001$ and $p < 0.002$, respectively) in the TAC/steroid group. Follow-up was relatively short at 3 months [27]. Although these are encouraging results, larger randomized trails with longer follow-up are needed.

Renal-sparing Protocols

The sentinel articles by Ojo *et al.* and Gonwa *et al.* brought a stark realization about the true incidence of renal failure after transplantation [6,28]. Oja *et al.* looked at approximately 70 000 patients who received a solid organ transplant from January 1, 1990 to December 31, 2000. Up to 21% of patients developed chronic renal failure within 5 years after receiving a non-renal transplant [28]. Gonwa *et al.* looked at 834 recipients of liver transplants between June 1985 and December 1994 who survived 6 months post-transplantation. At 13 years after liver transplantation, 18% of patients were diagnosed with severe renal dysfunction, a significantly higher percentage when compared with controls [6]. Both articles alluded to a direct role of CNIs.

Different strategies have been developed to help in this ongoing struggle. One approach has examined adding MMF and reducing the dose of the calcineurin inhibitor or eliminating the calcineurin inhibitor altogether. These studies have produced some encouraging results with up to 50% of patients showing at least a 15% improvement in renal function [29]. A number of studies have shown an increased risk of rejection when the CNI is completely removed [29–31].

Conversion from CNI to Sirolimus

Recent studies with small numbers looked at the impact of switching patients with chronic renal impairment from CNI to RAP. Twenty-eight patients with creatinine >1.8 after transplantation were eligible for conversion. Mean time to conversion was approximately 2 years. Sirolimus was initiated at 2 mg/day, and doses were adjusted to maintain levels of 4–10 ng/mL. Seven did not tolerate RAP and six progressed to end-stage renal disease. The subset of 14 patients (50%) who did tolerate conversion had a decline in creatinine that persisted to week 48 [32]. Questions still remain on the optimal time to conversion and whether it can be used in the early post-transplantation period. Large randomized trials are ongoing in an effort to answer these questions.

Calcineurin Inhibitor Avoidance

Very few studies have looked at complete calcineurin inhibitor avoidance. The latest data from the scientific registry of transplant recipients database show that >95% of patients are discharged on either TAC (majority) or CyA [33]. The concept of using agents without nephrotoxicity in solid organ transplant recipients where rejection has less of a negative impact on the long-term survival has sparked some enthusiasm, but to date little has been published to demonstrate success with this strategy.

Individualization of Drug Therapy

Tailoring medication therapy in the transplant recipient is a concept that has evolved dramatically over time and yet still has a long way to go. Early literature talks of "immunologic monitoring" as a means to individualize therapy through dissecting mechanisms of action, rejection, immunosuppressive medications, and graft facilitation [34]. This is still true today. The quandary is how far to take individualization. There is a need to individualize patient-specific regimens, and yet standardization of these regimens helps programs to quantify outcomes and strengthen cost containment.

New immunologic monitoring assays are becoming available that may help tailor immunosuppression. The

ImmuKnow assay portends to detect cell-mediated immunity. The assay measures the ability of T-helper lymphocytes to respond to mitogenic stimulation via quantification of the amount of ATP produced in CD4+ T cells after stimulation. Immune responses are reported in nanograms per milliliter of ATP and categorized as strong (≥525), moderate (226–524), or low (≤225) [35].

Today we are able to assign patients to protocols that best fit their needs, e.g., delaying the introduction of CNIs to allow for renal function to improve, corticosteroid avoidance for people with osteoporosis or hepatitis C, or hepatitis B immunoglobulin for patients infected with hepatitis B. Within each protocol, allowances are made for discretion.

With the advent of unlocking human DNA, new avenues have opened to true individualization based on drug metabolism. Pharmacogenetic typing offers the possibility of significant improvement in the individualization of immunosuppressive drug prescribing with reduced rates of rejection and toxicity.

Take-home points

- Immunosuppression in liver transplantation has evolved into a fine balance between toxicity and preventing rejection.
- Drug interactions are common between many immunosuppressive medications and require careful monitoring.
- The use of induction agents in liver transplantation has helped tailor immunosuppressive regimens for specific patient populations.
- Calcineurin inhibitors and newer generation antimetabolites have become mainstays in liver transplantation immunosuppression.

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CHAPTER 32

Liver Transplantation: Early and Long Term Management and Complications

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Summary

Post-liver transplantation (LT) care begins with immunosuppression induction and maintenance and continues with close monitoring of graft function, as well as renal, metabolic, and infectious diseases complications. A number of recipient, donor, and operative factors influence postoperative complications. Neurogenic, cardiovascular, renal, gastrointestinal, and metabolic side effects may manifest early or later in the post-transplant period, while primary disease recurrence and malignancy issues most often manifest later in the course. With improvement in survival rates after LT, due to advances in surgical techniques and immunosuppression drugs, non-transplant-related causes like cardiovascular disease and *de novo* malignancies are becoming responsible for most late deaths in the recipients. Liver transplant recipients hence require a multidisciplinary team approach from day 1 after the transplant, followed by a tailored screening and health maintenance regimen.

Case

John Doe is a 60-year-old malnourished male with decompensated alcoholic cirrhosis complicated by chronic hepatitis C, genotype 1a unresponsive to treatment. The patient's cirrhosis is complicated by hepatorenal syndrome (HRS) resulting in acute renal failure (ARF) requiring dialysis. His course is further worsened by esophageal variceal bleeding precipitating hepatic encephalopathy. He is listed for cadaver donor liver transplantation (LT) with a model for end-stage liver disease (MELD) score of 23 as attempts for a live donor failed.

The patient [cytomegalovirus (CMV) seronegative] received a CMV-seropositive organ donated after cardiac death (DCD) and underwent orthotopic LT (OLT) with a duct-to-duct biliary anastamosis and standard vascular anastamosis. Intraoperatively he received basiliximab and methylprednisolone. Prophylactic antibiotics and antivirals, prednisone, and mycophenolate were commenced. Postoperatively, hepatic arterial indices by Doppler duplex were normal. Insulin was commenced for hyperglycemia manifesting after OLT. As renal function improved, dialysis was discontinued on postoperative day 2 and tacrolimus was commenced on postoperative day 3. Liver enzymes, which climbed initially, trended down on postoperative day 4. After ensuring stable graft function, the patient was discharged on postoperative day 7.

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Immunosuppression

Immunosuppression induction and maintenance after LT demand careful drug selection. A typical induction regimen is a combination of different agents because each agent influences different portions of the rejection cascade, resulting in a beneficial cumulative effect. As no single induction and maintenance immunosuppression regimen is clearly superior in all situations, a tailored regimen guided by patient profile and transplant center experience is necessary. Calcineurin inhibitors (CNIs) in combination with tapered corticosteroids remain most widely used in immunosuppression induction and maintenance. Immunosuppressive regimens in living and cadaver donor LT vary little.

Induction

Immunosuppression induction commonly uses intravenous methylprednisolone at LT followed by an oral prednisone tapering regimen scheduled per transplant center protocols. Thymoglobulin, a rabbit-derived polyclonal antibody, substitutes in steroid-free regimens. Its use has a lower incidence of rejection, but increased incidence of post-transplantation lymphoproliferative disorders (PTLDs). Basiliximab and daclizumab, the two chimeric and humanized monoclonal anti-CD25 antibodies, are promising in LT recipients unsuited for full-dose CNIs and in steroid-evading induction regimens.

Maintenance

Cyclosporine and tacrolimus are generally the agents of choice. They engage the immunophilins—cyclophilin and FK506-binding protein 12, respectively, forming a complex that then engages calcineurin. Calcineurin inhibits transcription of several genes, including interleukin (IL)-2, critical to T-cell activation. Metabolism of CNIs depends on cytochrome P450, and drugs affecting this metabolic pathway can greatly affect serum levels. CNIs require trough level monitoring. C2 level (drug level 2 h after administration) of cyclosporine more accurately represents drug exposure but is logistically difficult. Cyclosporine and tacrolimus have similar 1-year patient and graft survival. Tacrolimus seems less nephrotoxic than cyclosporine with lower incidence of acute rejection and steroid-resistant rejection, but neurogenic and diabetogenic adverse effects increase. Mycophenolate (T- and B-cell inhibitor) and sirolimus [mammalian target of rapamycin (mTOR) inhibitor] are not nephrotoxic and are often used in renal insufficiency. However, sirolimus remains controversial due to hepatic artery thrombosis (HAT) incidence and perioperative wound healing impairment. Although azathioprine was the main transplant immunosuppressant in the early 1980s, it is uncommonly used today.

Graft Function

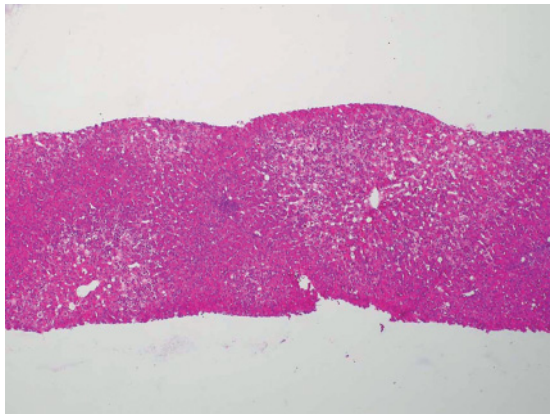
Prevention of graft failure depends on close monitoring of immediate postoperative graft function. Improvements in bilirubin, prothrombin time, acidosis, glucose metabolism, hemodynamics, hypothermia, urine output, and mental status indicate good graft function. Ischemia and reperfusion injury cause a rise in transaminases in the immediate post-LT period. Transaminases gradually decrease with improvement in graft function. Hence, the transaminase trend is more useful than actual levels in assessing graft function.

The major causes of graft dysfunction in the immediate postoperative period are primary non-function (PNF), preservation injury, and small-for-size syndrome. PNF is graft loss in the immediate post-LT period secondary to graft non-function of no defined cause (Figure 32.1). The reported incidence is 2–14% and etiology is multifactorial but probably related to ischemia–reperfusion injury. PNF requires emergent retransplantation. Preservation injury manifests within 72 h of LT and differs from PNF in severity and likelihood of recovery. Preservation injury generally improves within 3 days with supportive therapy. Small-for-size grafts are functionally insufficient in meeting recipient metabolic demand and are usually seen in split liver living donor LT (LDLT). A graft/recipient standard liver volume ratio of 40% is preferred in adult patients.

Vascular Complications

Arterial Complications

Arterial complications after LT range from 5% to 15%. Hepatic artery thrombosis (HAT; 58%), hepatic artery stenosis (HAS; 31%), and hepatic artery kinks (HAK; 6%) are the most common [1]. As the sole arterial supply of the transplanted liver and the bile ducts, hepatic artery



(a)

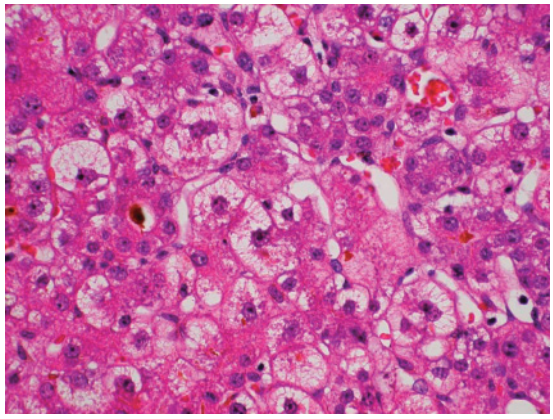


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Figure 32.1 (a,b) Preservation injury: liver biopsy, 7 days post transplant with preservation injury. Zone 3 cells demonstrate feathery degeneration with cholestasis (courtesy of Raouf E. Nakhleh MD, Department of Pathology, Mayo Clinic Jacksonville).

anastomosis patency is crucial to graft survival. Commonly performed within 24 h of LT, Doppler ultrasound (US) acceleration time from end-diastole to first systolic peak should be less than 80 ms with the resistive index [(peak systolic velocity/peak diastolic velocity)/peak systolic velocity] at 0.5–0.7. Up to 72 h post LT, the resistive index may be higher from postoperative edema, but biliary dilatation and focal strictures should raise suspicion of complications.

Hepatic Artery Thrombosis

HAT, the second leading cause of early postoperative graft failure, mostly occurs within the first 3 months, resulting in 20–60% mortality. Prolonged ischemia time, complex anatomy, difficult anastomosis, hypercoagulable state, rejection, and transplantation for primary sclerosing cholangitis (PSC) are risk factors. Fulminant hepatic failure, delayed biliary leak, and relapsing bacteremia are the presenting features. Doppler US (92% accuracy) and, perhaps, angiography are necessary for assessment. Treatment varies from transcatheter thrombolysis before balloon angioplasty for uncovered anatomic defects to urgent graft revascularization. Up to 60% of patients require retransplantation.

Hepatic Artery Stenosis

HAS usually occurs at the anastomotic site and may cause biliary ischemia and hepatic dysfunction or, when severe, thrombosis (Figure 32.2). Responsible factors are usually mechanical, resulting from clamps and perfusion catheters and leading to ischemia of the arterial ends. Management includes percutaneous endoluminal balloon angioplasty and stent placement to maintain hepatic artery patency. The reported success rate is approximately 80% for hepatic artery angioplasty with 1-year HAT rates of 19% (Figure 32.3). Anticoagulation and antiplatelet therapy post hepatic artery angioplasty are not established as effective options.

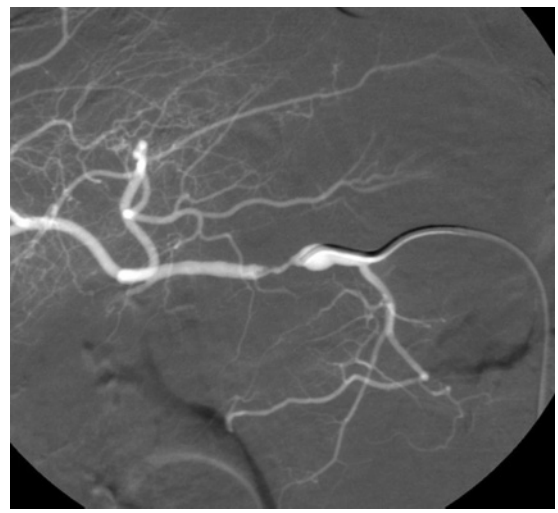


Figure 32.2 Hepatic artery anastomotic stenosis: Irregular stenosis involving the transplant hepatic artery anastomosis with approximately 85% diameter reduction (courtesy of Ricardo Paz-Fumagalli MD, Department of Radiology, Mayo Clinic Jacksonville).

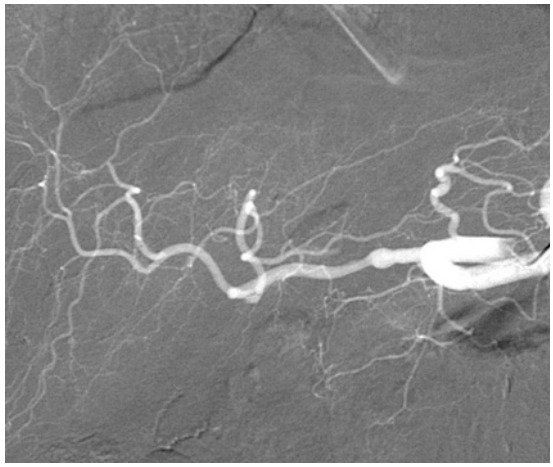


Figure 32.3 Hepatic artery anastomosis angioplasty: Marked improvement with only residual 10–20% narrowing following 5 mm balloon angioplasty (courtesy of Ricardo Paz-Fumagalli MD, Department of Radiology, Mayo Clinic Jacksonville).

Portal Venous Complications

Portal venous complications post LT are more common with split liver LT and LDLT due to technical difficulties in anastomosis creation. Portal venous anastomotic stenosis (PVS) and portal venous thrombosis (PVT) after OLT typically present with signs of resultant portal hypertension, that is gastrointestinal hemorrhage, ascites, and splenomegaly with or without thrombocytopenia. If PVS is significant, percutaneous angioplasty may be undertaken. Treatment of PVT requires mechanical and/or pharmacologic thrombolysis.

Biliary Complications

Case continued

At a routine postoperative day 14 follow-up, the patient reported mild fever and right upper quadrant abdominal pain of 1-day duration. Work-up revealed a cholestatic liver profile and a fluid collection near the porta-hepatis on a CT scan. CT-guided aspiration confirmed an aseptic biloma. Doppler US of the hepatic artery was normal. Endoscopic retrograde cholangiography (ERC) revealed a biliary anastomotic leak which was successfully managed with a stent.

The most common post-LT biliary complications are leaks and strictures but casts, sludge, stones, and sphincter of Oddi dysfunction may also manifest. The incidence of biliary complications in LDLT is 15–30%, and in OLT it is 11–25% with one-third of biliary complications occurring within 1 month of surgery and 80% within 6 months [2–4]. While strictures form over time, bile leaks generally occur within 3 months of LT.

Bile Leaks

Bile leaks (2–21% incidence) occur most often either at the anastomotic site or higher up in the donor duct, from the cystic duct remnant or the T-tube exit site related to elective or incidental T-tube removal (5–15%) or downstream obstruction or papillary dysfunction (Figure 32.4). Leaks after right lobe (RL)-LDLT develop within a month (5–18%), more often with Roux-en-Y hepaticojejunostomy than duct-to-duct choledochocholedochostomy. Surgical techniques and vascular factors most commonly cause early leaks, while late leaks (7% with a mean time to presentation of 118 days post LT) may stem from removal of biliary tubes, transhepatic anastomotic stents, or biliary stent migration and perforation.

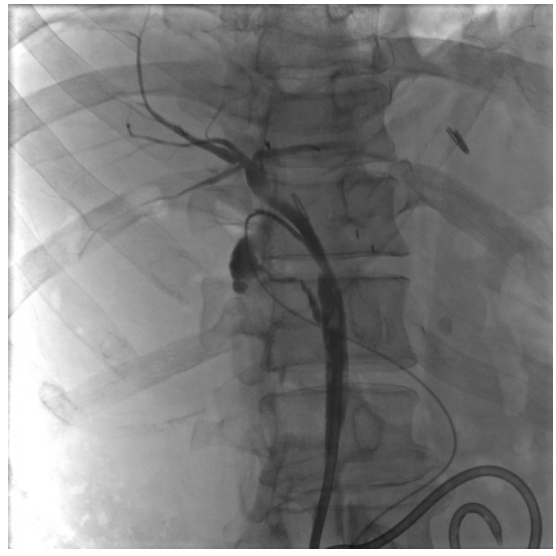


Figure 32.4 Cystic duct remnant leak. Contrast extravasation from the tip of the native cystic duct remnant with patent duct-to-duct biliary anastomosis. Contrast was injected through the pre-existing surgical biliary drain in the right abdomen (courtesy of Eric Walser MD, Department of Radiology, Mayo Clinic Jacksonville).

Biliary Strictures

The reported incidence of biliary strictures is 5–15% and the average time to presentation is 5–8 months after OLT, most within 1 year. For RL-LDLT the reported incidence is 8–32%. Early anastomotic strictures are mainly due to technical factors, while vascular insufficiency and fibrotic healing cause late strictures.

Biliary strictures are broadly categorized into anastomotic and non-anastomotic strictures. Anastomotic strictures (4–9% incidence) are localized to anastomosis and short in length. They are related to surgical technique, stenoses, bile leak in the postoperative period, or vascular factors. In RL-LDLT, bile leaks cause inflammation and subsequent fibrosis, an important factor in addition to technical factors for developing biliary strictures. Non-anastomotic strictures (5–15% incidence and average time to development of 3–6 months) are multiple, longer in length, and intrahepatic, and cause graft loss. Risk factors include HAT, chronic ductopenic rejection, ABO incompatibility, PSC as the primary pathology, DCD donors, older donors, donor use of prolonged vasopressors, preservative injury, and prolonged cold and warm ischemia times.

Presentation

Biliary complications present with cholestasis, pyrexia, or septicemia in the presence of coexistent cholangitis, anorexia, malaise, paralytic ileus, and right upper quadrant abdominal and/or right shoulder pain. However, pain may be completely absent due to hepatic denervation and immunosuppressants. Jaundice, acholic stools, bilious ascites, or respiratory complaints caused by pleural effusion or elevation of the right diaphragm are late symptoms. Gamma-glutamyl-transferase is the most effective indicator of biliary complications in the first 30 days after OLT and total bilirubin elevation is most sensitive between 30 and 90 days.

Evaluation

US, CT scan, magnetic resonance cholangiopancreatography (MRCP), scintigraphy [hepatobiliary imino-diacetic acid (HIDA) scan], and cholangiogram via a biliary T-tube or endoscopic approach can be used to evaluate biliary complications. Routine US is 38–66% sensitive (Figure 32.5). Doppler duplex US, on the other hand, effectively assesses the vascular patency which is crucial to investigating biliary complications. CT assists in detection and interventional treatment of intra-abdominal bile/fluid collections. MRCP (approximately 90% sensitivity and diagnostic specificity) and HIDA scan (75% sensitivity and 100% specificity) both lack therapeutic ability. Direct cholangiography (80% sensitive and 98% specific) offers therapeutic access and is only limited by biliary reconstruction type (hepaticojejunostomy or choledochojejunostomy).

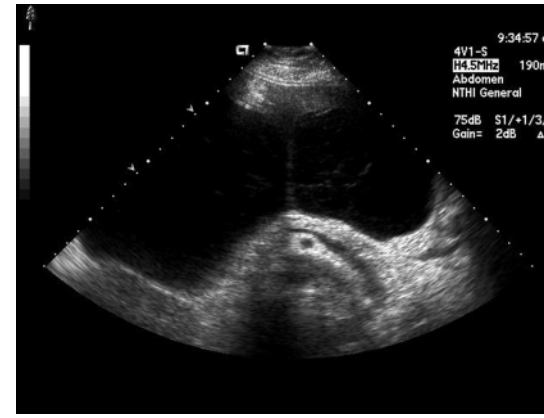


Figure 32.5 Biloma by ultrasound (courtesy of Eric Walser MD, Department of Radiology, Mayo Clinic Jacksonville).

Management

Most biliary leaks can be managed via ERC and stent placement (for 2–3 months with revisions when necessary) successfully greater than 95% of the time, but persistent leaks or large ductal defects require surgical revision. In LDLT patients, cut-surface leaks are managed by ERC and sphincterotomy to achieve optimal biliary flow, or a temporary percutaneous drainage for bilioenteric anastomosis cases. Anastomotic and common bile duct strictures are managed endoscopically with dilation and stenting. The long term success rate is greater than 70%, but interval change of stents and assessment of the strictures are required. Reported relapse rates are 30–40%, requiring surgical revision with Roux-en-Y anastomosis. Strictures related to vascular insufficiency are less responsive to endoscopic treatment (<28%). Treatment of diffuse intrahepatic strictures shows long term response to endoscopic therapy in only 50–75% of patients, a lower success rate than in anastomotic

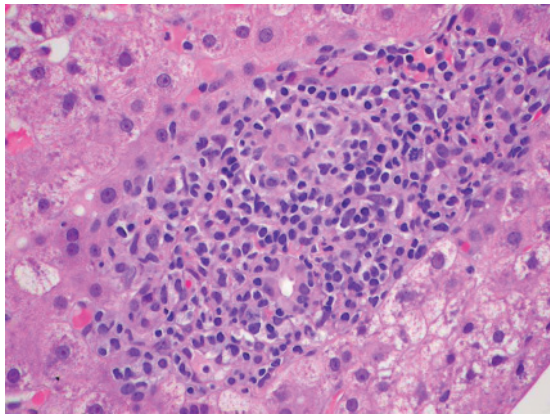


Figure 32.6 Acute rejection: a small portal tract is seen with mixed inflammatory infiltrate and duct damage characteristic of acute cellular rejection (courtesy of Raouf E. Nakhleh MD, Department of Pathology, Mayo Clinic Jacksonville).

strictures. Balloon dilatation and stenting of dominant strictures may provide temporary palliation, but advanced cases require retransplantation (Video 5).

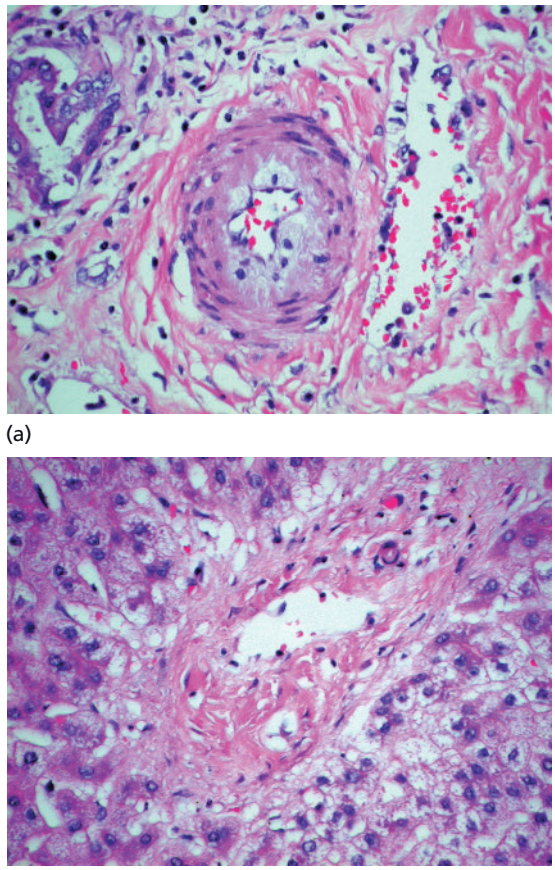
Rejection

Case continued

Despite successful biliary leak management, the patient's liver enzymes did not normalize. Allograft liver biopsy raised concerns of acute cellular rejection (ACR). Methylprednisolone in pulsed doses was administered and the tacrolimus trough level was maintained higher. Treatment resulted in a slight increase in creatinine and potassium, and fine intentional tremors in hands, headache, and insomnia in the patient. Subsequent liver biopsy confirmed ACR resolution.

The liver induces some degree of tolerance in the recipient compared to other solid organ grafts due to an unusually high percentage of unconventional lymphoid cells in it, including natural killer (NK) cells, that rarely are present in the blood. These lymphoid cells deliver a death signal to circulating recipient-derived T cells that migrate through the liver after transplantation. Due to advances in immunosuppression, liver allograft acute rejection dropped from a high of 75% in the early years of LT to less than 30%. Chronic rejection leading to graft loss develops in less than 3% of recipients. Rising liver enzymes, especially alongside subtherapeutic immunosuppression, should prompt rejection evaluation, including allograft biopsy. Liver allograft rejection could be hyperacute, acute, or chronic.

Hyperacute rejection or massive hemorrhagic necrosis is rare. It is most common in recipients with ABO-incompatible grafts resulting in rapid graft destruction from coagulative parenchymal necrosis. Acute or cellular rejection is more common. Histopathologic features include portal tracts infiltrated by lymphocytes, damaged bile ducts, and venular inflammation (Figure 32.6). Acute rejection responds well to increased immuno-



(a)

(b)

Figure 32.7 Chronic rejection. (a) Small artery shows foam cell arteriopathy characteristic of chronic rejection. (b) A small portal tract with bile duct loss (courtesy of Raouf E. Nakhleh MD, Department of Pathology, Mayo Clinic Jacksonville).

suppression or one to two pulses of high-dose corticosteroids. Steroid-resistant and severe rejections require thymoglobulin or muromonab CD3 (OKT3). Long term allograft function is not affected. While acute rejection within 90 days of LT responds well to treatment, late acute rejection, recurrent rejection, and steroid-resistant rejection often develop into chronic rejection.

Chronic rejection, ductopenic rejection, or vanishing bile duct syndrome, seen in a minority of LT recipients, may lead to graft loss. Progressive cholestasis, liver dysfunction and ultimately, graft failure are presenting features. Histopathologic features are the presence of arterial foam cells, the loss of bile ducts, and the pruning of distal branches of the portal venous system due to persistent inflammation and arterial foam cell infiltration (Figure 32.7). Retransplantation is necessary.

Infectious Diseases Complications

Case continued

Four months after LT, the patient developed significant nausea, vomiting, and diarrhea. Stool studies were negative. Elevated serum transaminase levels and CMV viremia were detected. Esophagogastroduodenoscopy (EGD) and colonoscopy with mucosal biopsies showed CMV tissue invasion. Reduced immunosuppression and initiation of ganciclovir improved the patient's symptoms.

Bacterial Infections

Nosocomial bacterial infections such as surgical-site infections, catheter-related bloodstream infections, pneumonia, urinary tract infections, and *Clostridium difficile* colitis are common within 30 days of LT. Perioperative antibacterial prophylaxis targeting gastrointestinal flora and *Staphylococcus aureus*, or modified regimens in patients with recent infections or colonization with resistant pathogens (methicillin-resistant *S. aureus*, vancomycin-resistant *Enterococci*, extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*), is provided for 24–48 h following transplantation. Trimethoprim–sulfamethoxazole prophylaxis is widely used to prevent *Pneumocystis carinii* pneumonia; its duration varies among centers.

Bilomas are intrahepatic or perihepatic fluid collections resulting from biliary complications occurring in approximately 10% of recipients. They primarily develop in the first year following LT. Fever and abdominal pain are the common clinical presentations, while asymptomatic liver enzyme and/or white blood cell count elevations appear in one-third of cases. Bilomas should be drained not only for therapeutic, diagnostic, and antibiotics guidance, but also to prevent peritonitis, bacteremia, and sepsis complications. *Enterococci*, coagulase-negative *Staphylococci*, and *Candida* are commonly cultured from these bilomas rather than Gram-negative or anaerobic bacteria. Percutaneous drainage is recommended until completely resolved. Most are managed non-surgically, except for persistent leaks or large ductal defects.

Post-LT peritonitis is another serious complication most often associated with wound infections or surgical complications such as biliary leak, intra-abdominal bleeding, biliary stricture, or bowel leak or perforation. Risk factors include higher pretransplant MELD score, longer surgical time, Roux-en-Y biliary anastomosis, and post-transplantation dialysis. Management includes correcting underlying problems and systemic broad-spectrum antimicrobial therapy based on local institutional resistance patterns (until specific isolate and susceptibility data emerge).

Fungal Infections

Predominant early post-transplant fungal infections involve invasive *Candida* and *Aspergillus*. Occasional infections include *Cryptococcus* and *Histoplasmosis* or *Coccidiomycosis* reactivation.

Antibiotic prophylaxis for spontaneous bacterial peritonitis, fulminant hepatic failure, retransplantation, greater intraoperative transfusion requirements, longer operation time, renal failure, and post-transplantation dialysis are recognized risk factors for invasive candidiasis in LT recipients. Fungal infections manifest as candidemia in an intravascular catheter or an intra-abdominal abscess and/or peritonitis, and surgical site or wound complications. Fluconazole usually treats *Candida albicans*, *C. tropicalis*, and *C. parapsilosis*, but for resistant strains (like *C. glabrata*) echinocandin, amphotericin B, or voriconazole are preferred. Treatment should include intravascular catheter removal, intra-abdominal abscesses drainage, and infected wound debridement. Retinal examination assists evaluation for endophthalmitis.

Invasive aspergillosis (which has a high mortality rate of 60%) occurs in fewer than 10% of LT recipients, half occurring after 6 months and approximately one-third after 1 year. Risk factors include poor graft function, retransplantation, post-transplantation renal failure, CMV infection, and use of sirolimus with tacrolimus in late-onset aspergillosis. Most cases are confined to the lungs, a diagnosis achieved from respiratory cultures supported by clinical and radiographic evidence of invasive pulmonary disease. Voriconazole is the drug of choice.

Fungal prophylaxis with nystatin for a month is common practice. Fungal prophylaxis in high-risk transplant recipients includes ambisome, or voriconazole if renal and hepatic functions permit, or caspofungin. Duration is transplant-center dependent but is usually until hospital discharge after LT or 6–12 weeks post LT.

When antifungals are used, CNI dosing should be decreased due to significant drug–drug interaction, and close monitoring of CNI serum levels is necessary.

Viral Infections

Viral infections in immunosuppressed recipients can result from reactivation of a donor or recipient virus. CMV, herpes simplex virus (HSV), varicella zoster virus, and Epstein–Barr virus (EBV) are frequently encountered pathogens. CMV is the most common.

CMV-seropositive recipients (i.e., with positive IgG antibodies) retain risk for CMV infection regardless of the donor serostatus, but the risk of primary infection increases when a seronegative recipient receives the liver from a seropositive donor. Risk also increases during and after acute rejection treatment with antilymphocyte antibodies and high corticosteroid doses. CMV infection ranges from positive viral proteins or nucleic acid in any body fluid or tissue specimen without clinical signs or symptoms (asymptomatic infection) to end-organ disease (tissue-invasive disease). Tissue invasion of the gastrointestinal tract and liver is common but is also seen in the lungs and central nervous system. CMV, which is an immunomodulatory virus, is an independent risk factor for bacteremia, invasive fungal infections, and EBV-related PTLD, and is also implicated in acute and chronic allograft injury. CMV-seropositive recipients undergo periodic surveillance, usually early post transplant, for CMV via pp65 antigenemia markers and quantitative polymerase chain reaction (PCR) assays. Most centers provide 3-month prophylaxis against CMV infection to patients at risk, that is seronegative recipients of a seropositive donor liver. For symptomatic CMV infection or tissue-invasive CMV disease, treatment is oral vanciclovir or intravenous ganciclovir. Dosing is renal function dependent. CMV quantitative markers can confirm resolution of infection.

Renal Complications

Case continued

At the patient's 6-month follow-up, he reported tremors in his hands, headaches, and insomnia. Physical exam was positive for a high systolic blood pressure, confirmed by his home blood pressure charting. Review of his blood work over the last month revealed slightly higher creatinine, intermittent supratherapeutic tacrolimus trough level, and hyperkalemia.

Acute Renal Failure

ARF post LT poses a greater risk than pre LT from increased mortality (28–75% incidence), significantly extended hospitalization and cost [5–8]. ARF post LT occurs in between 48% and 94% of patients, with 8–17% of patients requiring dialysis [5–7]. Optimal CNI dosing, today's preferred immunosuppressant, necessitates normal renal function. Any renal dysfunction thus affects graft survival indirectly. The most common cause of ARF immediately post LT is ischemic acute tubular necrosis (ATN), followed by CNI toxicity during late stages. Risk factors include pre-LT history of spontaneous bacterial peritonitis, ascites, encephalopathy, Child–Pugh stage C, prolonged hospitalization prior to transplantation, albumin less than 3 g/dL, serum creatinine greater than 1.5 mg/dL, and ischemia time greater than 12 h. Intraoperative risk factors include surgical time greater than 9 h, high volume blood product requirements, and ischemia times greater than 8 h. Postoperative risk factors are hepatic allograft dysfunction at day 4, severe fungal infection, and repeat surgery. High intraoperative red cell transfusions, ischemia time greater than 8 h, preoperative

encephalopathy, and history of ascites are significant independent prognostic factors.

Renal dialysis requirements post LT range from 8% to 17% and appear to be increasing due to an increasingly ill patient population selected for transplantation (8.29% during 1985–95 versus 12.45% during 1996–99) [8]. A preoperative serum creatinine greater than 1.9 mg/dL, a preoperative blood urea nitrogen greater than 27 mg/dL, an intensive care unit stay longer than 3 days, and a MELD score greater than 21 are risk factors predicting dialysis post LT. Patients with hemodynamic instability tolerate continuous forms of dialysis better than intermittent hemodialysis, but there is no proven survival advantage with continuous dialysis. Reported post-LT recovery from ARF with HRS is 58–77.4%. No data on renal recovery after LT exist for other forms of ARF.

Chronic Kidney Disease

Risk of chronic kidney disease (CKD) in LT recipients, mostly due to CNI toxicity, is 18.1–27.5% at 5 years post LT [9,10]. In addition to CNI toxicity, focal segmental glomerulosclerosis, underlying disease progression, ATN, and non-recovered HRS can cause end-stage renal disease (ESRD). Specific prognosticators for CKD/ESRD post LT are lacking, but a higher preoperative serum creatinine, increased incidence of HRS, intraoperative dialysis, repeat transplantation, and higher serum creatinine 1 year after transplantation are some of the risk factors for CKD after LT. One study showed that 9.5% of LT recipients developed ESRD within 13 years, with 28.2% surviving (54.6% in the control group) and 3% requiring kidney transplantation [11]. In the same study, patients with dialysis dependency after ESRD onset had a 6-year survival of only 27% compared to 71.4% for patients who subsequently received kidney transplantation.

Cardiovascular Complications

Cardiovascular event rates range from 9.4% at 5 years post LT to 25% at 10 years [12,13]. This accounts for 21% of deaths of LT recipients surviving more than 3 years [14]. Studies show that LT increases the prevalence of hypertension, diabetes mellitus, dyslipidemia, and obesity, leading to elevated cardiovascular event rates.

Hypertension after LT is primarily a consequence of immunosuppression and renal disease. Glucocorticoids cause hypertension by working through the renin–angiotensin system, vasopressor and vasodepressor systems via norepinephrine, angiotensin II, kallikrein–kinin system, and endothelial-derived relaxing factor nitric oxide. Cyclosporine works via the renin–angiotensin system. Both cyclosporine and tacrolimus impair nitric oxide-mediated vasodilatation, leading to renal vasoconstriction, glomerular filtration reduction, and increased sodium reabsorption.

Blood pressure should be monitored and hypertension treated to general population targets. Limited data exist on the effect of lifestyle modifications for hypertension in LT recipients, but lifestyle modifications effective in the general population are also applicable to LT recipients. Calcium channel blockers are preferred in LT recipients due to their vasodilator effect and reversal effect on CNI-induced afferent arteriolar vasoconstriction. LT recipients with proteinuria should receive angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Neurologic Complications

Overall, the rate of neurologic disorders post LT ranges from 11% to 42% [15]. Cerebral and systemic hemodynamic alterations during transplantation, graft dysfunction, embolic and hemorrhagic cerebrovascular accidents, opportunistic central nervous system infections, and immunosuppressant neurotoxicity are responsible for the neurologic complications. Management depends on identifying and rectifying the underlying etiology.

Major Complications

Immunosuppression neurotoxocity, particularly from CNIs, could produce major complications like cerebellar syndrome, posterior leukoencephalopathy, focal neurologic deficits, and even vegetative state (Table 32.1). Seizures (10–40% immediately post transplantation) are the second most common neurologic complication.

Minor Complications

Headaches, tremor (intentional), vivid nightmares, peripheral neuropathy, polyneuropathy, sleep disorders

Table 32.1 Major neurologic complications.

Complication	Symptoms	Pathophysiology
Cerebellar syndrome	Nausea and vomiting Headache Dizziness Nystagmus Ataxia Rigor nucali Encephalopathy	Cerebral ventricular widening and edema Non-specific edema and loss of Purkinje cells
Posterior leukoencephalopathy	Nausea and vomiting Fever Occipital headache Visual hallucinations Cortical blindness Seizures	Occipital and parietal extrapontine demyelinization Brain perfusion alterations
Focal neurologic deficits	Palpebral ptosis Dysarthria	White matter damage within motor pathways Ischemia
Vegetative state	Alert No communication or eye contact No emotional reactions	Possible calcineurin neurotoxicity
Metabolic encephalopathy	Sleep disorders Apathy Illusions Acoustic and visual hallucinations Disorientation Delirium Acute psychotic episodes Stupor and coma Seizures	Possible immunosuppression toxicity Electrolyte and osmotic disorders Systemic inflammation and infections
Seizures	Partial seizures Generalized seizures	Immunosuppression neurotoxocity Rapid electrolytes/osmolar changes Ischemic brain lesions Demyelinization
Central pontine melinolysis syndrome	Altered consciousness Convulsions Hypoventilation Hypotension Pseudobulbar palsy Quadriparesis	Symmetrical loss of myelin in the base of the pons Rapid correction of prolonged hyponatremia

(27.4%), and restless leg syndrome (4.3%) are common minor complications. Hemorrhage, ischemic stroke, and meningitis or meningoencephalitis should be ruled out in patients suffering headaches. CNIs are implicated in pathophysiologies of headache, tremor, and sleep disorders, while pressure or traction of nervous plexuses due to a prolonged operative course could cause peripheral neuropathy (paraesthesia, dysaesthesia, burning sensation in the hands or feet, lack of strength, and hyporeflexia). β-Blockers may treat tremors. Minor complications rarely necessitate immunosuppressant substitution.

Table 32.2 Major gastrointestinal infectious complications.

Pathogen	Time from LT (months)	Gastrointestinal pathology	Symptoms	Investigation	Treatment (in addition to immunosuppression reduction)
CMV	~6	Bleeding Erosions Ulcers Perforation	Dysphagia Nausea and vomiting Abdominal pain Gastrointestinal bleeding Diarrhea	Endoscopy with mucosal biopsies	Immunosuppression reduction Valganciclovir
EBV	~6	Oral hairy leukoplakia PTLD	Obstruction Bleeding Perforation	Endoscopy or open biopsy	Immunosuppression reduction Chemotherapy Rituximab Debulking surgery
HSV	~2	Ulcers	Odynophagia Dysphagia	Endoscopy with mucosal biopsies	Immunosuppression reduction Acyclovir
Candida	~6	Erosions White nodules/ plaques Ulcers	Dysphagia Heartburn Gastrointestinal bleeding	Endoscopy	Amphotericin Caspofungin Voriconazole

LT, liver transplantation; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; PTLD, post-transplantation lymphoproliferative diseases.

Gastrointestinal Complications

Case continued

One day, the post-transplant coordinator received a phone call from the patient's primary care physician inquiring about the need for a colonoscopy in investigating common pathogens and toxin-negative diarrhea of 2 weeks duration in the patient.

Transplantation-related drugs, with gastrointestinal side effects, can exacerbate pre-existing gastrointestinal diseases, modify the presentation of gastrointestinal diseases, predispose the gastrointestinal tract to infection, or intensify common pathogen diseases (Table 32.2).

For 6 months after LT, viral and other opportunistic gastrointestinal infections prevail, followed by community-acquired microbes. Repeated hospitalizations and acute rejection treatments foster opportunistic infection.

The gastrointestinal tract is affected in 10–30% of patients with CMV disease manifesting as esophagitis, gastritis, duodenitis, enteritis, or colitis, causing bleeding, ulceration, diffuse mucosal irritation, and rarely perforation. Intense immunosuppression or acute rejection treatment by pulsed steroids or antilymphocyte preparations could reactivate HSV, usually within 30 days of LT, causing oropharynx and esophageal ulcers presenting as odynophagia or dysphagia. Other viral pathogens affecting the gastrointestinal tract are adenovirus and calicivirus causing diarrhea.

The gastrointestinal tract, with its copious lymphoid tissue, is susceptible to PTLD. With minimal early symptoms, most patients present with obstruction, bleeding, or perforation. Approximately 85% of post-transplant lymphomas derive from B lymphocytes. Most are associated with EBV, with an increased risk in EBV-seropositive patients. Open or endoscopic biopsy is necessary for diagnosis and treatment planning, which may include reducing or discontinuing immunosuppression and chemotherapy, anti-CD20 monoclonal antibody (rituximab) in patients with CD20-positive lymphocytes, and/or surgery for debulking or managing complications.

Oral and esophageal candidiasis usually appears within 6 months of transplantation, except when high-dose

steroids to treat acute allograft rejection or broad-spectrum antibiotics are used. Although *C. albicans* dominates, *C. glabrata*, *C. tropicalis*, or *C. parapsilosis* could be causative pathogens.

Clostridium difficile, *Yersinia enterocolitica*, *Campylobacter jejuni*, *Salmonella* sp, and *Listeria monocytogenes* are the usual diarrhea-causing bacteria in LT patients, while *Microsporidium*, *Cryptosporidium*, *Isospora belli*, *Cyclospora*, and *Giardia lamblia* are the protozoans. Immunosuppression post LT could reactivate quiescent *Strongyloides stercoralis*.

EBV-associated oral hairy leukoplakia, Kaposi sarcoma lesions, mucosal warts, aphthous stomatitis from sirolimus, and gingivitis from cyclosporine are some oral lesions encountered in LT recipients. Reduced or modified immunosuppression and appropriate antiviral therapy are recommended. Non-healing or potentially malignant lesions warrant biopsy.

Diverticulitis is the most common cause of colonic perforation (1–2% incidence and 20–30% mortality) after abdominal organ transplantation followed by ischemic colitis and CMV colitis [16,17]. Reduced colon wall integrity due to lymphodepletion, retraction on the colon during surgery, and non-obstructing colonic dilatation in the early postoperative period causing postoperative ileus, could cause right-sided colonic perforation. Colonoscopy might decompress the colon and prevent a perforation.

Of the immunosuppressants currently in use, mycophenolate causes gastrointestinal side effects most often (27%), resulting in its discontinuation. Steroids are linked to peptic ulcers, but meta-analysis of patients on corticosteroids indicated that this complication is rare. Symptomatic peptic disease should be investigated and treated with acid suppression medicines or antibiotics as indicated.

Nutritional Complications

Nutritional problems are common in pretransplant ESLD patients and can lead to adverse outcomes, including decreased patient and graft survival. Reported protein-energy malnutrition (PEM) prevalence is almost 100% regardless of liver disease etiology, but is more prevalent in hospitalized alcoholic liver disease patients. Since the nutritional status of the ESLD patients may deteriorate while awaiting LT, nutrient/muscle depletion and vitamin/mineral deficiencies must be corrected. The total calories provided should be at least 1.2 times the basal energy expenditure (BEE); approximately 30–35 kcal/kg/day (60–70% of calories) from high-complex and simple carbohydrates and without protein restriction (up to 1.8–2.0 g/kg/day) [18,19].

In the immediate postoperative period, protein catabolism increases markedly due to stress, renal dysfunction, and sepsis, if present. Energy requirements do not rise significantly in uncomplicated transplant recipients, so calories equivalent to 120–130% of BEE calculations are generally adequate in the absence of pre-existing malnutrition. Recipients should receive 1.5–2.0 g of protein per kilogram (dry weight) during this period. If nutritional replacement therapy is required, oral supplements and nasoenteric tube feeding are preferred over total parenteral nutrition (TPN), and should continue until adequate oral intake stabilizes. This minimizes postoperative infection and metabolic complications associated with TPN. Common electrolyte abnormalities, particularly depletion of potassium, phosphorus, and magnesium, require close monitoring and supplementation.

Wound Complications

Possible wound complications include superficial to deep wound dehiscence or fascial dehiscence, perigraft fluid collection deep to the muscular fascia/seroma, superficial or deep wound infection, cellulitis, and lymphocele. In LT recipients, incisional hernia incidence is 5–17%, and wound dehiscence is 27% [20]. Cephalad epigastric hernias are more prevalent after the standard Chevron incision. Postoperative ascites may protract wound healing, causing hernia formation. Risk factors for wound infections include body mass index (BMI) over 30 kg/m^2, advanced age, surgical factors, co-morbidities, a depressed immune system, and concurrent abdominal infection pre LT. Immunosuppressants like mycophenolate, combined with CNIs and steroids, promote wound complications more than azathioprine. Steroids and sirolimus hinder wound healing.

Depending on severity and underlying factors, management ranges from simply packing the wound with gauze and waiting for secondary healing, to surgical intervention such as drainage or debridement with or

without closure, to stimulating healing with the vacuum sealing method. Deep-wound or fascial dehiscence and symptomatic incisional hernias require surgical repair.

Case continued

At 1-year follow-up the patient had gained weight. His fasting lipid profile was abnormal and diabetes was poorly controlled. Bone mineral density assessment showed deterioration. He confessed to resumption of tobacco smoking. Graft function was excellent but liver enzymes were slightly high. Allograft liver biopsy showed grade 2 and stage 1 hepatitis C virus (HCV) activity.

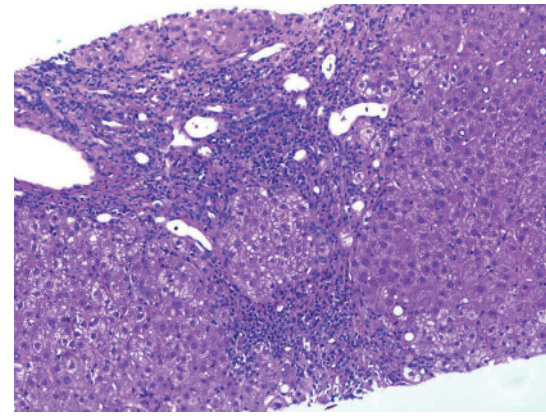


Figure 32.8 Recurrent hepatitis C infection. Predominantly lymphocytic portal hepatitis with interface hepatitis and fibrous expansion characteristic of recurrent hepatitis C. Note that the bile ducts are not damaged in contrast with acute rejection (courtesy of Raouf E. Nakhleh MD, Department of Pathology, Mayo Clinic Jacksonville).

Disease Recurrence and Complications

Hepatitis C

HCV recurrence/infection of the allograft is problematic among LT recipients with HCV infection. Allograft infection occurs immediately after reperfusion. Typically, serum HCV RNA levels increase rapidly around the second postoperative week and peak by the fourth month. Approximately 2–5% of patients develop severe cholestatic hepatitis leading to early graft failure. After 1 year, HCV RNA levels average 10–20-fold greater than pretransplant levels. Although hepatic fibrosis may accelerate post transplantation and cirrhosis occurs in 6–30% of patients within 5 years, approximately 30% show no evidence of fibrosis even after 5 years [21,22]. Factors influencing severe HCV recurrence and progression after transplantation include high pretransplant viral load (30% greater), living donor, donor over 50 years, warm ischemia time exceeding 60 min, graft steatosis, initial immunosuppression regimen, CMV infection, and multiple rejection episodes requiring treatment, especially with steroids (transient 4–100-fold increase in HCV RNA levels) and muromonab CD3 (OKT3). CNI impact on post-transplant HCV infection is unclear, and mycophenolate appears neutral or beneficial in the long term. Data conflict on interleukin-2 receptor antibodies and recurrence of post-transplant HCV infection.

Elevated liver enzymes in an HCV-infected LT recipient requires investigation into HCV recurrence. Confirmation often necessitates liver biopsy. Histologic features include prominent lobular inflammation, focal necrosis, acidophilic bodies, and macrovesicular steatosis (Figure 32.8). Lymphoid aggregates in portal tracts, interlobular bile duct damage, macrovesicular steatosis, and lobular infiltrates with apoptotic bodies indicate chronic changes. Although acute cellular rejection and recurrent HCV infection share certain histologic findings that complicate diagnosis, endothelialitis observed in rejection assists differentiation.

Prophylactic anti-HCV therapy prior to LT and preemptive antiviral therapy, that is within 2–6 weeks post LT, have limited roles but cause adverse effects in ESLD patients. A liver biopsy demonstrating a Metavir fibrosis grade greater than 1 with ongoing necroinflammatory activity suggests the need for therapy. Pegylated interferon initiated at full or reduced dose and ribavirin typically initiated at 600 mg/day and gradually increased to 1000 mg/day (800 mg/day for genotype 2 or 3) should continue for 48 weeks, except in genotype 2 and 3 patients achieving rapid viral clearance (24-week treatment). Several uncontrolled trials of pegylated interferon plus ribavirin reported significant variation in sustained viral response (22–59%); response predictors were early viral response, course completion, and favorable genotype.

Twenty percent develop worsening fibrosis despite viral clearance.

Therapy is associated with significant dose reductions and discontinuation of treatment due to adverse effects. Myelosuppression from interferon therapy is notable and half the cases require treatment. Ribavirin induces dose-related hemolysis requiring close monitoring of recipient renal function and appropriate dose adjustment, especially with CNI use. Though reports of acute and chronic rejection exist for interferon-based therapy, there is no compelling evidence for this.

Graft failure with recurrent HCV infection requiring retransplantation is on the rise. Studies demonstrate lower survival in these instances, predictors being shorter interval from first transplantation, bilirubin greater than 10 mg/dL, and serum creatinine greater than 2 mg/dL. Decisions to retransplant are case and transplant-center dependent.

Hepatitis B

Allograft infection with hepatitis B virus (HBV) can occur at reperfusion or delayed exposure related to persistent viral replication in extrahepatic sites. Risk factors for HBV recurrence include high HBV DNA titers and insufficient post-transplant HBV prophylaxis, acquired resistance to prophylaxis, and presence of hepatitis B-e antigen. Mutations in the HBV genome in either the surface antigen or the *YMDD* motif rarely cause breakthrough infection.

Post-transplant prophylaxis of HBV patients with hepatitis B immune globulin (HBIG) and therapy with oral nucleotide and nucleoside greatly decrease HBV recurrence. Most prophylactic regimens include high doses of HBIG (10 000 IU) in the anhepatic phase followed by daily dosing for the first week after transplantation. Subsequent treatment includes fixed and variable dosing schedules and intravenous/intramuscular administration to maintain anti hepatitis B surface antibody titers at 500 IU/L during the first week post-transplantation, 250 IU/L during weeks 2–12, and 100 IU/L after week 12 to minimize recurrence risk. The median rate of recurrent HBV in patients receiving long term HBIG therapy is approximately 20% (range: 5–50%) over 1–2 years [23]. Optimal durations of HBIG in patients receiving combination therapy with a nucleoside analog are unknown. Post-transplantation vaccination is a promising strategy requiring further research.

Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) recurrence post LT is approximately 11–23% with no correlation between antimitochondrial antibody titers and clinical or histologic recurrence. Average recurrence occurs at 3–7 years. The histologic hallmark remains granulomatous bile duct destruction. Lymphocytic cholangitis, ductular proliferation, ductopenia, and portal mononuclear infiltrates are not PBC specific and florid duct lesions may appear with HCV and ischemic cholangitis. Processes like acute or chronic rejection, graft-versus-host disease, biliary obstruction, viral hepatitis (HCV, HBV, CMV), and drug effects are in the histologic differential diagnosis.

Optimal immunosuppression to prevent PBC recurrence and ursodeoxycholic acid to treat recurrence remains controversial. Progression of recurrent PBC is often slow and may not necessitate retransplantation.

Primary Sclerosing Cholangitis

Post-LT PSC recurrence ranges from 9% to 47%. Hepatic arterial occlusion and preservation injury-related ischemic strictures should be considered in cholangiographic and histologic differential diagnosis. The rate of intrahepatic and non-anastomotic extrahepatic strictures is also higher (47% compared to 13% in controls), along with fibrous cholangitis (27% versus 5%) and obliterative lesions (14% versus 0%) in recipients who underwent the Roux-en-Y procedures [24]. Balloon dilation with or without placement of stents, surgical revision, or retransplantation are therapeutic options for biliary strictures. Fifteen percent of the transplant recipients require retransplantation likely due to biliary complications, disease recurrence, and chronic rejection.

Autoimmune Hepatitis

The autoimmune hepatitis reported recurrence rate is 16–46% in different case series, with limited data on recurrence time. HLA-DR3-positive recipients of HLA-DR3-negative grafts appear to be at risk for recurrent disease. Clinical, biochemical, serologic, and histologic criteria must be met, and rejection, viral infections, drug effects, and biliary obstruction must be excluded to diagnose recurrent disease. Increased immunosuppression maintenance is the preferred therapy.

Alcoholic Liver Disease

Recurrence of histologically significant liver disease from the direct effects of alcohol is rare and death following recurrence occurs in at most 5% of recipients. Predictors of relapse include duration of abstinence from alcohol and amount of daily alcohol consumption prior to transplantation. *De novo* oropharyngeal cancers, cardiovascular complications, increased use of tobacco, acute pancreatitis, and polyneuropathy are found more commonly among relapsers than abstinent patients.

Non-Alcoholic Steatohepatitis

Non-alcoholic steatohepatitis (NASH) recurs in 11–38% of LT recipients. While steroids use is a risk factor, weight gain after transplantation may contribute. Recognition of NASH is important as it may affect graft survival.

Hepatocellular Carcinoma

With well-defined selection criteria for LT patients with hepatocellular carcinoma (HCC), recurrence rates are low and survival is comparable to other diseases requiring LT. Predictors of HCC recurrence post-transplantation include poorly differentiated tumor, satellite lesions, portal vein invasion, tumor rupture, and lymph node involvement prior to transplantation.

Metabolic Complications

Dislipidemia

After LT, 16–43% of recipients develop increased plasma cholesterol levels and about 40% develop hypertriglyceridemia. Contributing factors include medications, dietary habits, and genetic control of the recipient peripheral lipid metabolism and the liver allograft. CNIs inhibit bile acid 26-hydroxylase, increase hepatic lipase activity, and decrease lipoprotein lipase activity. Corticosteroids cause weight gain, increase insulin resistance, acetyl-CoA carboxylase, free fatty acid synthetase, and HMG CoA reductase activity, and reduce lipoprotein lipase and the low-density lipoprotein (LDL) receptor activity. Up to 44% of patients receiving sirolimus develop dislipidemia.

Recommendations for LT recipients are similar to those for the general population; LDL cholesterol less than 100 mg/dL in very high-risk patients, less than or equal to 130 mg/dL in moderate high-risk patients and less than or equal to 160 mg/dL in low- or no-risk patients. Dietary modifications (cholesterol intake of <200–300 mg/day, total fat restriction to 25–30% of daily calories, saturated fats less than 7%, decreased amounts of *trans*-fatty acids, and increased intake of soluble dietary fibers) and HMG-CoA reductase inhibitors are treatment options. The choice depends on atherosclerotic cardiovascular risk stratification. Concern exists for drug interactions between CNIs and statins metabolized by the cytochrome CYP3A4; hence, statins should commence at the lowest dose and be gradually titrated upward using pravastatin, which has the least potential interaction. Use caution when calcium channel blockers are initiated as they may elevate statin levels.

Obesity

Onset and prevalence of obesity in LT recipients is 30–70%. Pathogenesis includes genetic factors, decreased physical activity, immunosuppressants (tacrolimus causes less weight gain than cyclosporine), diabetes, and dietary habits. Additionally, LT recipients who have preexisting obesity require postoperative management. Management includes dietary measures and counseling, enrollment in weight loss programs, exercise, pharmacologic agents, and bariatric procedures in select cases. For severe or morbid obesity, steroid-free immunosuppression should be considered or relatively lower doses given if the former is not feasible. Pharmacologic agents and bariatric procedures have not been adequately evaluated in the post-LT setting.

Diabetes Mellitus

The overall incidence of diabetes mellitus in LT recipients is approximately 15% and develops in 20–40% within the first year. Risk factors include older recipient age, family history, Afro-Caribbean race, obesity, preexisting impaired glucose tolerance, HCV infection, and use of corticosteroids and tacrolimus therapy, the greatest risk being corticosteroids dose and duration. Tacrolimus is more diabetogenic than cyclosporine.

In the immediate post-transplant period, insulin is routinely employed for optimal control of hyperglycemia. With hyperglycemia control as the goal, oral agents and insulin are instituted in stepwise fashion. Insulin monotherapy is preferred in patients with ketosis or symptomatic hyperglycemia. The International

Consensus Guidelines for solid organ recipients indicate measuring the fasting plasma glucose weekly for the first month after transplant, then at 3, 6, and 12 months post transplant, and subsequently every year. An HbA1c of less than 7% is ideal.

In LT recipients, only thiazolidinediones were studied, which demonstrated effective improvement of glycemic control. Thiazolidinediones may cause weight gain and are contraindicated in heart failure. Sulfonylureas and metformin should be avoided in severe renal impairment but the latter may be useful in overweight patients; meglitinides may be the safest. Alpha-glucosidase inhibitors frequently cause intolerable gastrointestinal side effects. Steroid reduction/withdrawal and conversion from tacrolimus to cyclosporine are effective strategies for managing diabetes after LT.

Gout

Recognition of hyperuricemia as an independent risk factor for insulin resistance, cardiovascular disease, and gout renewed interest in hyperuricemia management. Hyperuricemia and gout are less common in LT recipients than in other solid-organ recipients, with occurrence ranging from 5% to 84% for hyperuricemia and 1.7–28% for gout [25]. The risk increases in patients receiving cyclosporine therapy, but the mechanism by which cyclosporine contributes to hyperuricemia is not understood. The relationship between blood concentrations of CNIs and serum uric acid is inconsistent.

As in the general population, gout in transplant recipients is more common in men than women. It most often affects the first metatarsophalangeal joint but the sacroiliac joints may be affected also. The mean length of time before an initial attack of gout is between 17 and 24 months post transplant.

Acute gout attack management includes cautious use of non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, or corticosteroids with careful monitoring for potential interactions with transplant-related drugs. The combination of colchicine and cyclosporine appears to predispose patients to colchicine myotoxicity. The urate-lowering hypouricemic agent allopurinol interferes with azathioprine inactivation by inhibition of xanthine oxidase, leading to increased mercaptopurine and myelosuppression. The benzofuran derivative benzbromarone, a uricosuric agent, causes hepatotoxicity so liver enzyme monitoring is necessary. NSAIDs can precipitate acute renal failure, and long term use of oral corticosteroids could lead to intradermal tophi in renal-insufficient individuals.

Allopurinol 100 mg/day may be considered for patients with a history of gout. Acute gout may be treated with colchicine 0.6 mg every 2 h for up to five doses. If symptoms persist, a trial of a prednisone tapering regimen may be helpful.

Osteoporosis

Bone disease preceding transplantation, immunosuppressants, nutrition, lifestyle, and derangements of parathyroid–calcium–vitamin D and pituitary gonadal axes are important pathogenesis factors responsible for osteoporosis after LT. Glucocorticoids are most responsible for bone loss after transplantation, causing increased bone resorption. Animal models have shown that CNIs cause high turnover osteoporosis by stimulating osteoclast and osteoblast activity *in vivo*; resorption rates exceeding formation rates lead to a net loss in bone mass. Mycophenolate, sirolimus, and azathioprine show no effect on bone volume.

Due to antiresorptive mechanisms, bisphosphonates with calcium and vitamin D are preferred for prevention of glucocorticoid-induced osteoporosis. It is important to check vitamin D level in patients with osteoporosis and supplement as needed. Calcitonin may be of benefit in the late post-transplant period and is a safe alternative if other agents are contraindicated or poorly tolerated. Limited publications exist on replacement of sex steroids in transplant recipients with osteoporosis. Finally, glucocorticoid withdrawal may help improve osteoporosis.

Malignancy (Table 32.3)

Case continued

Concluding the annual visit, the patient promised to quit smoking after extensive discussion of oropharynx, esophageal, and lung cancers, and their association with tobacco smoking in LT recipients. After profound thanks to the transplant team for excellent care, the patient inquired about scheduling his next screening colonoscopy, and dermatology follow-ups in view of his past history of basal cell carcinoma.

Table 32.3 Malignancies post liver transplantation and suggested surveillance strategy.

Cancer	Type	Risk factors	Surveillance strategy (per risk factors)
Skin	SCC BCC	Fair skin Sun exposure History of SCC and BCC Actinic skin damage Alcoholic liver disease	1–3 years
Colon	Adenomatous polyps	UC History of neoplasia History of colonic neoplasia	1–5 years
Oropharynx Esophagus	SCC	Tobacco use Alcoholic liver disease Barrett esophagus	1–3 years
Lymphoma	PTLD—B cell	EBV seropositivity Aggressive immunosuppression Thymoglobulin	Periodic follow-up

SCC, squamous cell carcinoma; BCC, basal cell carcinoma; UC, ulcerative colitis; PTLD, post-transplantation lymphoproliferative disorders; EBV, Epstein–Barr virus; LT, liver transplantation.

The reported cumulative incidence of *de novo* malignancies after LT ranges between 5% and 50%, increasing with recipient's age, age at transplantation, and time since transplantation (6%, 20%, and 55% at 5, 10, and 15 years, respectively) [26]. Malignancy is reported more in LT recipients with alcoholic cirrhosis (27% versus 5%) [27]. Skin, colon, oropharyngeal, esophageal, and lung cancers in tobacco smokers are more common in LT recipients than in the general population. Tobacco and alcohol abuse prior to transplantation increase the risk of many post-transplantation malignancies.

Skin Cancer

Squamous cell carcinomas followed by basal cell carcinomas are the most common and aggressive malignancies in LT recipients; 20-fold higher risk with greater recurrence and metastases than age- and sex-matched general populations. Risk factors include fair skin and sun exposure but not immunosuppression. Dermatologic examination every year in LT recipients with a previous history of squamous and basal cell skin carcinomas and every 2–3 years in those with actinic skin damage or those with alcoholic liver disease is recommended.

Colon Cancer

The standardized incidence ratio for solid-organ recipients developing colon cancer is 2.5, with an increased risk of adenomatous colonic polyps compared to average-risk patients. Colon cancer occurs more often after LT in ulcerative colitis patients (7% within the first 2 years), requiring annual colonoscopy with random biopsies for dysplasia. Colonoscopy every 5–10 years in subjects with no previous history of colonic neoplasia and every 3–5 years in subjects with a previous history of neoplasia is suggested.

Oropharynx, Esophageal, and Lung Cancers

In general, the incidence of malignancies is increased in LT recipients transplanted for alcoholic liver disease. They are more prone to squamous cell carcinomas of the oropharynx or esophagus. Tobacco smoking is a recognized risk for the development of these carcinomas. No studies guide surveillance for these malignancies post LT, but otorhinolaryngeal examination every 1–3 years in alcoholic liver disease LT recipients and tobacco smokers is prudent.

Lymphoma

The majority of PTLD are B-cell malignancies associated with the Epstein-Barr virus with a strong predilection for hepatic infiltration in LT recipients. Risk factors include EBV seropositivity before transplantation and aggressive immunosuppression after transplantation, specifically thymoglobulin. Immunosuppression reduction, ganciclovir, and chemotherapy in refractory cases are management options in EBV-associated PTLD.

Vaccinations

LT recipients should receive vaccinations agai3(r pa0(v359(r PTLD359aa in EB4Tpients6me14(olog)-1(A(v)-1B30(c)13vaides obs(e B

Prudence discourages pregnancy when graft function is unstable and/or the interval from transplant is less than 24 months. Pregnancies in LT recipients should always be considered high risk and managed by a multidisciplinary team. Besides obstetric examinations, assessment of graft function, viral serology for hepatitis and CMV, microbiologic cultures of vaginal smears, and plasma levels of immunosuppressive drugs should be monitored closely. Allograft rejection may necessitate interruption of pregnancy. Vaginal delivery is possible.

Long term data on the offspring of transplant recipients are limited but show no increase of congenital anomalies.

Compliance

Recipient non-compliance rates reach 20–50%, causing potential organ loss. Compliance peaks during the early post-transplant period and decreases over time. Medical adherence depends on the type, number, and daily doses of drugs prescribed, with quantity less significant than daily dose; schedule compliance drops from 70% (once daily) to 20% (four times daily). Medication side effects (64%), long term effects (15%), cost (16%), and difficulty of use (14%) influence patients negatively, so a tailored regimen is necessary [30]. Medication non-compliance and appointment non-compliance are related. If appointment non-compliance persists, medication non-compliance should be suspected and addressed.

Considerably fewer patients return to pretransplant alcohol abuse. Studies show a 15% mean relapse rate, far below those found after inpatient detoxification therapy. However, most patients smoking tobacco prior to LT continue to do so in the second postoperative year.

within 72 h and differs in severity and recovery. Primary non-function requires emergent retransplantation but preservation injury generally improves within 3 days.

- The risk of hepatic artery anastomosis complications ranges from 5% to 15%. Hepatic artery thrombosis (58%), hepatic artery stenosis (31%), and hepatic artery kinks (6%) are the common complications. Management includes angioplasty with approximately 80% success. Anticoagulation and antiplatelet therapies are not standard therapies.
- The most common biliary complications are leaks and strictures with one-third of biliary complications occurring within 1 month of surgery and 80% within 6 months. Mortality rates are up to 10%. Endoscopic management of bile leaks has a success rate of greater than 95%. Dilation and stenting of strictures has a success rate of greater than 70% but those related to vascular insufficiency are less responsive (<28%).
- Cyclosporine and tacrolimus in combination with tapered corticosteroids are commonly used immunosuppressants. Close monitoring of their therapeutic level, drug–drug interactions, renal, metabolic, neurogenic, and infectious complications is necessary.
- Acute allograft rejection, characterized by lymphocyte-infiltrated portal tracts, damaged bile ducts and venular inflammation, responds to increased immunosuppression or high-dose corticosteroids. Severe rejection requires thymoglobulin or muromonab CD3 (OKT3).
- Transplant recipients are prone equally to infections from opportunistic pathogens and reactivation of donor or recipient viruses, especially during acute rejection treatment with high-dose corticosteroid or antilymphocyte antibodies. Prophylaxis in the immediate postoperative period is common.
- Post-transplant acute renal failure is multifactorial and varies between 48% and 94%, with 8–17% of patients requiring dialysis. Optimal immunosuppression requires normal renal function and hence, any dysfunction affects graft survival. Risk of chronic kidney disease, mostly due to calcineurin inhibitor toxicity, is 18.1–27.5% at 5 years. Approximately 3% require kidney transplantation eventually.
- Hepatitis C recurrence/infection of the allograft is a major problem, resulting in graft loss requiring retransplantation, which is on the rise. Metavir fibrosis grade greater than 1 with ongoing necroinflammatory activity may require therapy. Pegylated interferon plus ribavirin therapy has a varying sustained viral response of 22–59%. When unresponsive to treatment, cirrhosis occurs in 6–30% of patients within 5 years.
- Cardiovascular events range from 9% at 5 years to 25% at 10 years, accounting for 21% of deaths of recipients surviving more than 3 years due to an increase in the prevalence of hypertension, diabetes mellitus, dyslipidemia, and obesity. Metabolic complications are on the rise due to an improvement in survival rates resulting from advances in surgical techniques and immunosuppression.
- *De novo* malignancies after transplantation range from 5% to 50%, reported more in recipients with alcoholic cirrhosis (27% versus 5%) and tobacco abuse history prior to transplantation. Based on individual risk factors, tailored surveillance is necessary.

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VII

PART 7

Problem-based Approach to Biliary Tract and Gall-bladder Disease

33

CHAPTER 33

Gall Stones, Gall-bladder Polyps and Their Complications: Epidemiology, Pathogenesis, Diagnosis, and Management

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Summary
Gall stones are common in the USA, and diseases associated with gall stones are a significant cause of morbidity and mortality. Cholesterol gall stones are the most common kind in Western populations, resulting primarily from biliary stasis and altered cholesterol metabolism. Risk factors for cholesterol gall stones include advancing age, female gender (especially among people of Hispanic origin), obesity, diabetes, and family history. Gall stones most commonly cause cholecystitis, but can also present as cholangitis, pancreatitis, or symptomatic choledocholithiasis, and uncommonly may result in gall-stone ileus or Mirizzi syndrome. The clinical presentations of gall-stone-related diseases are widely variable, ranging from asymptomatic stones detected incidentally to severe pain with biliary colic or even multisystem failure associated with necrotizing cholecystitis, cholangitis, or pancreatitis. Gall-stone-related diseases can often be diagnosed non-invasively through clinical presentation in concert with ultrasonography, computed tomography, or magnetic resonance cholangiopancreatography. Laparoscopic cholecystectomy is the treatment of choice for symptomatic cholelithiasis, and may be offered for asymptomatic cholelithiasis in select groups. For choledocholithiasis and its complications, management usually involves both endoscopy and surgery. Endoscopic retrograde cholangiopancreatography (ERCP) is indicated when there is ongoing evidence of choledocholithiasis, unless the surgeon plans intraoperative bile duct clearance. ERCP is usually performed before surgery, but can be performed postoperatively in expert centers where stone extraction is routinely successful. For gall-stone pancreatitis, cholecystectomy should be performed early after recovery from the acute injury to reduce the risk of further episodes of pancreatitis. A laparoscopic approach is preferred, and again may include bile duct clearance, depending on local expertise. Gall-bladder polyps are uncommon and usually identified incidentally by ultrasonography. Polyps are significant in the gall bladder because some have malignant potential; their management is also surgical.

Gall Stones

Epidemiology

Gall-stone-related diseases are common in Western countries. The prevalence of gall stones is more than 10% in the USA and in European countries based on ultrasound studies [1]. Gall-stone-related disease was the most common inpatient gastrointestinal (GI) diagnosis, the fourteenth most frequently diagnosed condition overall, and accounted for almost 800 000 clinic visits and an estimated 750 000 cholecystectomies in the USA during the year 2000 alone. Cholecystitis was also among the top 20 causes of GI-related deaths [2].

Practical Gastroenterology and Hepatology: Liver and Biliary Disease, 1st edition. Edited by Nicholas J. Talley, Keith D. Lindor and Hugo E. Vargas.

The economic burden of gall-stone-related diseases is high, with total costs in the USA estimated to be US$5.8 billion per annum, which among digestive diseases is second only to reflux disease and exceeds the costs associated with colorectal cancer [3]. Among hospital admissions related to digestive disease, gall-stone disease is the most common diagnosis and has the highest cost per admission of over US$11 000 [2].

Although a genetic basis for gall-stone disease has not been clearly elucidated, inherited risk factors include sex and ethnicity. Among the more than 20 million Americans estimated to have gall-bladder disease, over 80% are female [4]. Women have a higher prevalence at all ages, with the exception of ages over 60 when men have parity with women. Among all patients with gall-bladder-related diseases, the highest prevalence is in women of Hispanic origin (26.7%). Non-Hispanic white women comprised the second largest group (16.6%), followed by African–American women (13.9%). Hispanic and non-Hispanic white men exhibited similar prevalence of gall-bladder disease at 8.9% and 8.6%, respectively, and African–American men have the lowest prevalence at 5.3%. Other risk factors that affect both men and women are older age, high body mass index (BMI), and lower alcohol consumption. Additional risk factors unique to women are smoking, higher number of live births, lower serum cholesterol level, as well as lower physical activity. Gall-stone disease is prevalent among people with diabetes, but it is not clear that diabetes itself confers an increased risk, because obesity, advancing age, and family history are shared risk factors for both gall-stone disease and diabetes [5].

Pathogenesis of Gall Stones

Bile plays an essential role in multiple physiologic processes including lipid digestion, cholesterol homeostasis, and hepatic toxin and metabolite excretion. It is composed of bile acids, water, inorganic electrolytes, phospholipids, and bile pigments. Bile acids are synthesized in the liver from cholesterol, stored in the gall bladder, and recycled through the enterohepatic circulation.

Stones form as a result of disruption of any of the complex mechanisms of synthesis and storage of bile and/or cholesterol. There are three main types of stones: cholesterol, black pigment, and brown pigment. Biliary sludge is similar to cholesterol stones in pathophysiology and composition.

Cholesterol stones form when there is overaccumulation of cholesterol in the setting of gall-bladder stasis. Cholesterol accumulation begins with oversaturation, as the result of either an increase in the synthesis and secretion of cholesterol or a decrease in the levels of bile salts, which are required to maintain cholesterol within water-soluble micelles or vesicles. When cholesterol is not so maintained, it can form aggregates that can then further accrue into crystals and ultimately stones. Gall-bladder stasis seems to play a role in this aggregation process, although the mechanisms of aggregation are not fully elucidated.

Brown and black pigment stones have distinct causes. Brown pigment stones form as a result of biliary infections and usually originate within the common bile duct rather than the gall bladder. Black pigment stones are composed mainly of calcium and unconjugated bilirubin. They form in the setting of excess bilirubin, which can occur with hemolysis, cirrhosis, and acute pancreatitis.

Case

A 48-year-old man with no significant past medical history presented to the emergency department 12 hours after an hour-long episode of moderately severe epigastric abdominal pain that radiated through to his back. He was afebrile. Physical exam revealed an overweight male with mild epigastric tenderness without rebound. There was no jaundice. Lab studies were notable for an alkaline phosphatase (AP) of 359 (55–142 IU/L), ALT 374 (7–45 IU/L), AST 276 (8–43 IU/L), total bilirubin 1.7 (0.1–1.1 mg/dL), and lipase 640 (7–60 IU/L). He was diagnosed with acute pancreatitis. He underwent an abdominal ultrasound, which showed multiple small gall stones and a normal-calibre common bile duct, and an abdominal computed tomogram which showed mild peripancreatic fat stranding and a normal pancreatic duct, as well as a normal common bile duct without filling defects.

Clinical Features

A gall stone may cause disease anywhere along its potential trajectory, beginning within the gall bladder and extending to its point of impaction within the bowel. Uncomplicated gall-stone disease results from stones localized within the gall bladder, and includes both asymptomatic gall stones and stones that temporarily cause symptoms but do not lead to frank gall-bladder inflammation. Complicated gall-stone disease occurs most commonly when the stone becomes persistently

Table 33.1 Features of biliary colic and common complications of gall stones.

	Symptoms/Signs	Lab studies	Imaging
Biliary colic	Episodic pain Poorly localized, epigastric or RUQ ± nausea and vomiting Follows meals	Normal	Ultrasonography: Normal or gall stones
Acute cholecystitis	Recurrent pain similar to biliary colic, may localize to RUQ May or may not relate to meals Murphy sign Fever Palpable gall bladder (uncommon)	Leukocytosis Mild elevations in bilirubin or alkaline phosphatase, lipase, or amylase (uncommon)	Ultrasonography: gall stones, thickened gall-bladder wall, pericholecystic fluid, radiological Murphy sign HIDA: non-filling of gall bladder
Choledocholithiasis	Asymptomatic Biliary colic Cholangitis Pancreatitis	Varies with complications Elevated bilirubin, lipase/amylase, or alkaline phosphatase	Ultrasonography, EUS, MRCP, ERCP: CBD stone and/or dilation
Cholangitis	Charcot triad: RUQ pain, jaundice, and fever One or two of these symptoms or signs, without the complete triad Reynold pentad: Charcot triad with hypotension and altered mental status	Leukocytosis Mild-to-moderate elevation in bilirubin, alkaline phosphatase, lipase or amylase Frequent bacteremia	Ultrasonography, MRCP, ERCP: CBD stone and/or dilation

CBD, common bile duct; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasonography; HIDA, hepatic iminodiacetic acid; MRCP, magnetic resonance cholangiopancreatography; RUQ, right upper quadrant.

impacted at the cystic duct, leading to gall-bladder wall inflammation or cholecystitis. Passage of the stone beyond the cystic duct may give rise to additional complications including biliary obstruction, cholangitis, and gall-stone pancreatitis (Table 33.1).

Effective management of gall-stone disease requires a thorough understanding of the natural history of the disease process, its symptoms and signs, the benefits and limitations of diagnostic studies, and options for medical therapy, as well as the availability of local expertise. Treatment can range from observation alone to urgent surgery, depending upon the acuity and severity of the disease, and often requires multidisciplinary teamwork of surgery, therapeutic endoscopy, and interventional radiology.

Uncomplicated Disease

Symptomatic gall stones occur in a minority of patients with gall stones. Biliary colic, which is actually constant rather than intermittent or "colicky" pain, is attributed to a gall stone obstructing the biliary neck. It is classically described as an intense, persistent, epigastric, or right upper quadrant (RUQ) pain, lasting from 15 min to several hours, often associated with nausea or vomiting, and may follow a large or fatty meal. Many patients, particularly older adults, may present with less classic symptoms such as poorly localized pain with abrupt onset or relief of the pain and no precipitating meal, so a high index of suspicion is important to recognize the symptoms before the development of complications. Among patients with initially asymptomatic gall stones, the estimated 5-year risk of developing biliary colic requiring treatment is approximately 7% [6]. Among those patients with biliary colic, most will have repeated attacks of pain, and 1–2% will progress annually to complicated disease requiring surgery [7]. Recognition of biliary colic provides an opportunity to treat the disease before the development of complications: most patients who ultimately develop complicated disease will have previously had symptoms.

Investigation of uncomplicated cholelithiasis should start with a transabdominal ultrasound scan and laboratory testing to confirm the presence of stones and assess for complications. Ultrasonography is a sensitive and specific imaging study for demonstrating stones within

the gall bladder. In uncomplicated cholelithiasis, serum studies should be normal. Elevated liver tests, pancreatic enzymes, or leukocytosis may reflect choledocholithiasis or a related complication (see below). If the diagnosis is still questionable after ultrasonography, a radionuclide or hepatic iminodiacetic acid (HIDA) scan is useful.

Laparoscopic cholecystectomy is currently the first-line treatment for symptomatic cholelithiasis. Lithotripsy and medical dissolution therapies are generally no longer used because of the high rate of recurrence of gall stones. For asymptomatic cholelithiasis, laparoscopic cholecystectomy is not routinely recommended, but may be helpful in special circumstances. Elective laparoscopic cholecystectomy should be considered in patients planning to travel to remote areas where complications could not be well managed, and those in groups at higher risk of development of symptomatic disease such as Native Americans, patients with sickle cell disease, children, morbidly obese individuals, and patients undergoing bariatric surgery (Figure 33.1). In the past, diabetic patients with asymptomatic gall stones were advised to consider prophylactic cholecystectomy because of the perception of higher surgical risk; more recent studies determined that people with diabetes do not have significantly different outcomes than those without diabetes if treated in a standard fashion [8].

"Porcelain gall bladder" is the term used to describe a brittle, bluish-appearing, calcified gall bladder. It is generally seen in association with cholelithiasis, although its pathogenesis is unclear. Often, it is identified incidentally on routine radiograph studies. Porcelain gall bladder may be associated with gall-bladder cancer; it has been suggested that the risk varies with the calcification pattern seen on ultrasonography [9]. Although a causal relationship has not been established, many experts advocate cholecystectomy for porcelain gall bladder even in asymptomatic patients. Until this issue is further clarified, cholecystectomy may be offered if there are no contraindications.

Complicated Disease

Acute Cholecystitis

Acute cholecystitis is the most common complication of gall stones, occurring in 20% of patients with symptomatic cholelithiasis [10]. Persistent gall-stone impaction in the gall-bladder neck, cystic duct, or Hartmann pouch causes gall-bladder stasis and inflammation. Although bacteria may be cultured in this setting, there is no clear evidence that infection is important in the initial pathogenesis of cholecystitis.

Patients with acute cholecystitis often present with protracted, progressive, biliary colic. Physical examina-

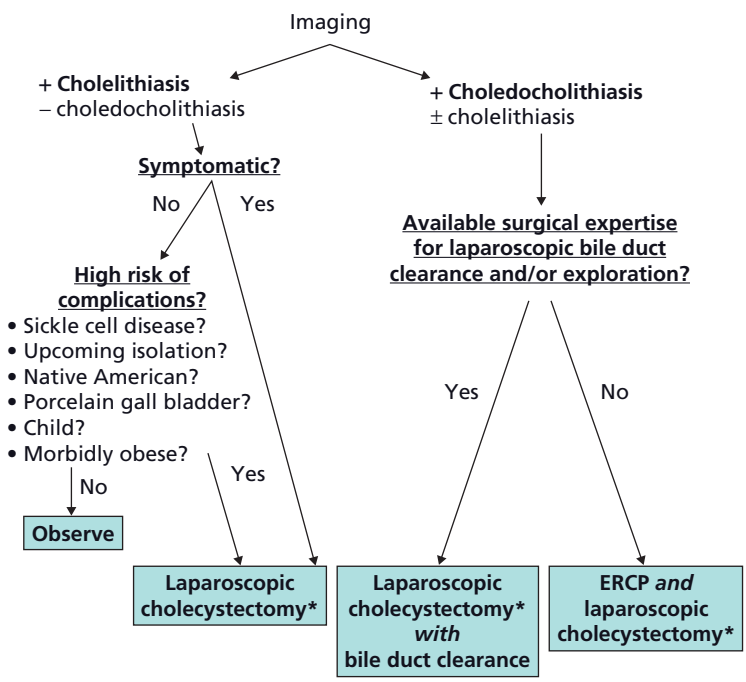


Figure 33.1 Management of uncomplicated gall stones: algorithm. Management depends on whether the patient has symptomatic cholelithiasis, and also choledocholithiasis. Cholecystectomy is indicated in select patients with asymptomatic cholelithiasis, in those who are symptomatic, or those who have evidence of choledocholithiasis, regardless of symptoms. Choledocholithiasis can be treated endoscopically or at the time of surgery. *Indications for open cholecystectomy: anatomic variant; coagulopathy; gangrene; suspect malignancy; polyps >18 mm; no local expertise in laparoscopic cholecystectomy. ERCP, endoscopic retrograde cholangiopancreatography.

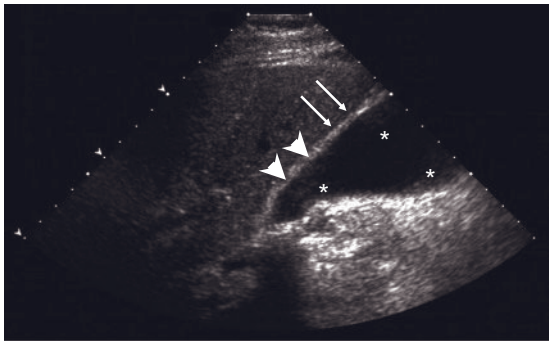


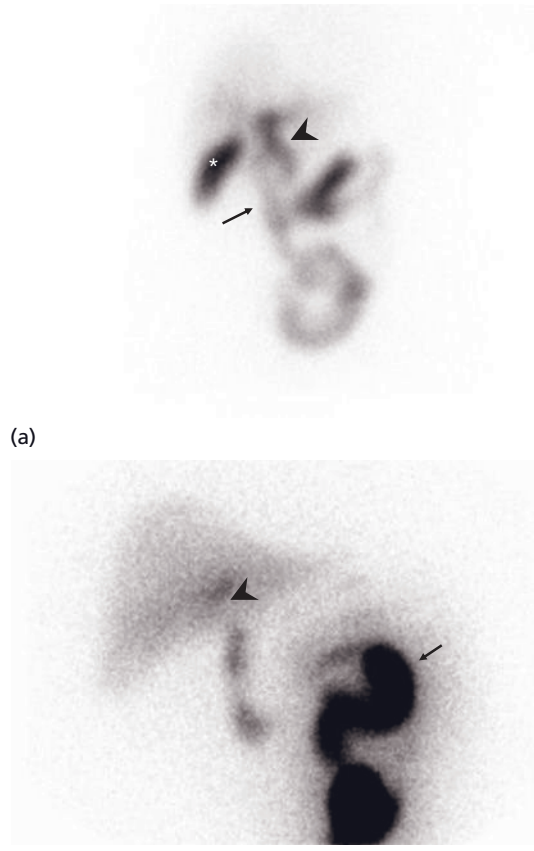
Figure 33.2 Ultrasound image of cholecytitis of the gall bladder demonstrates several small gall stones (asterisks). The gall-bladder wall is slightly thickened (arrowheads), with some fluid in the wall (arrows). These findings are consistent with acute cholecystitis. (Courtesy of MD Patel, MD, Department of Radiology, Mayo Clinic Arizona.)

tion may reveal RUQ tenderness and guarding; eventually one might palpate an inflamed gall bladder. The Murphy sign is specific for cholecystitis. Fever and leukocytosis are commonly present. The presence of jaundice is uncommon and generally mild, and should prompt consideration of choledocholithiasis or Mirizzi syndrome (see below). Initial evaluation includes imaging with ultrasonography (Figure 33.2) and often a HIDA scan (Figure 33.3). Ultrasound findings diagnostic of acute cholecystitis include cholelithiasis with gall-bladder wall thickening, pericholecystic fluid, and a positive sonographic Murphy sign.

HIDA has been shown to have a higher accuracy than ultrasonography (92% vs 77%), but ultrasonography is usually more readily available. A HIDA scan is therefore usually used to clarify an ambiguous ultrasound scan [11].

There is no broadly accepted diagnostic standard for acute cholecystitis. In an effort to codify the diagnosis, the Tokyo Guidelines from 2007 offer three categories of diagnostic findings; one criterion from each category must be fulfilled: (1) Murphy sign or pain/tenderness in the RUQ or an RUQ mass; (2) fever, leukocytosis, or elevated C-reactive protein; and (3) confirmation by ultrasonography or HIDA [12].

Laparoscopic cholecystectomy is the standard of care for patients with routine cases of acute cholecystitis. Preliminary medical management consists of intravenous hydration, with the possible addition of antibiotic therapy. Antibiotics have not generally been shown to be beneficial, but are a reasonable addition to surgical therapy if there is evidence of infection or a risk of complications from infection, as may occur in immunocompromised or elderly individuals. The laparoscopic approach reduces morbidity and length of hospital stay compared with open cholecystectomy, and has largely displaced open cholecystectomy even for most patients with more severe or complicated disease.



(a)

(b)

Figure 33.3 HIDA (hepatic iminodiacetic acid) images: tracer is injected intravenously and is selectively taken up by hepatocytes. It is then excreted into bile, and follows the path of outflow through the common bile duct (arrowhead) to the small bowel (arrow). (a) Anterior image of normal tracer uptake within the gall bladder (*). (b) Anterior image demonstrating non-filling of the gall bladder, suggesting acute cholecystitis with cystic duct obstruction. There is tracer in the common bile duct (arrowhead) and small bowel (arrow). (Courtesy of BD Nguyen, MD, Department of Radiology, Mayo Clinic, AZ.)

The timing of surgical intervention is controversial. Many surgeons argue for a "cooling-off" interval to reduce the risk of technically difficult surgery, which may require conversion to open cholecystectomy. A delay in surgery can, however, lead to other gall-stone-related

complications such as pancreatitis, obstructive jaundice, or recurrent or chronic cholecystitis. Although the controversy may persist, individual studies as well as meta-analyses have found no benefit from delaying surgery [13].

Case continued

He was admitted for volume repletion and pain management. His diet was slowly advanced and his abdominal pain did not recur. Repeat AST and ALT were normal; AP and total bilirubin were mildly elevated. General surgery was consulted and recommended a laparoscopic cholecystectomy. However, the patient wished to delay surgery as he felt an upcoming business meeting was of higher priority to him. He was dismissed 48 hours after presentation with plans for an elective cholecystectomy, scheduled in 3 weeks' time. Twelve days later, he returned with severe epigastric pain. He was febrile. Physical exam again revealed epigastric tenderness. Lab studies were notable for a mildly elevated white blood cell count, an AP of 463, ALT 3817, AST 4120, total bilirubin 2.3, and lipase 4119.

In patients with acute cholecystitis at high risk for surgery, such as acutely ill or elderly individuals, and those with significant comorbidities (e.g., cardiac disease, severe diabetes, cirrhosis), percutaneous cholecystostomy offers an alternative to urgent surgery for decompression of the gall bladder [14]. Using ultrasound guidance, cholecystostomy can be safely performed at the bedside with a high rate of success. Cholecystotomy gives time for the patient's condition to stabilize, allowing some patients to proceed to elective surgery, which has a lower mortality than emergency surgery. For patients who are not surgical candidates, percutaneous cholecystostomy also has been advocated as definitive treatment [15] (Figure 33.4).

Acalculous Cholecystitis

Acalculous cholecystitis is distinct from acute calculous cholecystitis in several ways. It is most commonly seen in

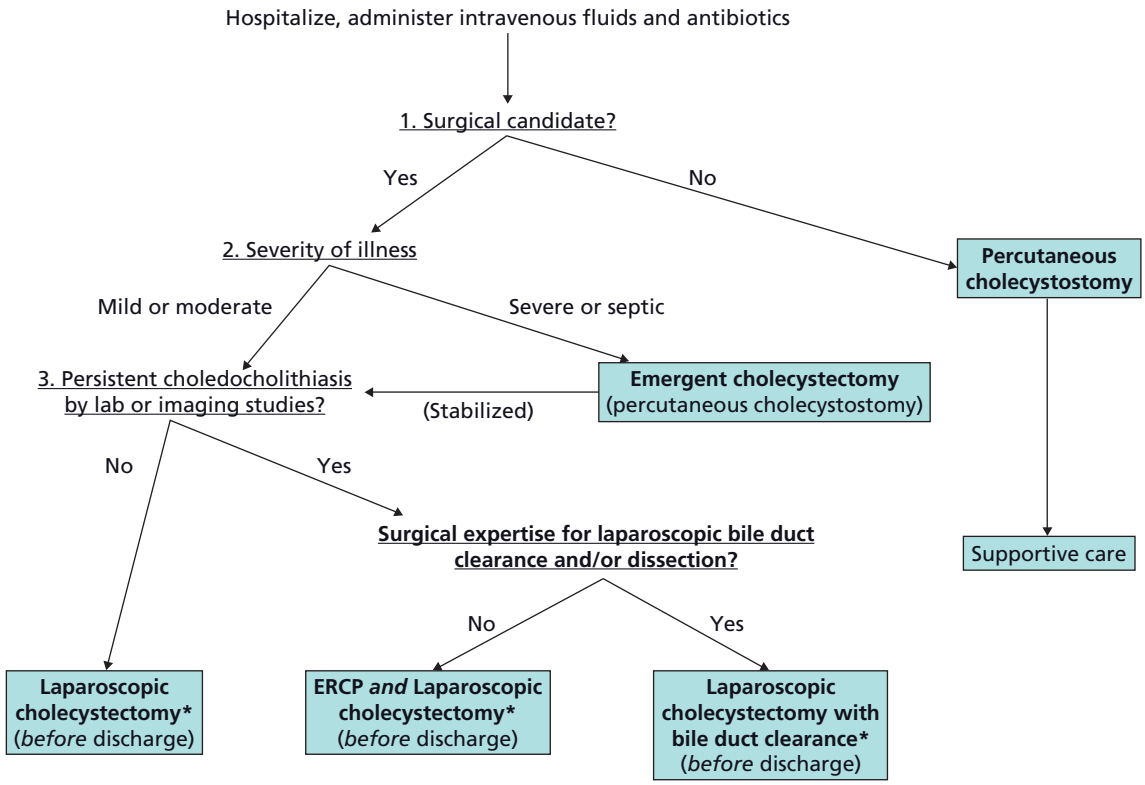


Figure 33.4 Management of acute cholecystitis: algorithm. Initially, the focus should be on stabilization and supportive care. Subsequent steps depend on the severity of illness and the patient's suitability for various possible interventions. Definitive treatment is a cholecystectomy, in suitable surgical candidates. *Indications for open cholecystectomy: anatomic variant; coagulopathy; gangrene; suspect malignancy; polyps >18 mm; no local expertise in laparoscopic cholecystectomy. ERCP, endoscopic retrograde cholangiopancreatography.

patients with severe underlying illness as well as in those receiving long-term parenteral nutrition. Cholecystitis is thought to occur through biliary stasis and ischemia, rather than through obstruction from a stone. As these patients are already quite ill, diagnosis can be delayed, and the combination of underlying illness and delayed diagnosis leads to high rates of complications and mortality. Complications include biliary gangrene or perforation, which occurs in over 50% of cases, and emphysematous cholecystitis, seen in 10% of cases. The overall mortality rate of acalculous cholecystitis is approximately 30% [16].

Diagnosis of acalculous cholecystitis requires a high index of suspicion; it should be considered early in critically ill patients. Physical examination is often not helpful, and laboratory studies are variable and non-specific, although jaundice and/or a palpable gall bladder are more commonly seen with this disease than with calculous cholecystitis. In the absence of symptoms and signs of the disease, imaging studies may be especially useful. The first study is usually ultrasonography, which may reveal pericholecystic fluid, wall thickening, or a positive Murphy sign. Computed tomography (CT) has very good sensitivity and specificity, but may not be practical for patients in the intensive care setting. CT should be performed secondarily, after indeterminate ultrasonography or in those patients who require more extensive evaluation for additional disease states. Diagnostic laparotomy or empiric percutaneous cholecystostomy may be justified in cases where imaging does not confirm the diagnosis.

Definitive management involves prompt cholecystectomy, as allowed by the patient's clinical condition. For patients who are not surgical candidates, percutaneous or surgical cholecystostomy can be temporizing, as can endoscopic retrograde transpapillary drainage. Antibiotics are an important adjunctive therapy in acalculous cholecystitis. Infectious disease consultation may be helpful to guide antibiotic selection, because patients with acalculous cholecystitis are often being treated with a complex antimicrobial regimen.

Emphysematous cholecystitis is an uncommon but potentially deadly type of acute cholecystitis, resulting from infection with a gas-forming organism. Similar to acalculous cholecystitis, it carries a high risk of gall-bladder gangrene and perforation. Emphysematous cholecystitis may occur in acalculous cholecystitis, or cholelithiasis may be present. Cholelithiasis has not been implicated specifically in the pathogenesis of the disease. Elderly men are the typical patients, many of whom have diabetes. The presentation may be similar to acute cholecystitis, although physical examination can occasionally disclose RUQ crepitus. Imaging with ultrasonography may not be diagnostic, because emphysema in the gall bladder can be confused with overlying bowel wall air. A CT scan is often useful when clinical suspicion is high. Management includes supportive care, antibiotics, and emergency or urgent cholecystectomy; in poor surgical candidates, percutaneous cholecystostomy should be considered [17].

Choledocholithiasis

Up to 15% of patients with cholelithiasis in the USA also have gall stones within the common bile duct (CBD) [18]. Patients with uncomplicated ductal stones may be asymptomatic, or they may present with symptoms of biliary colic. The natural history of untreated choledocholithiasis is not well delineated, but complications of choledocholithiasis include cholangitis and pancreatitis, and their secondary complications.

In uncomplicated choledocholithiasis, physical examination, laboratory results, and findings on imaging depend on the degree and duration of ductal obstruction. Physical examination may be unremarkable if there is no obstruction or only intermittent obstruction, or reveal jaundice, pruritus, and RUQ tenderness if there is prolonged or persistent obstruction. Laboratory tests may show evidence of biliary obstruction, with elevated total bilirubin (as high as 15 mg/dL) and elevated alkaline phosphatase. The alkaline phosphatase usually rises more quickly than the bilirubin, although the bilirubin level tends to better reflect the extent of ductal obstruction. Aminotransferases may be moderately elevated, although typically not as highly elevated as in acute hepatocellular injury. An acute elevation of the aminotransferases or new abnormalities of the amylase and/or lipase usually signal passage of a stone through the ampulla.

There are several options for imaging the CBD. Among non-invasive tests, transabdominal ultrasonography is currently the first-line study because of low cost and wide availability. Although it has a sensitivity of only approximately 50% for detecting stones in the CBD, it has a sensitivity of approximately 95% for identifying ductal dilation caused by obstructing stones. It is of limited use in obese patients or when there has been surgical manip-

ulation in or around the CBD. Abdominal CT with oral contrast has a sensitivity of approximately 92% for detecting ductal stones, and is especially useful as a first test when ultrasonography is not likely to be helpful [18]. Endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasonography (EUS), and magnetic resonance cholangiopancreatography (MRCP) have comparable sensitivities, specificities, and accuracies in diagnosing CBD stones [19]. ERCP has a sensitivity of 90–95% in detecting choledocholithiasis, but the role of ERCP in diagnosis is limited by its significant incidence of complications, particularly pancreatitis. ERCP is used for diagnosis primarily in cases in which the probability of choledocholithiasis is high and therapy is expected. EUS has a sensitivity for detecting a ductal stone of between 94% and 98%, which matches or exceeds that of ERCP, although it is less widely available. EUS is especially useful when there is low or intermediate suspicion of a ductal stone, where it provides sensitive diagnosis without the risk of ERCP. MRCP has sensitivity and specificity comparable to EUS, and can also be useful in providing detailed duct anatomy.

After diagnosis of choledocholithiasis, ERCP with sphincterotomy and stone removal is commonly performed, both to treat symptoms and to reduce the risk of complications (Figure 33.5).

Uncommonly, very large stones or stones in patients with altered anatomy from prior surgery may require percutaneous transhepatic decompression or surgical bile duct exploration. After bile duct clearance, patients are referred for laparoscopic cholecystectomy to prevent further complications of gall-stone disease, preferably during the same admission. In some centers, bile duct exploration and stone extraction may be performed intraoperatively during laparoscopic cholecystectomy without a preceding ERCP. This approach depends on appropriate surgical expertise, and even expert surgeons may prefer preoperative ERCP for choledocholithiasis recognized before surgery. Ursodeoxycholic acid is generally not effective for choledocholithiasis.

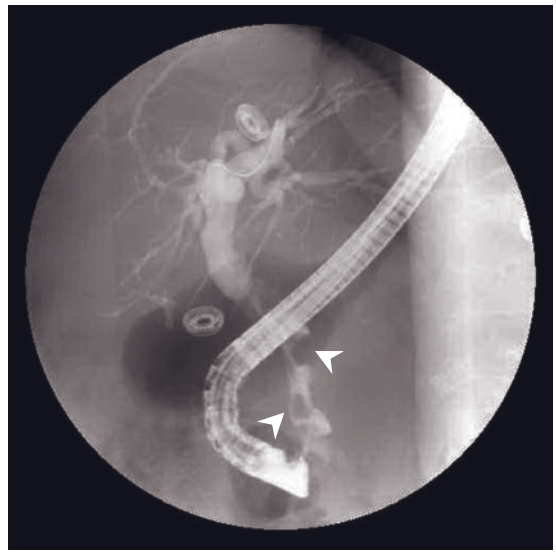


Figure 33.5 ERCP (endoscopic retrograde cholangiopancreatography) in choledocholithiasis. Cholangiogram is performed by cannulating and injecting dye into the common bile duct. It is used to elucidate intra- and extrahepatic bile duct anatomy. Here, cholangiography reveals two filling defects (arrowheads) consistent with retained gall stones, which in most cases can be extracted endoscopically. (Courtesy of ME Harrison, MD, Divisions of Gastroenterology and Hepatology, Mayo Clinic, AZ.)

Cholangitis

Cholangitis is infection and inflammation within the biliary tract. It occurs in the setting of biliary obstruction leading to bacterial stasis and proliferation. Obstruction is most commonly due to choledocholithiasis, but can also result from malignancy, external compression, biliary stricture from intrinsic biliary disease or previous surgical manipulation. Cholangitis can be rapidly fatal; it is one of a few indications for urgent ERCP or biliary surgery.

The presentation of cholangitis can range in severity from mild to life threatening. The Charcot triad of fever, RUQ pain, and jaundice is common but not universal. The additional presence of hypotension and altered sensorium, which defines the Reynold pentad, is ominous because it reflects spread of bacteria beyond the confines of the biliary tree. Laboratory studies in cholangitis generally show an elevated bilirubin and white blood cell count, and a variable but mild pattern of elevated aminotransferases. Transabdominal ultrasonography is the initial test of choice to identify bile duct dilation and stones. MRCP is useful in the stable patient when ultrasonography is not diagnostic, and may detect more subtle bile duct abnormalities or stones missed by ultrasound.

Management of cholangitis involves vigilance, planning, and swift intervention (Figure 33.6).

Once the diagnosis is suspected, one should provide intravenous fluids, obtain blood cultures, start empiric antibiotic therapy, and alert the interventional endos-

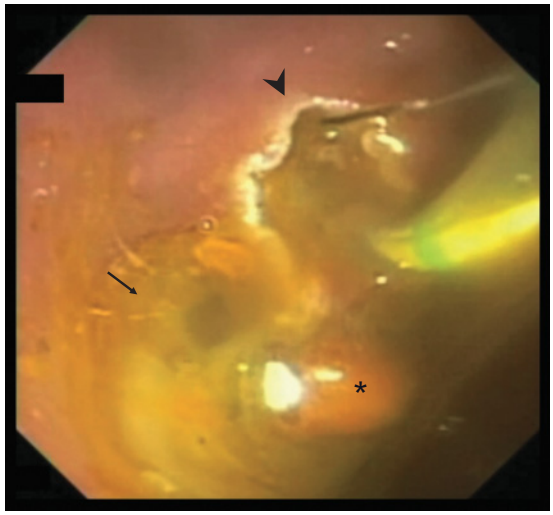


Figure 33.6 Image from ERCP (endoscopic retrograde cholangiopancreatography) for cholangitis: side-viewing endoscope facing the ampulla. Biliary cannulation and sphincterotomy resulted in immediate decompression of the common bile duct, with outflow of pus (arrow) and retained stones (*). Arrowhead highlights the post-sphincterotomy ampulla. (Courtesy of ME Harrison, MD, Divisions of Gastroenterology and Hepatology, Mayo Clinic, AZ.)

copist about a possible therapeutic ERCP. After initial resuscitation, the patient's clinical status should be monitored closely. If the patient shows evidence of clinical deterioration or multisystem failure (e.g., hypotension or confusion), or if there is no significant improvement in symptoms or hemodynamics over the subsequent 6–12 h, urgent ERCP is obligatory. ERCP may also be performed urgently for patients with risk factors for developing severe cholangitis because these patients will frequently develop worsening clinical status [20–23]. The following are the risk factors [2–23]:

- Historical:
  - Advanced age
  - History of smoking
- Abnormal laboratory tests:
  - Hyperbilirubinemia
  - Marked leukocytosis
  - Prolonged PT
  - Hypoalbuminemia
  - Hyperglycemia
- CT findings:
  - Papillitis
  - Hepatic parenchymal changes
  - Markedly inhomogeneous enhancement of the liver on arterial phase
  - Periampullary diverticulum.

Techniques for biliary decompression at ERCP include sphincterotomy, stone extraction, and placement of biliary stents (Figure 33.7 and Video 6). Cultures of biliary fluid should also be performed routinely if blood culture results are not yet available. Percutaneous transhepatic biliary decompression can be performed if ERCP is not feasible, but surgical decompression should be avoided because of its high rate of mortality in acute cholangitis. The vast majority of patients will respond to fluids and antibiotics, so ERCP can be performed electively. The patient with cholangitis and intact gall bladder should then undergo elective cholecystectomy because the risk of recurrent gall-stone disease is high [24].

Gall-stone Pancreatitis

The most common cause of acute pancreatitis is choledocholithiasis, resulting in gall-stone pancreatitis. Possible mechanisms include direct obstruction of the pancreatic duct, biliopancreatic reflux, or local ductal inflammation. Patients with gall-stone pancreatitis generally present with abdominal pain. The pain may be variable in character: biliary colic may be an early or persistent presentation, but epigastric or diffuse abdominal pain and pain radiating to the back may also occur. Laboratory studies should reveal amylase or lipase elevated at least two to three times the upper limits of normal. Abnormal liver tests are present in the vast majority of patients with gall-stone pancreatitis. Elevated aminotransferases, alkaline phosphatase, and bilirubin may be transient or persistent, reflecting the duration of obstruction due to a CBD stone.

For diagnosis of gall-stone pancreatitis, ultrasonography is the preferred initial imaging technique to detect both cholelithiasis and bile duct dilation. An abdominal CT scan with contrast may be an important secondary study to evaluate pancreatic parenchymal changes and peripancreatic inflammation, but is best deferred until 2–3 days after the onset of symptoms to accurately assess the severity of pancreatic disease (Figure 33.8).

If the CT study is equivocal, MRCP offers a sensitive test for choledocholithiasis without the risk of complications associated with ERCP. MRCP also may be used to definitively exclude choledocholithiasis in patients at low or intermediate risk before cholecystectomy. Patients at high risk of choledocholithiasis proceed directly to ERCP

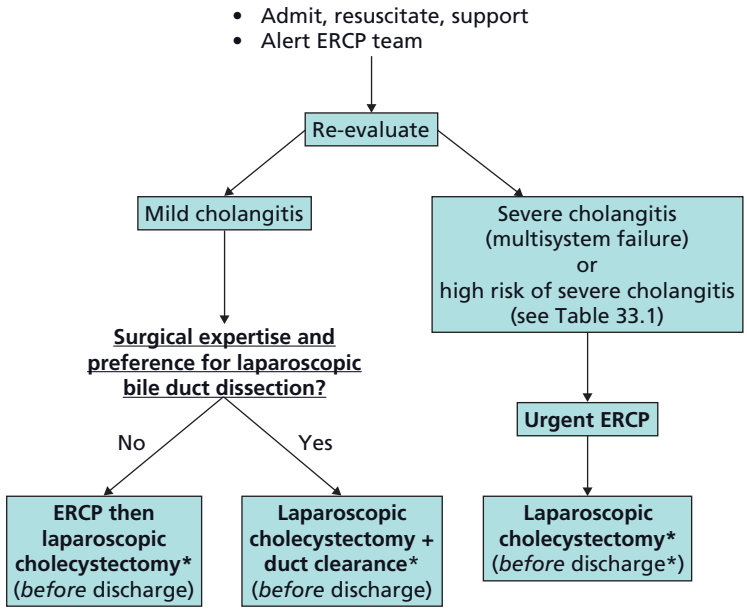


Figure 33.7 Endoscopic management of acute cholangitis: algorithm. As patient is being stabilized, begin to assess the severity of the cholangitis. If there is severe illness or failure to improve after close observation, prompt intervention is essential.*Indications for open cholecystectomy: anatomic variant; coagulopathy; gangrene; suspect malignancy; polyps >18 mm; no local expertise in laparoscopic cholecystectomy. ERCP, endoscopic retrograde cholangiopancreatography.

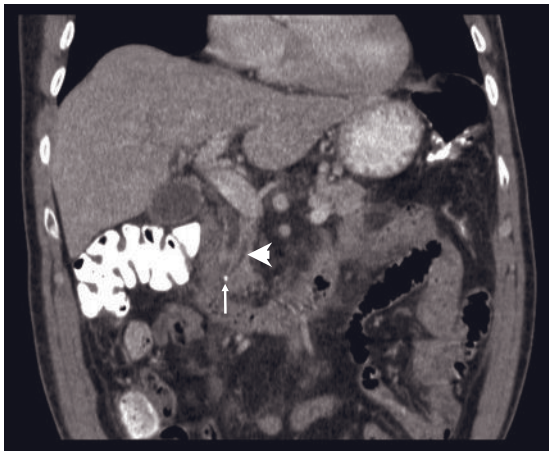


Figure 33.8 CT showing common bile duct (CBD) stone and pancreatitis. A 3-mm gall stone (arrow) obstructs the CBD at the confluence of the CBD and the main pancreatic duct The CBD and pancreatic duct (shown here, arrowhead) are dilated. There is moderate peripancreatic edema, consistent with acute pancreatitis. (Courtesy of H Vargas, MD, Divisions of Gastroenterology and Hepatology, and Joseph M Collins, MD, Department of Radiology, Mayo Clinic, AZ.)

for confirmatory diagnosis and therapy. For patients who have previously undergone cholecystectomy, MRCP is preferred to ultrasonography as the initial study because of greater sensitivity in detection of choledocholithiasis.

Management of gall-stone pancreatitis begins with the same approach used for other causes of acute pancreatitis with aggressive fluid administration, pain control, and close monitoring for evidence of sepsis or shock. When gall stones are identified, treatment of gall-stone pancreatitis becomes more specific: cholecystectomy is indicated to reduce the significant likelihood of further stone formation and recurrent pancreatitis. Cholecystectomy should be performed early in the course of treatment for those patients with mild-to-moderate pancreatitis. Despite these recommendations, cholecystectomy is often delayed, even in cases of mild pancreatitis [25]. In patients with severe or necrotizing acute pancreatitis, surgery should reasonably be delayed to allow for resolution of acute inflammation.

ERCP is performed during the acute episode of gall-stone pancreatitis in limited circumstances. Patients with gall-stone pancreatitis and concomitant acute cholangitis clearly benefit from early ERCP. The benefit

of early ERCP for patients with biliary obstruction without cholangitis is less certain but ERCP may reduce complications in this setting [26]. For patients predicted to develop severe pancreatitis, early ERCP has been recommended in the past but a recent meta-analysis has questioned this approach [27]. Performing an ERCP in the absence of these indications does not benefit the patient and unnecessarily risks ERCP-related pancreatitis as well as delay of surgery. After the acute pancreatitis has resolved, ERCP can be performed electively for retained choledocholithiasis. However, if there is no evidence of persisting choledocholithiasis, then evaluation of the CBD, by either ERCP or even intraoperative cholangiogram, is not indicated (Figure 33.9) [28].

Mirizzi Syndrome

Mirizzi syndrome is a rare complication of gall-stone disease that occurs when the gall stone becomes lodged in the cystic duct or Hartmann pouch and causes hepatic duct obstruction, either mechanically or by secondary inflammation. This obstruction causes cholecystitis, and with repeated episodes can lead to gall-bladder necrosis and development of a cholecystobiliary fistula. Recognition of Mirizzi syndrome is important for two reasons: first, it is valuable for the endoscopist or surgeon to avoid unnecessary manipulation of the bile duct, which may lead to a biliary leak or strictures; and, second, Mirizzi syndrome is associated with carcinoma of the gall bladder, occurring in up to a third of cases, which requires preoperative staging and may alter the surgical approach [29].

Patients with Mirizzi syndrome generally present with obstructive jaundice, with or without pain or fever. They may give a history of chronic, biliary-related symptoms, but these are usually not specific. Laboratory studies reveal a cholestatic pattern. Ultrasonography may allow preliminary diagnosis by showing cholelithiasis with impaction in the cystic duct, dilation of the common hepatic duct, and a normal-caliber CBD. CT can help distinguish the stone from a possible malignancy. Once the diagnosis is suspected, an ERCP should be done to confirm the diagnosis and identify a possible cholecystobiliary fistula. Additional lab tests should include a serum CA 19-9 to aid in detection of malignancy.

After confirmation of Mirizzi syndrome, open cholecystectomy should be performed. Laparoscopic surgery tends to have a poorer outcome, because there are usually adhesions around the cystic duct. Frozen sections of the gall bladder should be sent for pathologic evaluation for malignancy. In poor surgical candidates, an ERCP may be the definitive intervention using endoscopic hydraulic lithotripsy to remove the offending stone. Extracorporeal shock wave lithotripsy has also been advocated as an alternate modality [30].

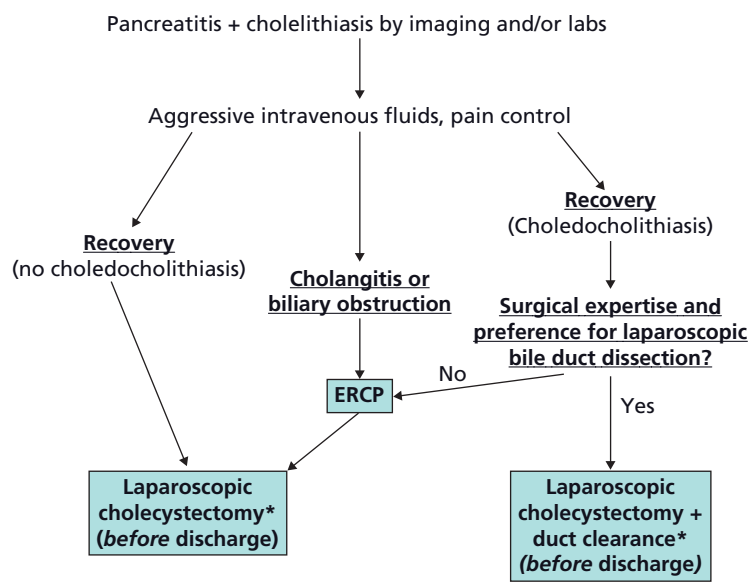


Figure 33.9 Management of gall-stone pancreatitis: algorithm. Initial management should focus on supportive care for the pancreatitis. If there is evidence of cholangitis or ongoing obstruction from choledocholithiasis then ERCP (endoscopic retrograde cholangiopancreatography) may be helpful but ERCP generally has a limited role. Cholecystectomy essentially eliminates the risk of future complications related to gall stones, and should be performed unless contraindicated. *Indications for open cholecystectomy: anatomic variant; coagulopathy; gangrene; suspect malignancy; polyps >18 mm; no local expertise in laparoscopic cholecystectomy. ERCP, endoscopic retrograde cholangiopancreatography.

Gall-stone Ileus

Gall-stone ileus refers to mechanical obstruction due to impaction of a gall stone within the bowel. The gall stone commonly develops within the gall bladder and erodes through the acutely inflamed gall-bladder wall during acute cholecystitis, thereby creating a fistula into the adherent bowel. The fistula typically terminates in the duodenum, but can develop between the gall bladder and any adjacent structure. Once the stone reaches the bowel, it may pass without causing any obstruction, but it can also become impacted, most commonly in the terminal ileum. Although the term "gall-stone ileus" is really a misnomer, because the syndrome results from bowel obstruction, a true ileus can occur secondarily. Gall-stone ileus occurs more frequently in elderly people, accounting for 25% of bowel obstructions in patients aged >65, versus 1–3% of obstructions for all age groups [31].

The clinical presentation of gall-stone ileus is, not surprisingly, that of a small bowel obstruction, which may include crampy abdominal pain, nausea, vomiting, and obstipation. As the obstruction is often not complete, there may be recurrent, transient symptoms and signs of obstruction as the gall stone progresses through the bowel ("tumbling phenomenon"). Many patients with gall-stone ileus have other comorbidities, so diagnosis may be delayed. This is one of the few circumstances in which an abdominal plain film is useful for evaluation of gall-stone disease. It may reveal bowel obstruction, pneumobilia, or a stone. CT may identify more precisely the location of obstruction, and ultrasonography can demonstrate a fistula, which is useful to see preoperatively.

Management of gall-stone ileus is surgical resection of the obstructing stone. Cholecystectomy should also be performed if feasible at the time of resection to avoid further gall-stone complications; otherwise it should be undertaken electively.

Gall-bladder Polyps

A gall-bladder polyp is any elevated lesion of the mucosal wall of the gall bladder, which encompasses a range of lesions including both true polyps and pseudopolyps. Although usually incidental findings, polyps are potentially significant because some can be confused with gall stones and others have malignant potential. Prevalence estimates for gall-bladder polyps vary significantly. One large, retrospective study in a Western population estimated that they occur in approximately 4% of adults, based on ultrasound findings [32]. Gall-bladder polyps in patients with primary sclerosing cholangitis (PSC) occur with a prevalence similar to that of the general population, but with a potentially greater likelihood of malignancy [33]. Gall-bladder polyps are classified simply as either benign or malignant. The most common type of gall-bladder polyp is the cholesterol polyp, a benign non-neoplastic polyp that comprises approximately 60% of all gall-bladder polyps. Malignancies are relatively uncommon, accounting for less than 10% of gall-bladder polyps, and are primarily adenocarcinomas. Inflammatory polyps, adenomas, hyperplastic polyps, and other miscellaneous growths comprise the remainder of gall-bladder polyps.

Clinical Features

Gall-bladder polyps are usually asymptomatic but may cause biliary colic. In rare cases, the polyp breaks free of the gall-bladder wall and causes obstructive jaundice or cholecystitis. There is no reliable correlation between the type of gall-bladder polyp and the pattern of symptoms.

Gall-bladder polyps are usually discovered incidentally by transabdominal ultrasonography, because they are so commonly asymptomatic. Most often, ultrasonography is the only test required for their evaluation: it not only has superior sensitivity for detection of gall-bladder polyps initially, compared with ERCP, CT, or oral cholecystography [34], but also differentiates polyps from stones in most cases. Gall-bladder polyps do not cast a shadow on ultrasonography nor do they move to a dependent position with changes in body position, as expected with stones. The primary limitation of ultrasonography is its inability to distinguish benign from malignant polyps, particularly when there are concomitant gall stones within the gall bladder and when the polyp is >10 mm in diameter. EUS has shown promise as an adjunct to transabdominal ultrasonography in the diagnosis of malignant polyps [35].

Cholesterol polyps are not neoplasms but rather accretions of cholesterol-containing residue. Cholesterol

ester and triglyceride deposits form within macrophages, or foam cells, localized to the gall-bladder epithelium. Similar to cholesterol gall stones, they are rare in children, tend to be more common in women, at least until age 60, and have no malignant potential [36]. Unlike cholesterol gall stones, however, the mechanism of formation of cholesterol polyps is unknown and they are found in association with gall stones only in the minority of patients. Cholesterol polyps usually occur in a diffuse pattern, lining the entire gall-bladder wall up to the cystic duct, giving the epithelium a characteristic "strawberry gall bladder" appearance on gross pathologic examination. Other times, the accretions may accumulate in a heaped-up pattern, forming pseudopolyps [36]. Gall-bladder pseudopolyps may be difficult to distinguish from adenocarcinoma on ultrasonography. One feature that helps distinguish pseudopolyps from adenomas and adenocarcinomas is that their echogenicity tends to be high, whereas the other lesions tend to have lower echogenicity, similar to the echogenicity of the liver [37].

Gall-bladder adenomas occur infrequently and are the only form of gall-bladder neoplasm with malignant potential. Despite their clinical significance, these adenomas are incompletely understood. In a cohort of over 2000 cholecystectomy patients, gall-bladder adenomas were diagnosed in only 0.4% on pathologic review [38]. An adenoma–carcinoma sequence has been demonstrated, but it is not known how frequently gall-bladder adenomas progress to cancer. On ultrasonography, gall-bladder adenomas are commonly solitary, pedunculated polyps ranging in size from 5 mm to 20 mm, which are often discovered together with gall stones. When small, these adenomas tend to be echogenic and homogeneous in appearance, but they become less echogenic and more heterogeneous as they increase in size. Large gall-bladder adenomas therefore can be confused with malignancies (Figure 33.10).

Carcinomatous gall-bladder polyps are the most common type of gall-bladder malignancy. Unfortunately, they are rarely detected as isolated polyps. Instead, carcinomatous polyps are usually identified after the polyp has transformed into a polypoid mass, and often the carcinoma has already metastasized by the time of diagnosis. A small minority of carcinomatous polyps may be detected incidentally as true polyps during evaluation for symptomatic gall stones, where they can present in a variety of forms, including sessile, pedunculated, or raised polyps of varying sizes [39].

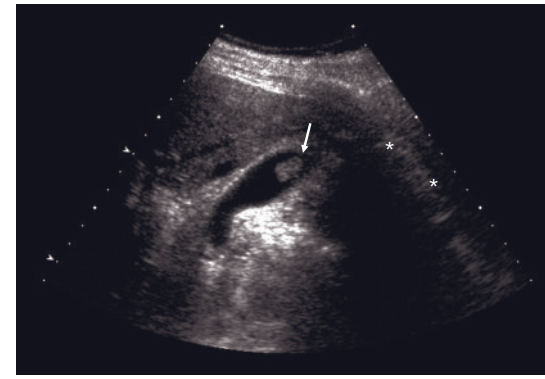


Figure 33.10 Ultrasound scan of gall-bladder adenoma: non-shadowing, fixed polypoid lesion measuring approximately 14 × 10 × 7 mm. Its large size suggests an adenomatous polyp. (Courtesy of Maitray D Patel, MD, Department of Radiology, Mayo Clinic, AZ.)

Adenomyomatoses of the gall bladder are a group of hyperplastic epithelial growths that extend into the muscularis; they too are not true adenomas. Adenomyomatoses may represent premalignant lesions, but there is still debate on this issue. Their overall prevalence is unknown, but they do occur more commonly in women than in men. Adenomyomatoses may appear polypoid, and focal areas of hyperplasia may span >10 mm in length, making them difficult to distinguish from a neoplasm. Identification of a characteristic "V"-shaped or "comet-tail" shadow, created by reflection of the ultrasound waves off the hyperplastic wall, can help support a diagnosis of an adenomyoma, but definitive exclusion of malignancy may require surgical resection [39].

In assessing risk of malignancy, larger gall-bladder polyps are at higher risk of malignant conversion. Polyps ≥10 mm should be considered suspicious for malignancy, and polyps >18 mm are usually invasive malignancies [37]. However, smaller polyps are not necessarily benign. Carcinomatous polyps as small as 6 mm have been reported [40], and sessile carcinomatous polyps ≤10 mm in size can be quite aggressive [41]. Other risk factors for

malignant conversion of polyps have been recognized, including patient age >50, concurrent gall stones, diagnosis of PSC, and possibly the solitary polyp.

There are neither consensus guidelines nor prospective data to guide treatment, so management of gall-bladder polyps should be individualized. Cholecystectomy is commonly recommended either when there are findings that suggest a premalignant or malignant neoplasm, or when gall stones are identified together with gall-bladder polyps, which limits the accuracy of ultrasonography and may be a risk factor for malignancy. Specifically, most experts recommend laparoscopic cholecystectomy if the polyps are large, symptomatic or sessile and if the polyp is found with stones or in patients with PSC. The management of gall-bladder polyps is as follows:

Cholecystectomy (laparoscopic):
- 10–18 mm polyp
- <10 mm polyp:
  - symptomatic
  - growth on imaging
- Polyp of any size:
  - sessile
  - solitary
  - with PSC
  - with cholelithiasis

Cholecystectomy (open):
- Polyp >18 mm.
- Observe with serial imaging
- Asymptomatic polyp <10 mm.

For a polyp >18 mm, open surgery is recommended: the polyp is highly likely to be a locally invasive malignancy, and should be staged preoperatively with CT or EUS [37]. To date, there are no clear guidelines for management of small, asymptomatic polyps, measuring <10 mm in size. These small polyps should be followed with serial ultrasonography every 6–12 months, and cholecystectomy offered for the polyps that enlarge over time. In the future, new technologies may offer more accurate characterization of gall-bladder polyps. EUS has already shown promise in characterizing gall-bladder polyps [35] (Figure 33.11).

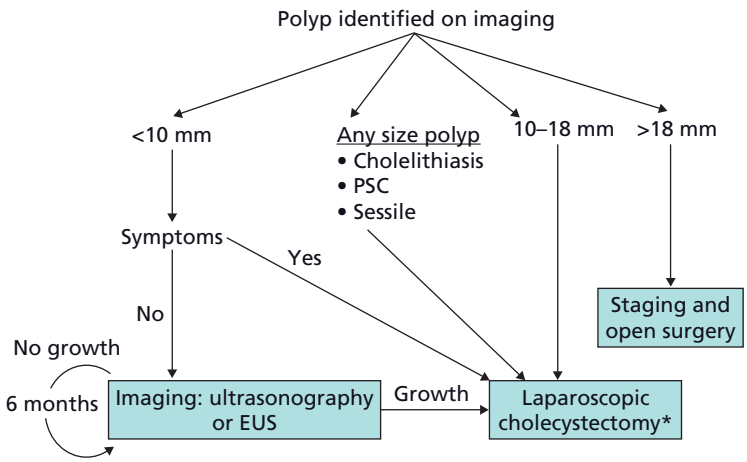


Figure 33.11 Management of gall-bladder polyps: algorithm. There are no consensus guidelines, but reported recommendations have been generally consistent. Small, asymptomatic polyps may be followed with serial ultrasonography, or by endoscopic ultrasonography (EUS) if ultrasonography is not definitive. Polyps >18 mm are at especially high risk for malignancy.

*Indications for open cholecystectomy: anatomic variant; coagulopathy; gangrene; suspect malignancy; polyps >18 mm; no local expertise in laparoscopic cholecystectomy. ERCP, endoscopic retrograde cholangiopancreatography; PSC, primary sclerosing cholangitis.

Take-home points

General

- Gall stones occur in approximately 10% of people in Western populations; cholesterol stones are most common.
- Gall stones are symptomatic in the minority of patients with gall stones.
- Acute cholecystitis is the most common complication of gall stones.
- Acute acalculous cholecystitis is distinct from calculous cholecystitis, and should be considered in critically ill patients.
- Gall-bladder polyps are usually incidental findings seen on ultrasonography; they can be significant because of potential malignancy.
- Gall-stone ileus is a mechanical obstruction, not true ileus.

Diagnosis

- Ultrasonography is sensitive and specific for demonstrating cholelithiasis and cholecystitis, and for identifying and characterizing most gall-bladder polyps.
- Ultrasonography is the preferred initial study for evaluation of choledocholithiasis and gall-stone pancreatitis in spite of its relatively low sensitivity because of low cost, wide availability, and minimal risk.
- MRCP, ERCP, or EUS is indicated for evaluation of choledocholithiasis when ultrasonography is not diagnostic because each is more sensitive and specific than ultrasonography.
- Plain abdominal films have limited usefulness in gall-stone disease and are primarily helpful in detection of gall-stone ileus.
- The clinical presentation of cholangitis varies widely: some patients are asymptomatic whereas others present moribund due to multiorgan system failure.

Therapy

- Laparoscopic cholecystectomy is the preferred therapy for management of cholecystitis and symptomatic cholelithiasis.
- Surgery should be considered for asymptomatic cholelithiasis only in select populations at high risk of complications.
- In the management of choledocholithiasis, ERCP is routinely advised for bile duct clearance followed by laparoscopic cholecystectomy. ERCP after cholecystectomy or surgical bile duct exploration at the time of cholecystectomy may be offered with appropriate local expertise.
- In gall-stone pancreatitis, early ERCP is clearly indicated for cholangitis. ERCP may offer benefit for predicted severe pancreatitis or pancreatitis with biliary obstruction.
- Laparoscopic cholecystectomy should be performed after resolution of gall-stone pancreatitis to reduce the risk of additional gall-stone-related complications.
- Percutaneous cholecystostomy is indicated for severe acute cholangitis in non-surgical candidates.
- Laparoscopic cholecystectomy is indicated both to manage gall-bladder polyps >10 mm and for treatment of polyps detected in the presence of stones, concurrent PSC, and symptomatic or solitary polyps of any size.
- Open rather than laparoscopic cholecystectomy is indicated when there is coagulopathy, gall-bladder gangrene, or anatomic variants that preclude laparoscopic surgery, where there is no local expertise for a laparoscopic approach and suspicion of malignancy.

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34

CHAPTER 34
Functional Gall-bladder and Sphincter of Oddi Disorders

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Summary
Functional disorders of the biliary tree include gall-bladder dyskinesia and sphincter of Oddi dysfunction (SOD). Both present as recurrent epigastric and right upper quadrant pain reminiscent of biliary colic, in the absence of biliary stones. Gall-bladder dyskinesia is defined by an ejection fraction below 35% after slow infusion of a weight-based dose of cholecystokinin. The pathogenesis of pain is unclear; nevertheless, cholecystectomy is the therapy of choice. Data are mixed as to whether subnormal gall-bladder emptying predicts improvement after surgery in patients with pain of suspected biliary origin.

SOD is defined as pain related to fixed or dynamic obstruction of the biliary or pancreatic ducts. It is commonly characterized by whether it involves the biliary and/or the pancreatic sphincter, and by the presence or absence of objective abnormalities of bile duct or pancreatic duct caliber or abnormalities of serum liver or pancreatic enzymes during pain. Diagnosis is classically made by manometric identification of basal sphincter pressures >40 mmHg during endoscopic retrograde cholangiopancreatography. SOD is treated by endoscopic sphincterotomy of the hypertensive sphincter(s). Prophylactic pancreatic stent placement is employed to reduce the risk of procedure-induced pancreatitis.

Case

Presentation and Findings

The patient, a 41-year-old woman, presents electively for recurring episodes of right upper quadrant pain. Her past medical history includes three normal pregnancies and a history of cholecystectomy 5 years earlier for gall-bladder stones that had presented as recurring episodes of biliary colic. She is now experiencing abdominal pains reminiscent of her prior biliary stone-related pain. The pain occurs 1–2 h after meals and lasts 30–90 min. It is steady in character and located in the right upper quadrant with modest extension to the back. It is occurring with increasing frequency and she rates it as 8/10 in severity. Episodes rarely induce nausea or vomiting, but they are not associated with diarrhea, fever, chills, or jaundice; they resolve gradually. During two more severe episodes she was evaluated in the emergency room, at which time physical exams noted only epigastric and right upper quadrant tenderness without peritoneal signs. Lab results on both occasions included normal values for alkaline phosphatase and bilirubin, but AST values of 95 and 88 IU/L. Pancreatic enzymes, hematology group, general chemistries, and a urinalysis were also normal.

Testing and Diagnosis

Investigation of the patient's symptoms begins with repeated evaluation of liver enzymes to assess whether the transaminase elevations were transient or are ongoing. They prove to be normal. Ultrasonography of the upper abdomen notes normal liver echotexture, a normal pancreas, and no evidence for biliary or pancreatic duct dilation. Magnetic resonance cholangiopancreatography (MRCP), performed to exclude choledocholithiasis, is normal. Progressive symptoms prompt a trial of acid suppression and sublingual hyoscyamine as needed with pain.

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When these prove unhelpful endoscopic retrograde cholangiopancreatography (ERCP) with sphincter manometry is undertaken. This demonstrates a normal mucosal exam without suggestion of esophagitis, gastritis, or peptic injury, and normal-caliber ducts without filling defects. The biliary sphincter is subjectively snug but without gross pathology. Manometry demonstrates reproducible phasic activity with peak pressures >150 mmHg and basal pressures of 50–70 mmHg (normal <40 mmHg) on two withdrawals through the biliary sphincter. Pressures in the pancreatic sphincter are normal. The study is considered diagnostic of biliary sphincter hypertension. Given the history of elevated levels of AST during pain, the diagnosis is type II biliary SOD.

Therapy and Outcome

Immediately after confirming elevated sphincter pressures and an otherwise normal endoscopic exam, including biliary and pancreatic ducts, a biliary sphincterotomy is performed. Dual sphincterotomy would be performed if both sphincters exhibited high basal pressures. Given the constellation of findings the likelihood of response is quoted at better than 85%. To reduce the risk of procedure-induced pancreatitis a prophylactic pancreatic stent is inserted at the end of the ERCP. A follow-up abdominal radiograph is performed 7–10 days later to confirm spontaneous migration of the prophylactic stent, as occurs in 80–85% of patients.

Table 34.1 Rome III diagnostic criteria for functional gall-bladder and sphincter of Oddi disorders.[a]

Must include episodes of pain located in the epigastrium and/or right upper quadrant and all of the following:

1 Episodes lasting 30 min or longer
2 Recurrent symptoms occurring at different intervals (not daily)
3 The pain builds up to a steady level
4 Intensity moderate to severe, enough to interrupt the patient daily activities or lead to an emergency department visit
5 The pain is not relieved by bowel movements
6 The pain is not relived by postural change
7 The pain is not relieved by antacids
8 Exclusion of other structural disease that would explain the symptoms

Supportive criteria:

The pain may present with one or more of the following:

1 Association with nausea and vomiting
2 Radiation to the back and/or right subscapular region
3 Nocturnal awakening

[a]From Behar *et al*. [1], with permission from Elsevier.

Definition and Epidemiology

Functional disorders of the biliary tree are divided into those related to the gall bladder (termed "gall-bladder or biliary dyskinesia") and those related to the sphincter of Oddi (termed "sphincter of Oddi dysfunction"). Both present as syndromes of recurrent right upper quadrant (RUQ) pain, analogous to stone-related biliary colic, but in the absence of biliary stones (Table 34.1). Gall-bladder dyskinesia is defined as pain associated with abnormal gall-bladder emptying, as determined by cholecystokinin (CCK)-stimulated radionuclide scanning, demonstrating a gall-bladder ejection fraction <35–40 % [1]. Episodic pain in the absence of gall stones or other potentially obstructive processes is relatively common; however, the differential diagnosis is broad and attribution to subnormal gall-bladder emptying is somewhat presumptive. Gall-bladder dyskinesia occurs in both genders at all ages. As with biliary stone disease, there is a predilection for young and middle-aged women.

Sphincter of Oddi dysfunction (SOD) is defined as recurrent, acalculous, upper abdominal pain resulting from static or intermittent biliary obstruction at the level of the sphincter, due to any combination of inflammatory, fixed fibrotic, or dynamic motility abnormalities [1]. Current convention further designates SOD as biliary, pancreatic, or combined type based on the portion of the sphincter involved. Classic and revised Milwaukee criteria are commonly employed to classify SOD into types I, II, and III on the basis of associated objective abnormalities of duct caliber and serum levels of the biliary and/or pancreatic enzymes (Table 34.2) [2,3]. In the course of clinical evaluation and management, suspected or *presumptive SOD* is distinguished from *confirmed SOD* on the basis of objective manometric assessment of sphincter function, as described below.

Abnormal sphincter motility has been described in up to 40% of patients with an intact gall bladder, with or without gall stones, but attribution of pain symptoms to the sphincter versus the gall bladder is not possible. Data are insufficient to ascribe a clinical pain syndrome, without enzyme or structural abnormalities, to the sphincter when the gall bladder is intact. Post-cholecystectomy recurrence of preoperative pain is relatively common and occurs in 10% or more of patients, depending on the precision in characterization of pain before surgery [4]. Among this group SOD is confirmed

Table 34.2 Modern Milwaukee criteria for characterization of sphincter of Oddi dysfunction.

Type	Characterizing feature(s)
Biliary I	Pain[a] + dilated CBD *and* elevated hepatic enzymes[b]
Biliary II	Pain + either dilated CBD *or* elevated hepatic enzymes
Pancreatic I	Pain + dilated PD *and* elevated pancreatic enzymes[c]
Pancreatic II	Pain + dilated PD *or* elevated pancreatic enzymes
Type III	Typical biliary or pancreatic pain alone; normal ducts /enzymes

CBD, common bile duct; PD, pancreatic duct.
[a]Pain—see Table 34.1.
[b]Hepatic enzymes: alkaline phosphatase, bilirubin, aspartate transaminase (AST) or alanine transaminase (ALT) more than twice normal on two or more occasions with prompt return to normal within 24–48 h.
[c]Pancreatic enzymes: amylase or lipase more than twice normal on two or more occasions with prompt return to normal within 24–48 h.

in about 10% of patients—constituting 1% of post-cholecystectomy patients overall [5]. SOD occurs at all ages and in both genders, but 75% or more of patients are middle-aged women. Pancreatic SOD presents with pain similar to biliary pain or that of mild acute pancreatitis. Idiopathic acute recurrent pancreatitis may be attributable to SOD (pancreatic type I or II) and abnormal pancreatic manometry has been reported in 25–75% of patients with idiopathic acute recurrent pancreatitis [1].

Pathophysiology

The pathogenesis of pain in the setting of diminished gall-bladder motility is uncertain. Diminished emptying develops in the presence of cholesterol supersaturation of bile [1], even before the formation of sludge or stones. Stasis of supersaturated bile may also contribute to the development of subclinical acalculous cholecystitis. Chronic acalculous cholecystitis is noted in more than two-thirds of patients who undergo cholecystectomy for gall-bladder dyskinesia [6]. Whether and how this mucosal inflammation contributes to intermittent biliary pain is unclear. Diminished clearance of supersaturated bile and sludge contributes to further progression to overt stone disease. Hence, diminished gall-bladder emptying may be an indicator of likely formation of microlithiasis and hence a proxy for detection of biliary stone disease. In a significant portion of patients with normal enzymes and negative ultrasonography, stone disease can be inferred by the detection of cholesterol crystals or bilirubinate sludge on microscopic inspection of bile or by detection of sludge or microlithiasis by endoscopic ultrasonography [7]. The term "cystic duct syndrome" was employed to explain acalculous pain and diminished gall-bladder emptying on the basis of forceful gall-bladder contractions against an overly narrow or diseased cystic duct [8]. It is little used today, as we now know that gall-bladder filling and emptying occur in a to-and-fro bellows fashion rather than via prolonged unidirectional flow.

The pathophysiology of SOD is also poorly understood. Type I SOD, often termed "papillary stenosis," presents with chronically dilated biliary and/or pancreatic ducts, elevated enzymes, and pain. It tends to have a fixed, fibrotic sphincter. This may be a consequence of inflammatory scarring induced by recurrent passage of sludge or microlithiasis. Types II SOD, which presents with episodic pain and either chronically dilated ducts or intermittent enzyme abnormalities, may represent a milder degree of fixed type I disease or an intermittent dynamic abnormality similar to type III SOD, in which there are no objective signs or symptoms other than elevated basal pressures. The pain induced by either static or dynamic abnormalities of sphincter pressure may extend from intraductal hypertension in the absence of a low-pressure decompressive gall bladder, or from the muscle itself—perhaps with associated visceral hypersensitivity analogous to that identified in patients with functional symptoms from other portions of the gastrointestinal track. Indeed SOD is noted more frequently in patients with other functional pain syndromes of the esophagus, stomach, and colon [9].

Presumptive type II pancreatic SOD is equivalent to acute recurrent pancreatitis (ARP) of unclear etiology. We now know that acute recurrent pancreatitis may be one presentation of subtle chronic pancreatitis, and may be associated with modest abnormalities in any of several genes classically associated with more severe chronic pancreatitis, such as heterozygous major or minor gene

variants of the cystic fibrosis gene [10]. When sphincter hypertension is identified in these settings it is unknown whether it plays a pathogenic role in ARP or represents only a response to pancreatitis.

Clinical Features

Gall-bladder Dyskinesia

Diagnostic criteria for functional pain from the gall bladder or the biliary or pancreatic sphincters have been established by the Rome III committee on functional gastrointestinal disease (see Table 34.1) [1]. They include moderate-to-severe pain that builds to a steady level, lasts 30 min or longer, disrupts usual activities, and presents in a recurrent but not a daily fashion. The pain is not relieved by postural change, bowel movements, or antacids, but may be associated with nausea or vomiting, nocturnal awakening, or radiation to the back or infrascapular area. Liver and pancreatic enzymes and indices of inflammation are normal. Alternate sources of similar pain, such as gastroesophageal reflux disease, peptic disease, duodenal ulceration, or other functional syndromes, should be excluded.

Sphincter of Oddi Dysfunction

Patients with SOD can present with any combination of pain, duct caliber change, or enzyme abnormality potentially referable to the biliary tree or the pancreas. Rome III criteria for both biliary and pancreatic SOD include presence of pain typical of biliary (or pancreatic) sources (see Table 34.1), and exclusion of potential alternative etiologies. By definition, type I biliary SOD presents with pain, a dilated bile duct (>10 mm diameter), and concurrent transient elevations of alkaline phosphatase, aspartate transaminase (AST), alanine transaminase (ALT), or direct bilirubin to twice normal on two or more occasions. The lab abnormalities generally resolve within 24–48 h. Type II biliary SOD presents with pain and *either* dilated duct *or* enzyme abnormalities. Pancreatic SOD often presents more centrally in the mid-epigastrium with extension to the back, analogous to acute pancreatitis pain, with the exception of a more transient duration in many cases. Types I and II pancreatic SOD present with mild and transient elevations of amylase and/or lipase. As with gall-bladder dyskinesia, non-biliary, non-pancreatic sources of pain should be considered and excluded, including transient sources of ischemic or mechanical pain, such as mesenteric ischemia, gastric or intestinal torsion, intussusception, and adhesive disease. They may be distinguished by the location and/or character of the pain. Both the patient groups and the symptoms of SOD overlap significantly with those seen with functional dyspepsia and irritable bowel syndrome, making attribution of symptoms difficult in the absence of objective criteria.

Diagnosis

Gall-bladder Dyskinesia

By definition the diagnosis of biliary dyskinesia requires careful characterization of biliary pain, exclusion of biliary stone disease, and demonstration of diminished gall-bladder emptying. Gall-bladder stones are generally detected or excluded by transcutaneous ultrasonography but they are detected with greatest sensitivity by endoscopic ultrasonography (EUS). Gall-bladder volumes can be determined before and after stimulation with CCK by calculation from ultrasound measurements of length and diameter or by radionuclide technetium scanning. Most studies administer CCK by rapid 3- to 4-min infusions, but prolonged weight-based infusions yield more reproducible data as well as higher ejection fractions [11]. Most studies of dyskinesia employ a threshold of 35% for determination of diminished emptying; others consider 40% the threshold of normal.

Two meta-analyses have attempted to clarify the utility of gall-bladder ejection fraction for selection of patients with acalculous biliary-type pain for cholecystectomy. In one study, 9 published reports totaling 974 patients, including 362 who underwent cholecystectomy, were pooled for analysis [9]. After surgery 94% of patients with low gall-bladder ejection fractions (GBEFs) did well compared with 85% of those with normal ejection fractions. Globally, the data did not support use of GBEFs to select patients for cholecystectomy. Sensitivity analysis suggested a trend toward utility of GBEFs for patient selection only among those with a complete response and absence of postoperative symptoms. There was no difference when the GBEF threshold for normal was 35% versus 40% and no difference when only studies employing prolonged CCK infusions were pooled. The second

meta-analysis reviewed 23 studies and determined that poor methodology in all precluded a pooled approach to the data [12].

Sphincter of Oddi Dysfunction

Symptom characterization is equally important for SOD. A significant proportion of patients with SOD also have other functional syndromes and demonstrable visceral hypersensitivity [3]. Other potential organic etiologies should be considered and excluded. Upper gastrointestinal endoscopy is useful for exclusion of reflux injury or peptic ulcer disease and either EUS or magnetic resonance cholangiopancreatography (MRCP) can be employed to identify potential biliary stone disease or pancreatic disease. The Rome III committee sought to avoid the need for early performance of ERCP in most patients due to the risks involved with its performance [1]. In patients with presumptive SOD type I, alternate diagnoses can be excluded and SOD can be confirmed together with therapeutic ERCP with endoscopic sphincterotomy. Early data suggested that, among patients with presumptive biliary types I, II, and III SOD, manometry demonstrates abnormal sphincter hypertension in 86%, 55%, and 28% of patients, respectively [13].

In types II and III patients, ERCP should be performed only for investigation of post-cholecystectomy pain in settings that are equipped and prepared to perform endoscopic manometry for diagnosis of SOD [14]. Indeed, for those patients with presumptive type III SOD, i.e., those without objective criteria before manometric investigation, alternate potential etiologies and other non-interventional approaches to pain are usually pursued before entertaining ERCP and manometry [3]. Depending on the symptom complex, these efforts may include exclusion of gastric or enteral dysmotility, and prolonged trials of acid suppression, smooth muscle antispasmodic agents, or even tricyclic antidepressants.

Endoscopic manometry remains the gold standard for assessment of potential sphincter dysfunction and prediction of response to sphincterotomy. Basal pressures are usually measured employing a low compliance perfused manometry apparatus and a 5 French manometry catheter, with two radially oriented measurement ports and one channel for either wire guidance (0.018 inch caliber wire) or aspiration during use in the pancreatic duct. Agents that influence smooth muscle tone are avoided; sedation employs either benzodiazepines and meperidine or propofol. Meperidine alters cyclic sphincter activity and peak pressures but not basal pressures. Dual station pull-throughs demonstrating reproducible physiologic recordings with basal pressures >40 mmHg are usually required to diagnose basal sphincter hypertension, the essential element of SOD. Some centers assess only the duct implicated by prior objective findings, if any; however, most now assess both sphincters and treat each based on independent findings [3]. Prophylactic pancreatic stenting is generally employed, whether therapeutic sphincterotomy is performed in one sphincter, both, or neither.

Due to the morbidity of endoscopic manometry during ERCP, a number of non-invasive studies have been investigated for indirect evaluation of sphincter function in patients with pain. Provocation with intravenous or subcutaneous morphine and prostigmine (Nardi test) sought to reproduce diagnostic enzyme elevations or typical pain after administration; however, it was shown to be highly non-specific. Most non-invasive tests employ some means of stimulating biliary or pancreatic flow while measuring duct dilation and decline after stimulation, or time to labeling of the bile duct and/or the duodenum with radionuclide scintigraphy [15]. Stimulation of bile flow can employ fatty meals or secretin injection or infusion, while measurement of duct caliber has used transcutaneous ultrasonography, EUS, and MRCP. Secretin-stimulated ultrasound, EUS, and MRCP studies have shown only modest correlation with sphincter of Oddi manometry, but some small studies have noted relative reproducibility and moderately good predictive value for improvement after sphincterotomy [16]. Scintigraphy generally employs technetium scanning to one or more parameters of bile excretion. The hepatic hilum-to-duodenum transit time has been defined as potentially more useful than other parameters; however, results from multiple studies are inconsistent and intra-patient reproducibility has been poor. Overall, the scintigraphic studies appear to predict response to sphincterotomy, particularly in those with dilated ducts and greater degrees of obstruction, but they are less accurate in those with milder abnormalities [12].

Differential Diagnosis

For details of the differential diagnosis see Table 34.3.

Table 34.3 Differential diagnosis for functional biliary conditions.

Gall-bladder dyskinesia and biliary sphincter of Oddi dysfunction (SOD)
- Cholelithiasis, choledocholithiasis
- Peptic ulcer disease
- Gastritis
- Gastroesophageal reflux disease
- Non-ulcer dyspepsia
- Irritable bowel syndrome
- Chronic abdominal pain syndrome(s)

Pancreatic SOD
- All of above, plus
- Acute recurrent pancreatitis from other etiologies:
  - Alcohol
  - Biliary stone disease
  - Anatomic anomalies
  - Autoimmune pancreatitis
  - Minor or heterozygous major cystic fibrosis gene abnormalities
- Miscellaneous chronic pancreatitis

Therapeutics

Gall-bladder Dyskinesia

Standard therapy for gall-bladder dyskinesia is cholecystectomy. This removes the potential source of inflammatory pain and potentially painful hypertensive contractions against relative resistance. The following are evidence-based therapies supported by randomized controlled trials:

- Gall-bladder dyskinesia:
  - Cholecystectomy for patients with pain and subnormal gall-bladder ejection fractions [17,18]
- Sphincter of Oddi dysfunction:
  - Nifedipine for pain in confirmed biliary type II SOD [16,19]
  - Biliary sphincterotomy for pain in confirmed biliary type II SOD [20,21].

Sphincter of Oddi Dysfunction

Medical, endoscopic, and surgical therapies have been proposed for SOD; however, there are few controlled trials to guide current practice. Proposed medical therapies include nitrates, calcium channel blockers, and hormonal agents. Only nifedipine has been studied in randomized outcome studies. Nifedipine (30–60 mg/day) was shown to significantly reduce the severity and frequency of pain and analgesic requirements in two randomized controlled crossover trials of 12 and 28 patients [18,19,22].

Sphincter ablation via endoscopic sphincterotomy is the usual first-line therapy for types I and II SOD. In papillary stenosis, or type I SOD, sphincterotomy is usually performed empirically, without prior manometric evaluation. Performance of manometry to guide intervention is the standard of practice for presumptive type II SOD; however, the data are quite mixed regarding correlation of therapeutic response to clinical presentation versus findings on manometry or radionuclide scanning [2]. Many centers perform sphincterotomy semi-empirically for these patients if the duct dilation is prominent or the enzyme abnormalities are clearly transient and occur only with pain episodes [23]. Others avoid empiric therapy in this group, based on poor prediction of response from presenting findings alone [24]. In type III SOD diagnostic manometry and concurrent endoscopic therapy are usually reserved for those with convincing histories and failed medical management. Manometric assessment is considered mandatory for election of endoscopic therapy.

Several maneuvers have been proposed as alternate means of predicting the clinical response to subsequent sphincterotomy. In two studies of 44 patients overall, pain relief with temporary 7 Fr biliary stents was predictive of subsequent response to sphincterotomy in patients with and without abnormal manometry [21,25]. Similarly, botulinum toxin injection into the sphincter of Oddi, or into the pancreatic portion of the sphincter, was shown to be predictive of subsequent benefit from sphincterotomy for manometrically confirmed biliary type III [26], and pancreatic [27] SOD.

Placement of a temporary prophylactic pancreatic stent to limit the severity and frequency of post-ERCP pancreatitis is now the standard of practice during either diagnostic or therapeutic ERCP for possible SOD [28]. They reduce the risk of procedural pancreatitis by at least 50% and they largely eliminate severe episodes. Prophylactic stents with retention barbs or pigtail loops on only the duodenal end migrate spontaneously in about 85% of cases whether 3, 4, or 5 Fr stents are employed [17].

Management

For the management algorithm see Figure 34.1.

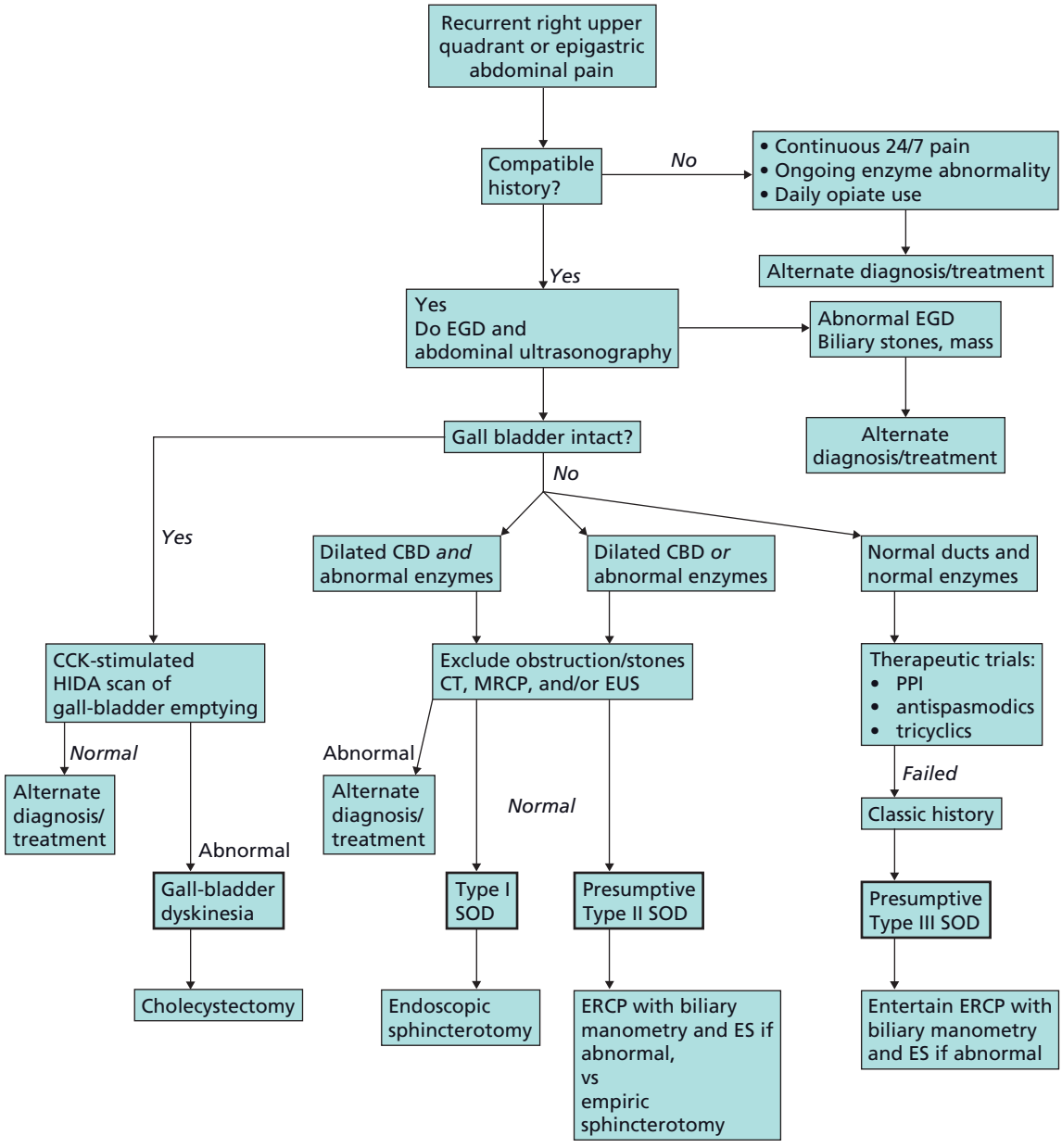

Figure 34.1 Algorithm for evaluation of abdominal pain and possible functional biliary conditions. CBD, common bile duct; CCK, cholecystokinin; CT, computed tomography; EGD, esophagogastroduodenoscopy; ERCP, endoscopic retrograde cholangiopancreatography; ES, endoscopic sphincterotomy; EUS, endoscopic ultrasonography; HIDA, hepatic iminodiacetic acid; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; PPI, proton pump inhibitor; SOD, sphincter of Oddi dysfunction.

Prognosis

Only one randomized study has been performed for gall-bladder dyskinesia [18]. In this study 103 patients were evaluated and 21 had low GBEF. This group was randomized to cholecystectomy or no operation and followed symptomatically for 15–54 months (mean 34 months); 10 of 11 operated patients resolved their symptoms while all 10 in the non-surgical group remained symptomatic. Two of the latter group later responded to surgery. A recent meta-analysis of pooled data on 274 patients from 5 studies noted 98% symptomatic relief with cholecystectomy and 32% relief with non-surgical conservative therapy [19]. Similarly, the meta-analyses on the predictive utility of radionuclide ejection fraction for symptom relief noted symptomatic response to cholecystectomy in 95% of patients with abnormal ejection fractions and 85% among those with normal ejection fractions, perhaps emphasizing the importance of a carefully obtained history [11].

Sphincterotomy relieves post-cholecystectomy pain of SOD in 85% of those with type I SOD, independent of manometric findings [2]. Based on two randomized controlled trials and numerous uncontrolled series, data suggest that approximately 70% (range 60–95%) of those with manometrically confirmed biliary type II SOD benefit from sphincterotomy, whereas approximately 20% benefit from sham sphincterotomy [13,20,29]. Similarly, limited uncontrolled data suggest that about 70% of patients with manometrically confirmed type II pancreatic SOD also benefit from sphincterotomy [13]. Data for presumptive type III SOD are less consistent. A single randomized study that is available only in abstract form demonstrated 62% benefit among 13 patients treated with sphincterotomy compared with 30% response among 10 treated with sham intervention [30]. Results of numerous uncontrolled series vary from estimates of 37% response to sphincterotomy among numerous pooled series [13] to as high as 70% when optimal dual sphincter evaluation and therapy are employed [3]. Uncontrolled SOD data are hindered by inconsistent symptom characterization, follow-up, and attention to potential sources of bias. Thankfully, a National Institutes of Health-sponsored, randomized, sham-controlled study of sphincterotomy for type III SOD (EPISOD trial—Evaluating Predictors and Interventions in Sphincter of Oddi Dysfunction) is now under way (see http://clinicaltrials.gov/ct2/show/NCT00688662?cond=%22Sphincter+of+Oddi+Dysfunction%22&rank=1).

Take-home points

- Functional disorders of the biliary tree include gall-bladder dyskinesia and sphincter of Oddi dysfunction.
- Key to the diagnosis is careful assessment of the pain history. Both conditions present with recurrent epigastric and right upper quadrant pain reminiscent of biliary colic, in the absence of biliary stones.
- Gall-bladder dyskinesia is defined by an ejection fraction <35%.
- Gall-bladder dyskinesia is treated with cholecystectomy.
- Sphincter of Oddi dysfunction is commonly characterized by whether it involves the biliary and/or the pancreatic sphincter, and by the presence or absence of objective abnormalities of the bile duct or pancreatic duct caliber or by abnormalities of serum liver or pancreatic enzymes during pain.
- SOD is classically confirmed by manometric identification of basal sphincter pressures >40 mmHg during ERCP.
- SOD is treated by endoscopic sphincterotomy of the hypertensive sphincter(s).
- Prophylactic pancreatic stent placement is employed to reduce the risk of procedure-induced pancreatitis.

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CHAPTER 35
Cancer of the Gall Bladder and Biliary Tree

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Summary

Malignancies of the gall bladder and bile ducts are uncommon tumors of the gastrointestinal tract. Presentation of gall-bladder cancer can vary from an incidental pathologic finding after cholecystectomy to invasion of the liver, bile ducts, and other perihepatic structures. Surgical resection is the mainstay of therapy; the extent of resection depends on the depth of tumor invasion into the gall-bladder wall and liver, and invasion of local structures. Hilar cholangiocarcinoma (CCA) (e.g., Klatskin tumor) often presents with painless jaundice. Hepatic resection is usually required to achieve a potentially curative resection. Unfortunately, many tumors are unresectable at the time of presentation. Liver transplantation following neoadjuvant therapy has emerged as an effective treatment for selected patients with early stage hilar CCA that is either unresectable or arising in the setting of primary sclerosing cholangitis.

Gall-bladder Cancer

Definition and Epidemiology

Cancer of the gall bladder is an uncommon malignancy of the gastrointestinal tract. The most common histologic type of gall-bladder cancer is adenocarcinoma. Other rare cell types include papillary, mucinous, clear cell, signet-ring cell, adenosquamous, squamous cell, and small cell carcinoma. The incidence of gall-bladder carcinoma in the USA is 1.1 cases per 100 000 patient-years, yielding approximately 3300 cases annually. The incidence of gall-bladder cancer varies across races; higher rates are observed in Native Americans and Hispanics as compared to African Americans and caucasians.

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Risk Factors

Gall-bladder cancer is uncommon, yet it is still the most common malignancy of the biliary tract. Women are three times more likely than men to develop gall-bladder cancer, and most patients develop disease after the fourth decade of life. The most important risk factor in the development of gall-bladder cancer is the presence of cholelithiasis [1]. Case controlled studies have estimated the relative risk of gall-bladder cancer to be anywhere from two to 30 times more common in subjects with cholelithiasis [2]. It is also notable that the size of gall stones is a risk factor for gall-bladder cancer in a racially diverse cohort of patients [3].

Bacterial infections with *Salmonella* and *Helicobacter* species have also been implicated in the pathogenesis of gall-bladder cancer [4]. A study from India reported that gall-bladder cancer was eight times more common in chronic *Salmonella typhi* carriers than those who are not [5]. In Asian patients, the risk for gall-bladder cancer in

patients with bile cultures positive for *Helicobacter bilis* was five to seven times that of non-infected control patients [6]. The putative mechanism of carcinogenesis is that the bacteria involved increase the conversion of primary bile acids to secondary bile acids – compounds that are known carcinogens [7].

The well known "adenoma to carcinoma" paradigm of gastrointestinal malignancies has been observed in the case of gall-bladder cancer [8]. In the overwhelming majority of patients, the gall-bladder polyps noted by imaging are benign cholesterol polyps, adenomyomas, or inflammatory polyps. Only 5% of polyps are of the adenomatous type.

Presentation

Three common patient scenarios occur with gall-bladder cancer. The first is gall-bladder cancer suspected preoperatively based on signs, symptoms, and subsequent imaging. The second is gall-bladder cancer discovered at the time of cholecystectomy for presumed symptomatic cholelithiasis or acute cholecystitis. The third is gall-bladder cancer found incidentally on pathologic examination after uncomplicated cholecystectomy. In general, symptoms for patients with unsuspected gall-bladder cancer mimic those of biliary colic (e.g., intermittent right upper quadrant pain). More advanced cases of gall-bladder cancer present with jaundice, weight loss, cachexia, and obstruction from local invasion of the duodenum.

Diagnosis

Ultrasonography is the best first diagnostic test for patients presenting with typical symptoms of gall-bladder disease. Gall-bladder cancers can be seen as an asymmetric wall thickening, a polypoid lesion projecting into the gall-bladder lumen, or a mass invading the liver parenchyma or surrounding structures [9,10]. In cases where gall-bladder carcinoma is of clinical concern, color Doppler ultrasound can be used to determine blood flow within the mass, a feature highly suggestive of malignancy, and to determine the presence of vascular invasion of the primary tumor [11].

Computerized tomography (CT) is useful in obtaining more information about vascular invasion, nodal disease, local invasion, and distant metastases for patients suspected of having advanced gall-bladder cancer [12,13]. Recently, magnetic resonance imaging (MRI) with magnetic resonance angiography (MRA) and magnetic resonance cholangiopancreatography (MRCP) has been used to evaluate the extent of hepatic, vascular, and bile duct invasion in gall-bladder cancer [14]. Positron emission tomography (PET) has also been noted to be of value in gall-bladder carcinoma [15]. Corvera *et al.* noted that 23% of patients with gall-bladder carcinoma had changes in management due to findings on a preoperative PET scan [16].

Staging

The American Joint Committee on Cancer (AJCC) TNM (tumor, node, metastasis) classification and staging are shown in Table 35.1. The tumor (T) classification is based on depth of gall-bladder wall invasion, local vascular invasion, or invasion into surrounding structures. Local lymph node (N) involvement may include the hilar (cystic duct, common bile duct, hepatic artery, and portal vein), celiac artery, periduodenal, peripancreatic, or superior mesenteric artery lymph nodes. Other lymph nodes sites are considered distant metastases. Direct extension of the gall-bladder carcinoma into the liver or adjacent organs is not considered metastatic (M) disease.

Resection and Outcomes

The extent of surgical therapy strongly depends on the T stage of the tumor, the proximity of the tumor to critical vascular and biliary structures, and the presence of metastatic disease. The goal of any cancer operation is to clear all disease with negative surgical margins (R0 resection). T1a tumors (often found incidentally in a cholecystomy specimen) are usually cured with cholecystectomy alone and do not require reresection or lymphadenectomy [17,18]. T1b tumors can have regional lymph node metastases and patients may benefit from adequate staging when subjected to lymphadenectomy [19]. Goetze and Paolucci have reported that patients with T1b tumors undergoing reresection of the gall-bladder fossa (or hepatic lobectomy) have improved survival compared to patients who have undergone cholecystectomy alone [20].

T2 tumors are not cured by simple cholecystectomy and require, at minimum, resection of the gall-bladder bed (liver segments IVB and V), accompanied by regional lymphadenectomy. The right hepatic artery, portal vein, and right bile duct lie in close proximity to the gall-bladder fossa, and involvement of these structures

Table 35.1 TNM classification and staging of gall-bladder cancer [reproduced from the *AJCC Cancer Staging Manual*, 6th edn, 2002, with permission from the American Joint Committee on Cancer (AJCC)].

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requires a right hepatectomy for an R0 resection. Involvement of the cystic duct stump with tumor also requires radical resection of the common bile duct and reconstruction of bilioenteric continuity with a Roux-en-Y choledochojejunostomy. The 5-year survival after liver resection of T2 gall-bladder carcinoma is approximately 55%.

T3 and T4 tumors are treated similarly to those noted above. Due to local invasion of the tumor into surrounding structures and involvement of the major hepatic vas-

culature, resection for cure is less likely [21]. An aggressive approach at Memorial Sloan Kettering achieved a 5-year survival rate of 67% in T3 disease and 33% in T4 disease, but no patients with positive lymph nodes survived beyond 2 years.

Cholangiocarcinoma

Definition and Epidemiology

Cholangiocarcinoma (CCA) is a malignancy arising from the bile duct epithelium (cholangiocytes) anywhere along the length of the biliary tree. These tumors can arise from the peripheral bile ducts (intrahepatic CCA); the right, left, and common hepatic ducts (hilar CCA; e.g., Klatskin tumor); or the distal common bile duct. The relative distribution of these tumors is difficult to elucidate because tumor registries have included intrahepatic CCAs with other primary liver cancers (e.g., hepatocellular carcinoma), and hilar CCAs have been misclassified as intrahepatic tumors. Based on the Surveillance Epidemiology and End Results (SEER) database, the incidence of intrahepatic CCA has increased from 0.32 per 100 000 in 1975–1979 to 0.85 per 100 000 in 1995–1999 [22]. Similarly, the incidence of extrahepatic CCA has decreased from 1.08 per 100 000 in 1979 to 0.82 per 100 000 in 1998. Given these data, there are approximately 5000 cases of CCA diagnosed annually in the USA, with approximately half arising in the extrahepatic bile ducts and half arising in the intrahepatic ducts. The remainder of this review will concentrate on intrahepatic CCA and hilar CCA.

Risk Factors

Several risk factors have been associated with the development of CCA; many of these involve chronic inflammation of the bile duct epithelium as the putative causative agent. Primary sclerosing cholangitis (PSC) is a well known risk factor and accounts for approximately one-third of CCA cases. The annual risk of CCA in a patient with PSC is 0.6–1.5%, which is 100-fold higher than the rate observed in the general population [23,24]. Cystic diseases of the biliary tree, such as choledochal cysts and Caroli disease, also predispose to CCA. Although reported series are small, up to 28% of patients with untreated choledochal cysts may develop CCA [25]. In Asia, a common risk factor for CCA is infection with the liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis*. The life cycle of these organisms includes human consumption of undercooked fish bearing these organisms, which migrate to the biliary tree and produce more eggs. Chronic inflammation from these eggs is thought to predispose to CCA. Another risk factor for CCA is exposure to the radiocontrast agent Thorotrast (a radioactive suspension of thorium dioxide particles) that was used from the 1930s through the 1960s [26]. The risk for CCA and other hepatobiliary cancers is approximately 200 times that of non-exposed patients and the latency period for these cancers averages 35 years.

Presentation

The presentation of hilar CCA is usually obstructive jaundice. Patients complain of darkening of their urine; yellow discoloration of the skin, sclera, and mucous membranes; and pruritus. Patients may also have weight loss and fatigue from the occult malignancy. It is uncommon for patients to have cholangitis due to the insidious nature of the obstruction unless they have had previous episodes of cholangitis due to underlying PSC.

Diagnosis

Ultrasonography is the best first test for patients presenting with obstructive jaundice. Typically, ultrasonography will show dilation of the intrahepatic bile ducts. Ultrasonography can also determine the presence of intrahepatic metastases, occlusion of the hepatic arteries and the portal vein, or enlargement of lymph nodes that are concerning for metastatic disease. The next test is usually CT of the chest, abdomen, and pelvis. CT provides more detail needed for surgical consultation. Local invasion, relationship of the tumor to the hilar vessels, atrophy of the liver, regional and distant lymph node metastases, and distant metastases can all be readily appreciated with CT.

Endoscopic retrograde cholangiopancreatography (ERCP) is often performed at this juncture to investigate the extent of bile duct involvement and to provide biliary drainage. ERCP provides important information about the distal extent of the tumor along the bile duct and allows biopsy or brushing of the bile ducts to obtain histologic or cytologic material to support the diagnosis of CCA. A biliary stent may be inserted to alleviate obstruction or treat cholangitis. Often the proximal (intrahepatic) extent of the tumor is not well appreciated

by ERCP and patients must undergo a percutaneous transhepatic cholangiogram (PTC). PTC may also be necessary for drainage prior to a major hepatic resection. MRI is being used more extensively because of its ability to obtain information similar to that of a CT, but also to assess the vasculature with MRA/magnetic resonance venography (MRV) and the biliary tree using MRCP. Unfortunately, with current technology, the spatial resolution of MRCP is far less than direct cholangiography in terms of determining resectability. Angiography is infrequently obtained in this era.

Staging

The American Joint Committee on Cancer (AJCC) TNM (tumor, node, metastasis) classification and staging are shown in Table 35.2. The tumor (T) classification is based on extent of bile duct penetration, local vascular invasion, or invasion into surrounding structures. Local lymph node (N1) involvement generally includes the hilar (cystic duct, common bile duct, hepatic artery, and portal vein) lymph nodes alone. Other lymph node sites are generally considered metastatic disease. Metastatic disease (M1) includes distant lesions, satellite lesions within the liver parenchyma, and involvement of non-local lymph nodes.

Chemotherapy

The most common chemotherapeutic drugs for CCA are 5-flurouracil and gemcitabine. Both drugs have been tested in combination with a variety of other drugs, including cisplatin, oxaliplatin, paclitaxel, and others. No studies were randomized and most were either statistically underpowered or based on case reports. These studies all demonstrated poor response rates. Currently there is no randomized evidence showing a clear survival benefit for a specific chemotherapeutic regimen.

Resection and Outcomes

The resectability of CCA is predicated on the exclusion of extrahepatic and non-locoregional lymph node metastases. Laparoscopy is generally used to exclude peritoneal disease. Any obviously enlarged N2 level lymph nodes (e.g., peripancreatic, periduodenal, periportal, celiac, or superior mesenteric artery lymph nodes) are excised to rule out metastases. It is important to determine the extent of vascular invasion early in the course of resection of the tumor.

The extent of resection required for hilar CCA is determined by the anatomic involvement of the bile ducts with tumor. The Bismuth–Corlette classification (Figure 35.1) is used to guide resection. The resection of Bismuth–Corlette type 1 CCA (2 cm below the hepatic duct confluence) only requires resection of the extrahepatic biliary tree, the gall bladder, and regional lymph nodes. The surgical management of Bismuth–Corlette type 2 (<2 cm from the hepatic duct confluence) is similar to type 1 CCA, but may require removal of a portion of the caudate lobe or segment IVA due to their proximity to the hepatic hilus. Type 3a (involving the hepatic duct confluence and the right bile duct) and 3b (involving the hepatic duct confluence and the left bile duct) CCA are best addressed with resection of the extrahepatic biliary tree, the gall bladder, hepatic lobectomy, and regional lymphadenectomy. In all cases, bilioenteric continuity is restored with a hepaticojejunostomy. Type IV CCA (tumor extension to the right and left biliary radicals, or multifocal tumors) is rarely resectable by conventional means.

In general, the outcome of patients with unresectable CCA is poor, 5% or less at 5 years. In an early report by Nakeeb *et al.*, the rate of major hepatic resection was only 14% and the 5-year survival was 11% [27]. Since that time, improvements in 5-year survival have paralleled the increased utilization of major hepatic resection. In most contemporary series, 75–100% of patients had major hepatectomy (more than four segments resected, usually via a formal lobectomy) and 5-year survivals have ranged from 25% to 48% [28]. Morbidity in these series has varied from 27% to 76% and mortality from 0% to 12%. More recent reports have described a combination of extended hepatic resection (generally right trisegmentectomy) with concomitant vascular reconstruction (of the remnant left portal vein) [29]. Complete tumor excision (R0 resection) was achieved in 65% of patients treated with extended resection and the 5-year survival in these patients was 57%.

Transplantation

Early in the era of liver transplantation, CCA was thought to be an ideal indication for this procedure because the radicality of the procedure could address oncologic problems such as bilateral or diffuse hepatic duct involvement, invasion of the hepatic vasculature, and damaged

Table 35.2 TNM classification and staging of extrahepatic bile duct cancer [reproduced from the *AJCC Cancer Staging Manual*, 6th edn, 2002, with permission from the American Joint Committee on Cancer (AJCC)].

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hepatic parenchyma from predisposing diseases such as PSC. Several different groups utilizing only liver transplantation have reported 0–47% 5-year survival with recurrence rates of 50–80%. Given these results were not significantly different from those of hepatic resection and the scarcity of donor livers, interest in liver transplantation for CCA waned.

Several groups had reported encouraging results using radiation therapy for unresectable CCA or as neoadjuvant therapy prior to hepatic resection. Based on these findings, a protocol was developed at the Mayo Clinic for neoadjuvant chemoradiotherapy followed by liver transplantation for CCA that is either unresectable or arising in the setting of PSC. The general protocol is shown in

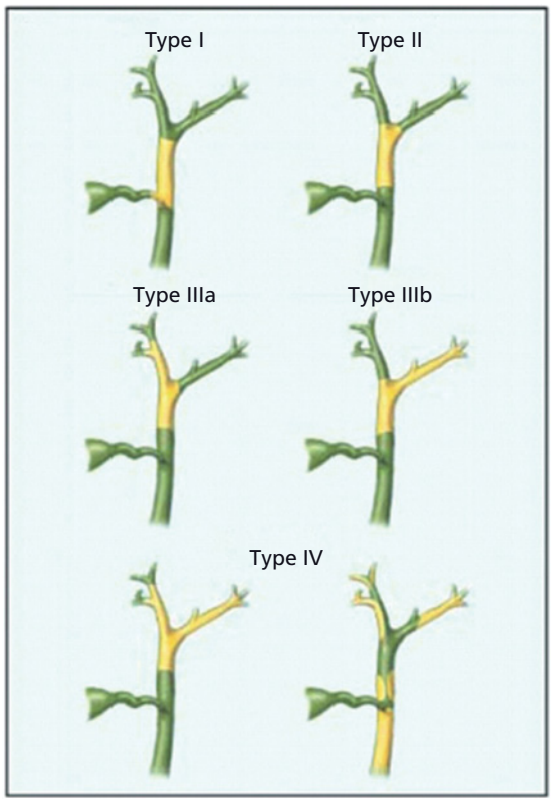

Figure 35.1 Bismuth–Corlette classification of hilar cholangiocarcinoma (reproduced from Groen *et al.*, *N Engl J Med* 1999; **341**:1369, with permission from the Massachusetts Medical Society).

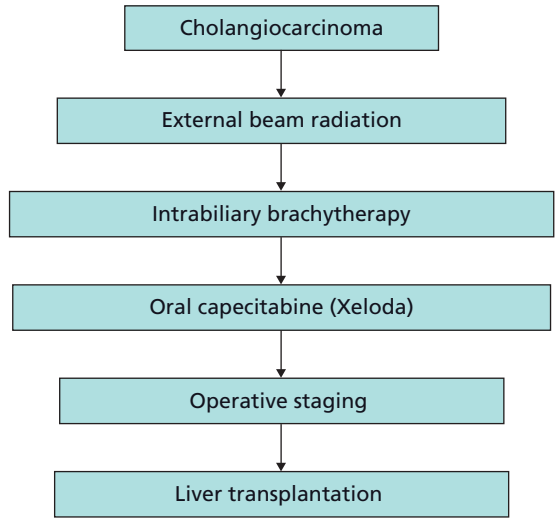

Figure 35.2 Current Mayo Clinic protocol for liver transplantation with neoadjuvant chemoradiation for hilar cholangiocarcinoma.

Figure 35.2. The success of this protocol is attributable to patient selection, neoadjuvant therapy with external beam radiation and intrabiliary radiation, operative staging of all patients prior to liver transplantation to exclude those with lymph node metastases or extrahepatic spread.

The early results of this protocol were encouraging and demonstrated proof of concept [30]. Twenty-five patients were enrolled and seven were eliminated due to metastatic disease or death during neoadjuvant treatment. Of the remaining 18 patients, six had metastases at their staging laparotomy. At 44 months of follow-up, patient survival was 100% with only one recurrence. A more recent analysis of this data examined 71 patients enrolled over an 11-year period and compared them to 54 patients with CCA who were explored for possible surgical resection [31]. Nine patients had disease progression or could not complete the neoadjuvant treatment, 14 patients had positive staging operations, and 38 finally underwent liver transplantation. Fifty-four patients were explored for surgical resection, and 28 patients had unresectable disease. Five-year survival after liver transplantation was 82% compared to 21% after resection. There were significant differences between these two groups (e.g., patient age and incidence of PSC), but it does not diminish the fact that the liver transplant patients had superior outcomes despite having more advanced disease. The most recent data from the Mayo Clinic show 80% 5-year survival after transplantation for patients with hilar CCA arising in PSC and 60% survival for those with *de novo* CCA.

Widespread application of liver transplantation for CCA has been limited by organ allocation and prioritization for deceased donor transplantation. Fortunately, the United Network for Organ Sharing has recently addressed this problem and provided guidelines for the regional review boards to grant requests for model for end-stage liver disease (MELD) score adjustments. Transplantation for patients with potentially resectable disease is highly controversial. Patients with *de novo* CCA have not fared as well as those with underlying PSC, and their survival after transplantation is only modestly better than after

resection. A randomized controlled trial has been proposed to definitively answer these questions, but it would be very difficult to carry out.

Conclusions

Gall-bladder carcinoma and CCA are relatively rare but important entities in the realm of gastrointestinal malignancies. The diagnosis of gall-bladder cancer is often delayed due to the paucity of symptoms. The optimal treatment of gall-bladder cancer is determined by the depth of invasion of the tumor in the gall-bladder wall – from simple cholecystectomy for T1a tumors to major hepatic resection for T2 tumors or greater. CCA is predisposed by several conditions familiar to the gastroenterologist, including PSC. Surgical therapy is guided by the pattern of bile duct and vasculature involvement noted on preoperative imaging. Complete tumor extirpation usually involves major hepatic resection and reconstruction of the biliary tree. Liver transplantation following neoadjuvant therapy is effective therapy for patients with unresectable hilar CCA or hilar CCA arising in PSC.

Take-home points

- Gall-bladder cancer is the most common malignancy of the biliary tract.
- Risk factors for gall-bladder carcinoma include cholelithiasis, bacterial infections of the biliary tree, and adenomatous polyps of the gall bladder.
- T1a tumors of the gall bladder are often discovered serendipitously at the time of cholecystectomy for gall stone disease and require no further treatment.
- More advanced tumors are best treated with resection of at least segments IVA and V of the liver and any involved structures.
- Hilar CCA (Klatskin tumor) risk factors include PSC, liver flukes, and chemical exposures.
- Surgical resection is the mainstay of treatment and complete resection often requires hepatic lobectomy and Roux-en-Y biliary reconstruction.
- Liver transplantation with neoadjuvant chemoradiotherapy has been used successfully in some centers for highly selected patients with unresectable hilar CCA and hilar CCA arising in PSC.

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36

CHAPTER 36
Biliary Strictures and Leaks

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Summary
Biliary leaks and strictures are commonly encountered clinical problems in gastroenterology. Bile leaks are most commonly due to iatrogenic duct injury during laparoscopic cholecystectomy which occur at a rate of approximately 3%. Bile leaks can usually be treated endoscopically by performing a sphincterotomy and placing a biliary stent. Patients with refractory leaks or complete transection of the bile duct require surgical management. Biliary strictures occur due to a variety of mechanisms, including iatrogenic, inflammatory and neoplastic causes. Endoscopic biliary dilatation and stenting is the mainstay of therapy for biliary strictures. Malignant biliary strictures and those refractory to endoscopic therapy may require surgical intervention.

Case

A 32-year-old man underwent laparoscopic cholecystectomy (LC) for acute cholecystitis. His operative course was complicated by significant bleeding, necessitating the placement of multiple clips to achieve hemostasis. Four days later he presented with increasing abdominal pain radiating to his right shoulder, fever, and dark-colored urine.

Physical examination was notable for right upper quadrant abdominal tenderness and scleral icterus. Laboratory studies revealed conjugated hyperbilirubinemia (total bilirubin 3.5 mg/dL) and mild elevations in serum aminotransferases (AST/ALT < 1.5 × upper limit of normal [ULN]). Computed tomography (CT) revealed a normal appearing liver with a non-dilated biliary tree, metallic clips at the hepatic hilum, and free fluid in the paracolic gutters. The patient underwent endoscopic retrograde cholangiography which revealed free flow of contrast into the peritoneum and no filling of the intrahepatic biliary tree (see Figure 36.1).

The patient subsequently underwent percutaneous cholangiography which confirmed a transected common bile duct with a large bile leak proximal to the transection. A percutaneous biliary tube was left to external drainage for several weeks for biliary decompression and to allow resolution of the local inflammatory reaction. The patient subsequently underwent surgical reconstruction of his biliary tree with a Roux-en-Y hepaticojejunostomy.

Introduction

The etiology, symptoms, and management of biliary strictures and leaks differ significantly. Whereas a variety of inflammatory, infectious, and neoplastic processes can cause biliary strictures, biliary leaks are most commonly due to iatrogenic injury (most commonly during LC). The evaluation and management of biliary leaks and strictures will be addressed separately.

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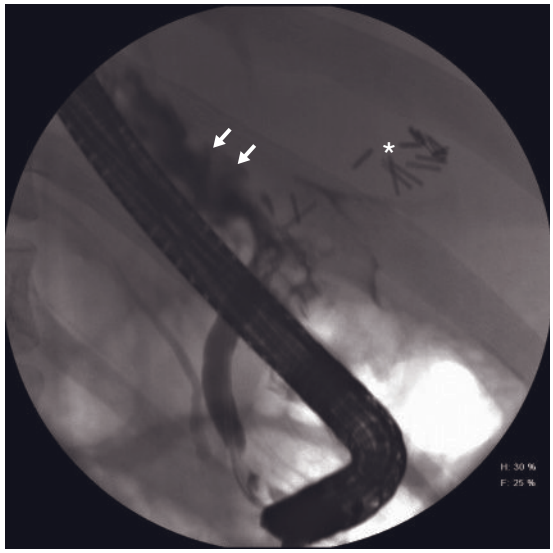


Figure 36.1 Endoscopic retrograde cholangiogram demonstrating a large bile leak (arrows) and complete transection of the common bile duct (note lack of filling of intrahepatic biliary tree). The presence of multiple surgical clips (asterisk) suggests a difficult intraoperative course.

Biliary Leaks

Definition and Etiology

Disruptions of the biliary tree resulting in bile leaks are usually iatrogenic in nature secondary to surgical or endoscopic manipulation of the bile ducts. Common surgical procedures which may be complicated by biliary leakage include cholecystectomy (laparoscopic and open), liver transplantation, and hepatic resections. Cholecystectomy is one of the most frequently performed surgeries in the USA, with approximately 750 000 cases performed annually [1,2]. Due to the relatively short recovery period compared to open cholecystectomy, LC has become the preferred surgical approach for symptomatic gall-bladder disease. The reported incidence of biliary leaks complicating LC is as high as 3%, several fold higher than that for open cholecystectomy (0.5%) [3,4]. The most common sources of biliary leaks following cholecystectomy are (1) the cystic duct stump or (2) accessory ducts of Luschka, which are small penetrating branches of the right hepatic duct in the gall-bladder fossa [5,6]. While the absolute rate of biliary leaks complicating LC is small, given the large number of LCs performed each year, iatrogenic biliary injury during LC is a major cause of biliary leaks [1,2].

Biliary leaks are also a significant complication following other forms of hepatobiliary surgery. As the numbers of patients with end-stage liver disease increases, more liver transplantations are done each year. In cadaveric liver transplantation, the biliary anastomosis is typically a duct-to-duct anastomosis (choledochocholedochostomy) with an overall biliary leak rate of approximately 10% [7]. However, due to the persistent shortage of suitable donor organs, increasing numbers of living donor liver transplantations (LDLTs) are performed each year. Due to the increased complexity of the biliary reconstruction during LDLT, biliary complications are the most common complication of LDLT. The reported incidence of bile leaks following LDLT is as high as 38% and is significantly impacted by the volume of LDLTs performed by the transplant center [6–8]. Biliary leaks following LDLT can originate from either the biliary anastomosis or from the cut surface of the liver allograft. The management of biliary leaks in liver transplant recipients is further complicated by the immunosuppressed state of the patient, leading to a potential increase in infectious complications [8].

Biliary leaks can also complicate hepatic and biliary resections. The reported rate of biliary leaks complicating hepatic resection (both anatomic and non-anatomic) and biliary resection with bilioenteric anastomosis ranges from 4% to 8.1% [6,9–11]. Not unexpectedly, technical surgical factors such as non-anatomic resections, vascular injury (with resultant biliary ischemia), and perioperative radiotherapy have been identified as predictors of postoperative bile leaks [9,11].

Biliary leaks can also result from iatrogenic bile duct injury during non-operative interventions such as endoscopic retrograde cholangiopancreatography (ERCP). Biliary leaks can occur from perforation of the bile duct from guide wire insertion or during therapeutic interventions such as biliary dilatation and stent placement; however, the overall incidence of biliary perforation complicating ERCP is low. In a single-center study from the Mayo Clinic, 34 bile duct perforations were observed among 12 427 procedures, yielding a rate of 0.3% [12–14].

Lastly, non-iatrogenic etiologies for biliary leak include trauma and spontaneous leaks. Both blunt trauma (most

frequently motor vehicle accidents) and penetrating injuries have the potential to cause biliary leaks. This complication of abdominal trauma is relatively rare (9%) and is often associated with other abdominal injuries such as liver laceration [6,15–17]. Traumatic biliary leaks are managed similarly to iatrogenic injuries (see below). Spontaneous biliary leaks are rare with scattered reports among both adults and children in the medical literature [18,19]. Patients typically present with peritonitis. In adult patients, underlying gall-stone disease is the most common etiologic factor.

Diagnosis

The diagnosis of biliary leak is largely dependent on imaging studies and may frequently be delayed. A high clinical index of suspicion is pivotal for early diagnosis and bile leaks should be considered in patients with unexpected symptoms following biliary tract manipulation or hepatobiliary surgery. Patients typically present with symptoms of bile peritonitis with abdominal pain, tenderness, nausea, vomiting, and fever. Laboratory derangements are non-specific and include leukocytosis and modest elevation of serum bilirubin levels [20].

Imaging modalities used to visualize the biliary tree may be used to diagnose biliary leaks, including non-invasive imaging with ultrasound, computerized tomography (CT), hepatobiliary iminodiacetic acid (HIDA) scans, and magnetic resonance cholangiopancreatography (MRCP). Direct cholangiography via the percutaneous (PTC) or endoscopic retrograde approach (ERCP) offers therapeutic potential but is usually performed after the presence of a bile leak is confirmed with non-invasive imaging.

Ultrasound is inexpensive and widely available, and is able to demonstrate fluid collections within the abdomen. However, ultrasound is highly operator dependent and cannot differentiate between bilomas and other fluid collections such as hematomas. Additionally, biliary dilatation may be absent in non-obstructed segments of the liver [21]. Although ultrasonography is an adequate screening test, other imaging modalities are needed to make a diagnosis of biloma. CT imaging has a higher sensitivity relative to ultrasound, can provide detailed images of fluid collections regarding their size and position, and can assess for coexisting vascular injury. While the layering of a hematocrit may be visualized and distinguish large hematomas from bilomas, CT imaging, like ultrasonography, cannot always differentiate between types of abdominal fluid collections.

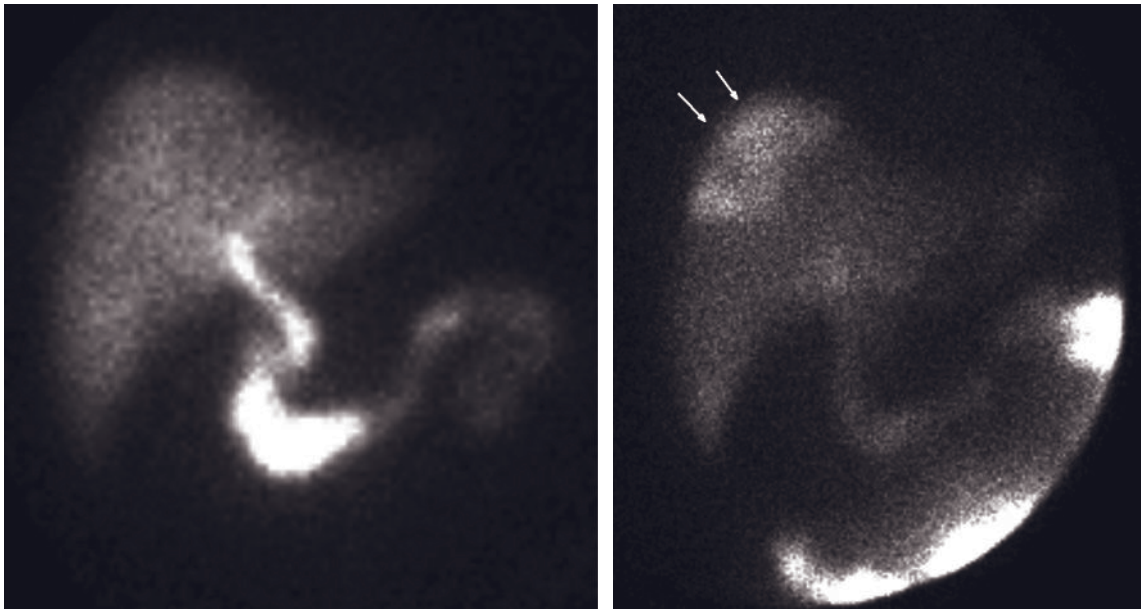
HIDA scans use a technetium-99m radiolabeled tracer that concentrates in the bile. While their use in the evaluation of biliary colic has decreased, HIDA scans remain a valuable tool in the evaluation of bile leaks. HIDA scans are highly sensitive for bile leaks with any measurable radiotracer visualized outside of the liver indicating a biliary leak (Figure 36.2) [21–23]. While HIDA scans can confirm the presence of a bile leak prior to invasive cholangiography, they do not accurately localize the source of the leak.

MRCP provides detailed images of the biliary tree non-invasively. Recent studies have confirmed the accuracy of diagnosis of iatrogenic biliary lesions via MRCP but comparative studies are lacking [24]. Limitations of MRCP include the lack of potential for therapeutic interventions and the additional cost of a non-invasive study prior to definitive management via invasive cholangiography. Metallic objects, such as surgical clips, and patient motion can significantly degrade MRCP images.

Direct cholangiography for visualization of the biliary system remains the gold standard for diagnosing bile leaks. The biliary tree can be accessed percutaneously or endoscopically via ERCP. In addition to being able to identify the exact source of the leak, these methods of direct cholangiography are the mainstay of non-surgical management of bile leaks. Percutaneous transhepatic cholangiography (PTC) and ERCP are invasive procedures that require operator expertise. Risks include sedation complications, bleeding, cholangitis, and pancreatitis (Table 36.1).

Management and Therapy

Biliary leaks require rapid intervention as they can be a source of significant pain and morbidity. While bile leaks can be managed with percutaneous drainage, endoscopic therapy has become the most common form of management. Surgical repair is typically reserved for patients failing endoscopic management or those with transected bile ducts. Drainage of bile collections to an extracorporeal source or via the small intestine and decompression of the biliary tree are the mainstays of therapy in minor biliary leaks [6]. Percutaneous tubes can be placed surgically at the time of biliary damage, or percutaneously through imaging modalities such as CT, ultrasound, or fluoroscopy.



(a) (b)

Figure 36.2 (a) Technetium-99m hepatobiliary iminodiacetic acid cholescintigraphy (HIDA) scan demonstrating prompt biliary tracer excretion. (b) Delayed images confirm the presence of a bile leak with a biloma at the dome of the liver (arrows).

ERCP is the most common form of management of bile leaks and is less invasive than PTC. ERCP interventions of nasobiliary drain placement, sphincterotomy, and biliary stent placement have been shown to be effective management techniques in biliary leaks [14,25]. Biliary stents do not need to cross the area of the bile leak, as transpapillary stent placement and sphincterotomy provide a path of low resistance for the bile to drain into the bowel and to allow for healing of the damaged bile duct. Endoscopically placed stents are typically left *in situ* for 4–6 weeks. These stents must subsequently be removed, requiring repeat ERCP. Success rate for the endoscopic management of bile leaks is greater than 80% [14].

Biliary leaks which require surgery are those caused by major damage to the biliary tree, such as complete transection of the common bile duct, or those not amenable or not controlled by biliary stenting. The type of surgical repair depends upon the site of the leak and the preoperative anatomy. Surgical therapies include end-to-end biliary anastomosis, Roux-en-Y repair, and hepaticojejunostomy.

Biliary Strictures

Definition and Etiology

Biliary strictures can be characterized by their etiology (benign versus malignant), distribution (focal versus diffuse), or location (intrahepatic versus extrahepatic) (Table 36.2). A detailed medical history and physical examination can provide important clues to the etiology of biliary strictures. It is important to identify prior abdominal surgery, radiation, or biliary tract instrumentation as potential risk factors for iatrogenic strictures. Biliary strictures typically present with symptoms of cholestasis, including jaundice and pruritus. Significant unintentional weight loss suggests a malignant biliary stricture. Physical examination may reveal cutaneous excoriations if the pruritus associated with cholestasis is severe. The presence of stigmata of chronic liver disease, such as spider angiomata, and splenomegaly suggests a chronic disorder such as primary sclerosing cholangitis.

Laboratory evaluation of patients with biliary strictures will typically reveal elevated liver chemistries with

Table 36.1 Imaging modalities for the evaluation of biliary leaks.

Imaging technique	Advantages	Disadvantages
Non-invasive		
Ultrasonography	• Widely available • Relatively inexpensive • No ionizing radiation • Sensitive for small amounts of intra-abdominal fluid	• Cannot distinguish between bile and other fluids • Biliary segments decompressed by a bile leak are non-dilated • Operator dependent
Hepatobiliary iminodiacetic acid cholescintigraphy	• Highly sensitive for detection of bile leaks	• Cannot localize source of bile leak
Computed tomography	• Widely available • Allows evaluation of important vascular structures and other pertinent anatomy • May distinguish between bilomas and hematomas	• Requires intravenous contrast for optimal images • Ionizing radiation
Magnetic resonance cholangiopancreatography	• No ionizing radiation • Provides detailed cholangiogram images • Allows evaluation of important vascular structures	• Requires intravenous contrast for optimal images • Image quality degraded by metallic objects such as surgical clips • Subject to motion artifacts from respiratory movement • Less widely available • Relatively expensive
Invasive		
Percutaneous transhepatic cholangiography	• Allows access to proximal biliary tree when distal ducts occluded or transected • Allows therapeutic biliary drainage and stenting	• Most invasive • Less widely available • Requires skilled operator
Endoscopic retrograde cholangiopancreatography	• Less invasive • More widely available • Allows therapeutic biliary drainage and stenting	• Highly operator dependent • Risk of pancreatitis

a cholestatic pattern. Serum alkaline phosphatase is typically elevated more than twice the ULN, and total and direct bilirubin levels are elevated. Significant elevations of alkaline phosphatase in the absence of hyperbilirubinemia suggest either an infiltrative hepatic disorder (e.g., amyloidosis) or elevation in non-biliary alkaline phosphatase isoenzymes (e.g., alkaline phosphatase bone isoenzyme). Total bilirubin levels exceeding approximately 8 mg/dL suggest underlying hepatic dysfunction as opposed to biliary obstruction alone. Laboratory evaluation of patients with biliary strictures should include assessment of hepatic synthetic function (serum albumin level, prothrombin time) to assess for the presence of underlying chronic liver disease. Care must be taken in assessing coagulopathy associated with biliary strictures as prolongation of the prothrombin time may simply reflect vitamin K malabsorption due to cholestasis rather than hepatic synthetic dysfunction. Patients with prolongation of prothrombin time should be treated with parenteral vitamin K supplementation and be reassessed. Additional serologies such as serum immunoglobulin levels and cancer antigen 19-9 (CA19-9) measurement may be appropriate for the evaluation of biliary strictures in selected cases.

Benign Strictures—Focal

Postoperative Strictures. Among focal benign strictures, iatrogenic injury is a common etiology. Focal strictures may be postoperative in nature and are most likely to occur at the site of inadvertent biliary injury, such as bile duct injury during LC, or at the site of a biliary–biliary or biliary–enteric anastomosis. As with bile leaks

Table 36.2 Clinical characteristics of biliary strictures.

Etiology	Distribution	Location	Clinical features
Autoimmune pancreatitis	Diffuse	Intrahepatic and/or extrahepatic biliary tree	• Edematous "sausage-like" pancreas • Retroperitoneal fibrosis • Elevated IgG4 levels • Responsive to steroid therapy
Cholangiocarcinoma	Focal	Hilar (most common), extrahepatic biliary tree	• Weight loss • Elevated CA19-9 levels • History of primary sclerosing cholangitis
Chronic pancreatitis	Focal	Distal extrahepatic biliary tree	• History of recurrent acute pancreatitis or alcohol abuse • Steatorrhea • Chronic abdominal pain
Ischemic	Diffuse	Intrahepatic and/or extrahepatic biliary tree	• History of hepatobiliary or liver transplant surgery • History of vasculitis
Primary sclerosing cholangitis	Diffuse	Intrahepatic and/or extrahepatic biliary tree	• History of inflammatory bowel disease
Postoperative	Focal	Site of biliary anastomosis	• History of biliary tract surgery

complicating cholecystectomy, the incidence of bile duct injury leading to strictures has increased with the adoption of laparoscopic surgical techniques [1,2]. Postoperative strictures are typically smooth and tapered in appearance when visualized with cholangiography. The clinical presentation is frequently delayed and occurs weeks to months following surgery as scar tissue contracts leading to stricture formation [26].

Biliary stricture formation is a common complication of liver transplant surgery and may occur at the donor-to-recipient biliary anastomosis (choledochocholedochostomy) or at the biliary–enteric anastomosis (hepaticojejunostomy). The rate of biliary stricture formation following LDLT is significantly higher than following cadaveric liver transplantation with up to 40% of patients developing some form of biliary complication [7,8].

Chronic Pancreatitis. A history of steatorrhea in a patient with a distal biliary stricture suggests pancreatic disease as an etiology. Up to a third of patients with chronic pancreatitis can develop distal common bile duct strictures. Patients with chronic pancreatitis-related biliary strictures frequently present with abdominal pain in addition to cholestasis [14,27]. Evaluation for causes of chronic pancreatitis (recurrent acute pancreatitis, alcohol abuse) is recommended and pancreatic neoplasms must be excluded.

Other Causes. A variety of other causes of benign biliary strictures have been reported and include radiation-induced strictures, parasite infestation, tuberculous lymphadenopathy, and biliary varices [28–31].

Benign Strictures—Diffuse

Primary Sclerosing Cholangitis (PSC). PSC is a chronic cholestatic disorder of unknown etiology. It is strongly associated with inflammatory bowel disease, occurs most frequently in men, and typically affects younger patients. Chronic inflammation of the bile ducts leads to multifocal biliary strictures in patients with PSC. Stricture formation often involves both the intrahepatic and extrahepatic biliary tree [32]. Over time, progressive cholestasis leads to liver fibrosis and dysfunction in patients with PSC. Careful physical examination may reveal stigmata of chronic liver disease such as cutaneous spider angiomata. While strictures in PSC are amenable to endoscopic therapy, they often recur [14,32]. PSC is a major risk factor for the development of cholangiocarcinoma and care must be taken to exclude a superimposed

cholangiocarcinoma during the evaluation of biliary strictures in patients with PSC [33].

Autoimmune Pancreatitis/IgG4-Associated Sclerosing Cholangitis. Autoimmune pancreatitis is an inflammatory disorder which is associated with systemic manifestations and an inflammatory cell infiltrate characterized by immunoglobulin G4 (IgG4) staining cells. A subset of patients with autoimmune pancreatitis develop biliary involvement leading to focal or diffuse biliary stricturing. Patients are typically older and present with painless jaundice; the clinical presentation can masquerade as a malignant process [34]. Features which suggest autoimmune pancreatitis include elevated serum IgG4 levels, an edematous and featureless pancreas on imaging, and abnormalities outside the pancreatobiliary tract such as retroperitoneal fibrosis [35]. Patients frequently respond to corticosteroid therapy with normalization of liver enzymes and resolution of biliary strictures, but relapse is common following steroid withdrawal [34].

Ischemic Cholangiopathy. While ischemic cholangiopathy has been reported to complicate vasculitis and hemoglobinopathy, it most commonly occurs following hepatic artery injury during surgery [36,37]. Vascular injury can occur during LC, resulting in diffuse biliary stricturing. Biliary ischemia most commonly complicates liver transplantation where thrombosis of the hepatic arterial anastomosis can lead to disastrous biliary ischemia with multifocal structuring and biliary abscess formation. Risk factors for ischemic cholangiopathy in liver transplant recipients include prolonged preservation time and the use of organ grafts from non-heart beating donors [38].

Malignant Strictures

Malignant diseases of the pancreatobiliary tract which present with biliary strictures and obstruction include cholangiocarcinoma and pancreatic adenocarcinoma. Cholangiocarcinoma most commonly presents with a hilar mass which causes bilateral biliary obstruction (Klatskin tumor). Cholangiocarcinoma can also present as a more distal extrahepatic biliary stricture without significant mass effect. Cholangiocarcinoma must be considered in patients with PSC and a dominant stricture. Adenocarcinoma arising in the head of the pancreas prototypically presents with painless jaundice and irregular distal common bile duct stricture (Figure 36.3). Biliary strictures may also be caused by extrinsic compression of the biliary tree from intrahepatic metastases or from bulky malignant perihilar lymphadenopathy [39].

Management and Therapy

The mainstay of therapy of biliary strictures is endoscopic retrograde cholangiography with biliary dilatation and stenting. The success of endoscopic management of biliary strictures is dependent upon the etiology of the stricture, its location, its length, and the skill of the operator. Focal strictures are more amenable to endoscopic management than diffuse stricturing. Cross-sectional imaging with CT or MRCP can provide the biliary endoscopist with important information regarding the characteristics of the stricture, the presence or absence of metastatic disease in malignant strictures, as well as the number and location of undrained hepatic segments prior to biliary intervention, and is, therefore, strongly recommended [40,41] (Figure 36.4).

Benign postoperative strictures are amenable to balloon dilatation. When required, plastic biliary stents

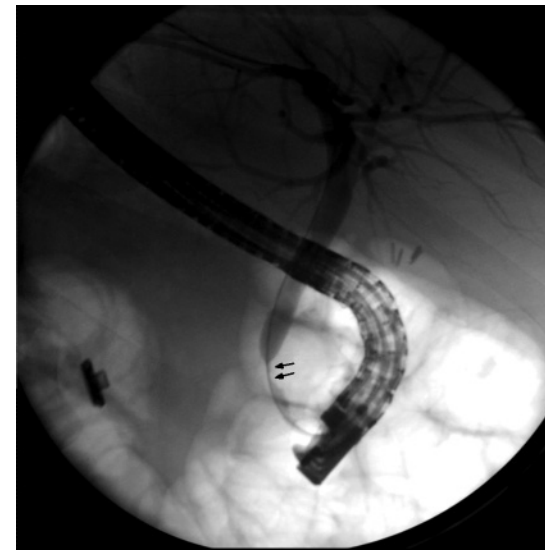


Figure 36.3 Endoscopic retrograde cholangiogram demonstrating a distal biliary stricture (arrows) in a patient presenting with painless jaundice. Tissue sampling confirmed the diagnosis of pancreatic adenocarcinoma.

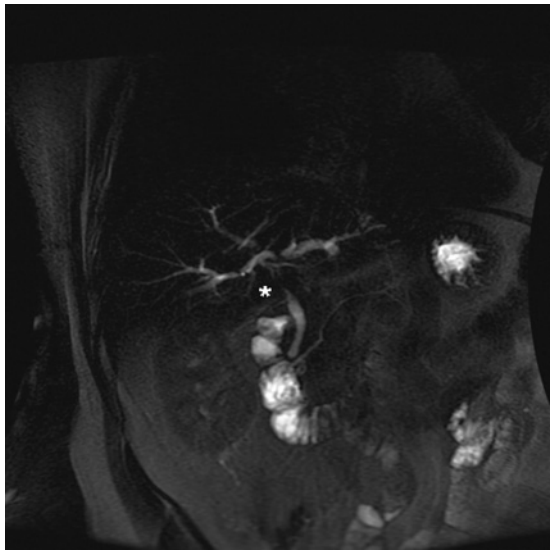


Figure 36.4 Magnetic resonance cholangiopancreatogram demonstrating short stricture of the common hepatic duct (asterisk) near its bifurcation.

are placed endoscopically to dilate the stricture. Multiple stents may be used to increase the caliber of the stricture. Plastic biliary stents should be replaced at 6–8-week intervals to prevent stent occlusion and secondary cholangitis. In difficult cases, multiple stent exchanges may be necessary, with increasing stent numbers and diameter, before the stricture resolves. In patients in whom endoscopic stenting is not possible, PTC with antegrade stent placement may be necessary. Refractory strictures require surgical correction, although this is infrequent [14,26].

Benign strictures due to PSC are typically amenable to endoscopic therapy. Balloon dilatation of dominant strictures may be sufficient to achieve patency in patients with limited disease. Patients with difficult strictures may benefit from biliary stenting to promote patency following balloon dilatation. In patients with a dominant stricture, brushings for cytology to exclude underlying cholangiocarcinoma are required [14,32]. Patients with cholestasis from diffuse biliary strictures are more difficult to manage. Multifocal strictures in both the right and left intrahepatic systems may require percutaneous drainage or a combination of percutaneous drainage with endoscopic stenting. In patients in whom cholestasis does not resolve following biliary stenting, small duct disease and advanced fibrosis need to be considered. Patients with refractory cholestasis or evidence of advanced hepatic fibrosis should be referred for a transplant evaluation.

Benign strictures secondary to chronic pancreatitis are frequently difficult to manage endoscopically and controversy over the most appropriate approach to management exists. The recurrence rate of biliary strictures due to chronic pancreatitis following endoscopic stenting is high, and patients with chronic calcific pancreatitis are the least likely to respond, with durable response rates of less than 10%. Surgical decompression has been considered the gold standard and is recommended for patients with biliary strictures secondary to chronic pancreatitis who have failed endoscopic therapy [14,27,42]. Patients with chronic pancreatitis are at increased risk for the development of pancreatic adenocarcinoma, and the possibility of an underlying malignancy should be considered in all patients with difficult to manage biliary strictures secondary to chronic pancreatitis.

Autoimmune pancreatitis with IgG4-associated cholangitis is a recently recognized disease entity. When IgG4-associated cholangitis is suspected, due to elevated serum IgG4 levels, the presence of typical pancreatic findings or other associated features, a trial of corticosteroid therapy should be considered [34,35]. In patients with steroid-responsive disease, the optimal long term treatment strategy remains unknown.

Malignant biliary strictures are frequently unresectable at presentation. The main goal of therapy is to relieve cholestasis, treat pruritus, and promote biliary drainage. In patients with distal obstructing lesions (e.g., pancreatic head adenocarcinoma), both hepatic lobes can be drained by stenting the common bile duct. In patients presenting with hilar cholangiocarcinoma, both hepatic lobes are frequently obstructed. The palliation of cholestatic symptoms typically requires that only one hepatic lobe be decompressed. Contamination of the atrophic and obstructed lobe should be avoided to prevent bacterial seeding of undrained fluid collections [14,33]. Cross-sectional imaging (CT or MRI) obtained prior to intervention provides the biliary endoscopist with critical information about the location of atrophic liver segments that will not benefit from drainage.

For patients who require biliary decompression during the course of evaluation of malignant biliary strictures before a determination regarding future surgery or radiotherapy is made, plastic biliary stents should be used due

to their ease of removal. Once a determination about surgical candidacy is made, consideration should be given to the use of self-expanding metal biliary endoprosthesis which maintain patency significantly longer than plastic stents in patients with unresectable disease [14,33]. Patients with complete malignant biliary obstruction may require a percutaneous approach for biliary decompression. Patients with cholangiocarcinoma and a good performance status may benefit from photodynamic therapy (PDT). In PDT a photosensitizing agent which accumulates in rapidly dividing cells is given to the patient parenterally. Patients are then treated with phototherapy delivered into the bile duct via a laser fiber advanced through ERCP [43]. PDT has been demonstrated to provide a modest survival benefit in addition to biliary stenting in patients with unresectable cholangiocarcinoma and should be considered an important palliative therapy. Limitations to PDT include patient photosensitivity following drug infusion as well as the lack of widespread expertise in the technique [44].

Take-home points

- Bile leaks most commonly occur following iatrogenic injury to the biliary tree during laparascopic cholecystectomy. The rate of biliary leaks following laparoscopic cholecystectomy is 3% and is several fold higher than following open cholecystectomy. The most common source of bile leaks following cholecystectomy are leaks from the cystic duct stump or the accessory ducts of Luschka in the gall-bladder fossa.
- Technetium-99m HIDA scans are highly sensitive for bile leaks with any measurable radiotracer visualized outside of the liver indicating a biliary leak.
- Bile leaks can be successfully managed with ERCP and biliary stenting in over 80% of cases. Biliary stents need not cross the bile leak to be effective, as sphincterotomy and transpapillary stenting provide a low resistance path for bile flow.
- Cross-sectional imaging with CT or MRI is strongly recommended prior to invasive cholangiography in the evaluation and management of biliary strictures and leaks.
- Biliary strictures can be classified based on etiology (malignant versus benign) as well as location and distribution.
- Focal biliary strictures are more amenable to therapy than diffuse stricturing processes. Strictures can be managed with biliary dilatation and stenting. Refractory strictures may require surgical intervention.

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