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R. Lawrence Reed, II
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Acute Cholecystitis

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Preface

On October 7, 2013, we moderated a panel discussion at the American College of Surgeons Annual Clinical Congress in Washington, DC, on the treatment of acute cholecystitis in high-risk patients. The interest in this symposium exceeded our expectations as the session attracted over 1000 attendees. The superb speakers (several of whom have become chapter authors of this text) discussed new therapies for the traditional conundrums of the management of gallbladder infections. The questions by the audience reflected the problems both the community surgeon and the experienced academic frequently faced in the management of acute cholecystitis. Clearly, the session and its response awoke our sensibilities to the magnitude of the challenges surrounding the management of acute cholecystitis in today's increasingly complex patients.

This presentation and its response alerted us to the potential utility of a book describing the management travails posed by the modern patient with acute cholecystitis. We remarked how the disease was not just "biliary colic" anymore but instead an increasingly frequent and heterogenous mix of outpatients with comorbidities and inpatients with "difficult gallbladders." Concurrently, we saw new technologies encroaching on the traditional operations with the ambition of decreasing patient morbidity. All these issues occurred in a disease process that every general or acute care surgeon would face weekly at a minimum. These observations solidified our resolve to create this text upon preliminary discussions with our eventual publishing company.

We wanted the work to tackle the complicated issues surrounding patients with acute cholecystitis. These areas focused on unusual presentations of biliary disease as well as the impaired physiologic states of the most critically ill medical patients.

We were fortunate to attract such a diversity of talented authors who shared our interest in the subject matter. Some are acknowledged luminaries in the surgical establishment while others are rising stars. All are interested in the management of surgical infections. We are indebted to them in producing exceptional treatments for each of their respective topics.

We finally also wish to thank the several individuals who were essential in the completion of this work. First and foremost in our gratitude would be our families and friends who supported us in this endeavor. Special thanks also go to the students and residents now and in the past who have inspired us to ask and answer questions regarding the perpetual improvement of our surgical practice. We are also grateful to our editors at Springer who believed in the mission of this text.

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History of Medical and Surgical Management of Acute Cholecystitis

1

Philip S. Barie and Philipp Franck

Awareness that bile and the gallbladder play some sort of role in health and disease dates from antiquity, but not to a knowledgeable degree except for the last two centuries. Although this volume deals specifically with acute cholecystitis, little is written specifically about it from an historic perspective. Therefore, discussed herein is the history of gallbladder surgery and some of those who pioneered the field, which it is hoped will make for informative and enjoyable reading. This is a story of ancient history, ignorance and superstition, anatomists doing clandestine postmortem examinations, the emergence of the scientific method, surgical audacity, and remarkable advances in technology.

The Liver and Biliary Tree in Antiquity

The stereotypical sequence of events that has characterized man's conquest of disease is tripartite: First, pathology is discovered and described (in antiquity, often clandestinely at the autopsy table). Thereafter, abnormal or altered physiology is described, followed by the correlation of clinical signs and symptoms [1]. Effective therapy usually lagged behind if it existed at all; for example, the use of ineffective nostrums to dissolve gallstones has continued almost to the present day.

Ancient writings that reference the liver and biliary tree have been dated to about 2000 B.C.E.; a Babylonian clay model of a sheep's liver that depicts the hepatic, cystic, and common ducts is in the collection of the British Museum [1]. Modern scholars have speculated that such models were considered to be divine and served as teaching tools for Babylonian and Assyrian priests instructing their students. That the liver itself, regarded as the "seat of the soul" for many centuries, was the centerpiece of Promethian torment in Greek mythology, underscores the centrality of the liver in belief systems of the time.

The *Liver of Piacenza*, an Etruscan artifact found in 1887 in a field near Gossolengo, Piacenza, Italy, is now preserved in the Municipal Museum of Piacenza (Fig. 1.1). It is a life-sized bronze model of a sheep's liver covered in Etruscan inscriptions that has been dated to the late second century B.C.E, a time during which the Piacenza region was garrisoned by Roman legions [2]. The Piacenza liver parallels the Babylonian artifact by representing major anatomic features-gallbladder, caudate lobe, posterior vena cava-as sculpted protrusions (Fig. 1.1). The outer rim of the Piacenza liver is divided into 16 sections that correspond to the 16 astrological

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Fig. 1.1 The Liver of Piacenza. Image in the public domain at www.wikipedia.com

houses of the heavens, each the "dwelling place" of an individual Etruscan deity.

The earliest extant anatomic evidence of biliary calculi dates from approximately 1500 B.C.E. [3], with multiple gallstones found in the remains of the Princess of Amenen from Thebes, whose well-preserved mummy harbored a gallbladder that contained at least 30 calculi. For more than a millennium, little changed thereafter regarding the mystical interpretation of the liver and biliary system.

Beginning with Hippocrates (460–370 B.C.E.) there developed gradually an appreciation for organ dysfunction and how this might result in disease. Hippocrates himself recorded that "in case of jaundice, it is a bad sign when the liver becomes hard [4]." Aristotle (384–322 B.C.E) recognized jaundice as a symptom of liver disease, but because his original writings have been lost, conjecture is the basis for the evaluation of his thought [5].

Mystery and ignorance characterized conceptualization of biliary tract disease for the next 15 centuries or more, extending through the time of Galen (129–201) and beyond. Galenic thought emphasized a more direct relationship between organs and clinical disease, and surmised that biliary disease could be treated by diet (after all, they had little else). However, Galen persisted in believing in the centrality of the liver to human life, struggling unsuccessfully to establish that the liver was to the total body what William Harvey later established the heart to be. With the collapse of Roman civilization, and the dissipation of its authority over disparate, far-flung populations, medical science devolved to superstition and quackery. Historical records of the period are scant, and records of scientific inquiry are nonexistent.

Avicenna (987–1037) wrote of biliary fistulae that developed in the aftermath of incision and drainage of an abdominal wall abscess [5], many of which were undoubtedly from the gallbladder. It is unlikely that anything more was understood or undertaken, given the rudimentary nature of the anatomic drawings Avicenna collected into compendia.

In 1506, Antonio Benivieni (1440–1502) published the detailed description of two autopsies performed on females who died after a syndrome of right upper quadrant abdominal pain [6]. Gallstones were clearly described although not understood for what they were, but attributed to disease of the liver capsule, which caused the said capsule to sag or droop and form a "bag." Nonetheless, the observations represented the first correlation of biliary colic with autopsy findings. Other anatomic observations were made, nearly contemporaneously, by Andreas Vesalius (1514–1564), Gabriele Falloppio (1523–1562), and Jean Fernel (1497–1558); Fernel also described calculi passed per rectum and speculated about bile stasis as biliary pathophysiology for the first time. In 1761, Giovanni Battista Morgagni (1682–1771), heralded as the father of modern anatomic pathology, published the great work *De Sedibus et Causis Morborum per*

Anatomem Indagatis "Of the seats and causes of diseases investigated through anatomy," in five books printed as two folio volumes, which, once and for all, made pathologic anatomy a science, and altered forever the course of medicine.

During the ensuing three centuries, the growing appreciation for human anatomy led to a series of brilliant, crucial anatomic observations by the likes of Glisson, Heister, Santorini, Winslow, Wirsung, and Vater (Table 1.1). Better knowledge of anatomy, combined with more sophisticated understanding of biliary physiology [6], led to the hypothesis that biliary calculi could result from stasis within the gallbladder, and eventually, more than a century later to the idea that surgical extirpation might be possible. It would take the discovery of ether as a general anesthesic in 1842, and the more widespread availability of chloroform, to take the next leap forward, although cholecystectomy was still not

Table 1.1 Eponymous contributions to biliary tract anatomy and surgery

Gross anatomy
Glisson (1597–1677): Francis Glisson, of Dorset, England, turned to medicine relatively late in life, receiving his medical degree from Cambridge in 1634 at age 37 years. He published his greatest publication, *Anatomia Hepatis*, in 1654. He was the first to describe thoroughly the distribution of a common capsule investing the hepatic artery, portal vein, and bile duct, also the first to describe a sphincteric mechanism around the orifice of the common duct, and first to deduce that portal venous blood traversed a hepatic microcirculation to reach the vena cava
Heister (1683–1758): A thoroughly trained anatomist and surgeon, Lorenz Heister of Frankfurt-am-Main, Germany was a powerful force in the education of European surgeons (his 1743 *Chirugia* was the most popular surgical work of the eighteenth century). The "valves" of the cystic duct (shown later to be folds of mucosa that are present only in primates) were described first in his 1720 *Compendium Anatomica*, but are but a small example of his many contributions and teachings to advance the art of surgery
Santorini (1687–1737). The Venetian Domenico Santorini received his medical degree from Pisa in 1701, and in 1706 became a demonstrator of anatomy. His brilliance was abetted by the dissection of criminals obtained from the jails by consent of the prince. Despite his fame and skill, Santorini was impoverished and could not afford to publish contemporaneously, therefore his observation of a second pancreatic duct (made previously by others) was published posthumously in 1775. He would have doomed to obscurity had it not been for the physiologist Claude Bernard, who, in 1866 while studying pancreatic physiology, reaffirmed his contribution
Winslow (1669–1760): Jakob Benignus Winslow, born in Odense, Denmark of Swedish parents, received his medical degree from the University of Paris in 1705 after having been disowned (his father, a Lutheran minister, was displeased when young Winslow embraced Catholicism). He went on to a 40-year tenure as professor of anatomy. Among many eponymous structures, the epiploic foramen bears his name owing to his 1732 publication *Exposition Anatomique de la Structure du Corps Humain*
Wirsung (1600–1643): A Bavarian, little is known of the education of Johann Georg Wirsung, other that that he studied medicine and was appointed a prosector in anatomy at Padua. After his pupil, Maurice Hoffman, dissected the main pancreatic duct of a rooster and showed it to Wirsung, the latter was the first, in 1642, to replicate the dissection and finding in a human cadaver. No treatise or book survived his untimely death from a gunshot wound
Vater (1684–1751): Abraham Vater, a native of Lutherstadt-Wittenberg, a city in Saxony-Anhalt, Germany, described an elevation of the duodenal mucosa where "double ducts come together in a single combination" along with Paul Gottlob Berger. Their finding was referred to repeatedly in published materials as the Vater-Berger duct until the 1774 publication of *Bibliotheca Anatomia* by Albrecht von Haller (1708–1777), an illustrious pupil of Herman Boerhaave (1668–1738) who has been called "the father of modern physiology," which omitted attribution to Berger
Surgical (*operative*) *anatomy*
Calot (1861–1944): A French native, Jean-Francois Calot was interested primarily in the surgical correction of deformities arising from tuberculous bone disease, although he published extensively on orthopedic surgery. His doctoral thesis on cholecystectomy, published in Paris in 1890, described the isosceles triangle, whose base is bounded by the common hepatic duct, and the sides the inferior edge of the cystic artery and the superior edge of the cystic duct. Modern definitions replace the cystic artery with the liver edge as the superior border of Calot triangle. The cystohepatic angle, as it is also known, contains the cystic artery, the right hepatic artery, the accessory right hepatic artery, accessory bile ducts (if present), and the lymph node accompanying the cystic artery, described variously by Hartmann, Broca, and Mascagni as well as Calot. Thorough understanding of this anatomic triangle is crucial to the safe conduct of cholecystectomy

Table 1.1 (continued)

Courvoisier (1843–1918): Ludwig G. Courvoisier, a native of Basel, Switzerland, graduated in medicine from the university of his home city. After travel in Europe and a stint as a military surgeon during the Franco-Prussian War, he established a private clinic in Basel. The biliary tract was a principal interest of his, and he published extensively on diseases and management of biliary tract disorders, being among the first to describe the operative extraction of a common duct calculus. In an 1890 monograph reviewing 187 cases of bile duct obstruction, observation was made that led to *Courvoisier's law* (or Courvoisier gallbladder or sign), which states that in the presence of an enlarged nontender gallbladder accompanied by mild jaundice, the cause is unlikely to be gallstones
Hartmann (1860–1952): Henri Hartman had Alsatian and Parisian parentage; he studied in Paris and remained there his entire life. He performed and recorded meticulously at the Hotel Dieu in Paris more than 1000 operations annually for more than 20 years, and more than 30,000 in all. Hartmann became interested in surgical asepsis after Louis Pasteur (1822–1895) made a presentation to the Academy of Medicine in 1878, and dedicated himself to its study. Among many contributions, he described the ampulla or vesicle of the gallbladder as a pouch
Kocher (1841–1915): Theodor Kocher was born and lived his entire life in Bern, Switzerland, where he assumed the chair of surgery at age 31 and retained it for 45 years. He was awarded the Nobel Prize in Physiology or Medicine in 1909 for his work on the physiology and surgery of the thyroid gland, the first surgeon to receive the prize. Among innumerable contributions to surgery, physiology, and instrumentation, Kocher standardized in 1903 a technique for mobilization of the duodenum that has come to be known as the *Kocher maneuver*. Developed originally as an adjunct to gastroduodenostomy, it has since been used extensively for biliary and pancreatic operations when performed via his eponymous right subcostal incision
Morison (1853–1939): James Rutherford Morison, and Englishman, graduated in medicine at Edinburgh in 1857, where he was influenced greatly by Joseph Lister, First baron Lister (1827–1912) and also Watson and Billroth. He became associated with the Royal Victoria Infirmary in Newcastle in 1888, where he remained for 50 years. He described the eponymous Morison pouch (technically the hepatorenal space, below the lower pole of the right kidney after mobilization of the hepatic flexure, but now colloquially, but incorrectly, the right subhepatic space adjacent to the gallbladder fossa) in 1894
Oddi (1864–1913): Ruggero Oddi was born in Perugia, Italy, and as a student rediscovered the bile duct sphincter described initially by Glisson. His doctoral dissertation in 1889 for his degree from the University of Florence was the first to measure the resistance of the sphincter and the nonphysiologic dilation of the common duct that occurs post-cholecystectomy
Roux (1857–1934): Cesar Roux was a native of Mont-la-Ville, Vaud, Switzerland. Roux studied medicine at Bern, surgery with Kocher, and pathology with Theodor Langhans (1839–1915). He returned to Bern to assist Kocher after a 2-year sojourn visiting prominent surgical clinics throughout Europe. Roux was named Professor of Clinical Surgery and Gynecology upon the founding of the medical school of the University of Lausanne in 1890. He was among the first, in 1883, to recommend appendectomy for inflammation. He had great interest in surgical gastroenterology and described the eponymous en-Y anastomosis in 1897 for gastroenterostomy and in 1907 for bypassing esophagogastric neoplasia, since adopted widely for bile duct reconstruction

even imagined. As recently as 1859, learned contributions to the medical literature suggested creation of a cholecystocutaneous fistula as the operation of choice for the surgical management of symptomatic biliary calculi [5].

The Origins of Gallbladder Surgery

As intracavitary surgery became possible under general anesthesia, refinements of applied anatomy and surgical technique followed soon after. Contributions by such anatomists and surgical luminaries as Calot [7], Courvoisier, Hartmann, Kocher, Morison, Oddi, and Roux (Table 1.1) were instrumental, but pivotal advances, by design or happenstance, predated most of their observations.

In 1676, a physician named Joenisius removed extruding gallstones from a spontaneous biliary fistula of the abdominal wall, and thus has been credited with the first cholecystolithotomy [8]. Jean-Louis Petit (1674–1750) a French surgeon and the inventor of the tourniquet, described a cholecystotomy in his general treatise on surgical operations, on which he worked 12 years, and which was finished after his death by François-Dominique Lesné (1722–1800) [8]. By 1743, Petit was aware that drainage of the gallbladder via transabdominal incision was hazardous if the

gallbladder was not adherent to the abdominal wall, and that it was possible to drain or aspirate the gallbladder if it was [9]. Without imaging, the presence of adhesions could only be surmised. Therefore a two-stage approach was devised: First, the abdominal wall was incised down to the peritoneum, and caustic potash (potassium hydroxide) was applied to induce scarring. Some time thereafter, the second procedure to aspirate the gallbladder was undertaken after adhesions had formed. By 1800, the approach was customary if the gallbladder was distended but nonadherent [9].

By 1859, anesthetics were in general use; that year the German-born London physician Johann Ludwig Wilhelm Thudichum wrote that is should be possible, in known cases of symptomatic cholelithiasis, to make an incision and suture the intact gallbladder to the wound edge, and a few days thereafter to incise the gallbladder to create a fistula, which in due course could be explored for the removal of calculi. Apparently, this suggestion was not acted upon at the time [8].

The first reported case of formal operation for gallstone disease resulted from a surgical misadventure, although the outcome was successful. John Stough Bobbs (1809–1870) was a prominent Indianapolis physician, who had been trained in the apprenticeship model without much formal education [10]. However, in 1848 he was a co-founder of the Indianapolis Medical Society, and in 1849 became the inaugural Dean of the Indiana Central Medical School, where he instructed in anatomy and surgery [10]. In 1867, 31-year-old Mary E. Wiggins Burnsworth presented to him with a tender mass in her right lower quadrant. By history, the mass had been enlarging slowly in size for 4 years. She was unable to exercise, or pursue her vocation of operating a sewing machine. Bobbs believed she had ovarian pathology, and decided to operate. The operation took place on June 15, 1867 on the third floor of a building that housed a drugstore in downtown Indianapolis. Surgery was performed under chloroform anesthesia, with which Bobbs was familiar from his experience as a military surgeon during the American Civil War, but without benefit of asepsis or antisepsis. Cutting down directly on the mass, a cystic lesion was found that was attached to the right lobe of the liver, with adherent omentum. When opened, it yielded clear fluid (hydrops of the gallbladder) and between 40 and 50 calculi. Apart from postoperative urinary retention and a superficial incisional surgical site infection, she made a good recovery and lived thereafter for 46 years.

Credit for the first cholecystostomy accrues to James Marion Sims (1813–1884) (Fig. 1.2) [11], a pioneer of gynecologic surgery, who famously introduced silver wire sutures for the successful repair of rectovaginal and vesicovaginal fistulae. Sims, on April 18, 1878, operated on a female with jaundice in a one-stage procedure, and encountered a distended gallbladder, which he incised and then extracted multiple calculi therefrom. The opened gallbladder was anastomosed to the corner of the incision, leaving a drain within (of cotton gauze, as rubber drains were unknown at the time). Sims' patient succumbed 8 days later, probably from hemorrhage secondary to hypoprothrombinemia, but cholecystostomy

Fig. 1.2 James Marion Sims. Image in the public domain at www.wikipedia.com

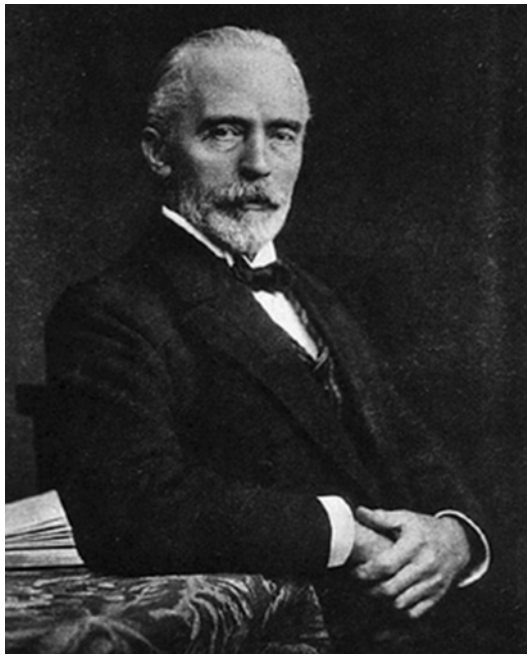

Fig. 1.3 Theodor Kocher. Image in the public domain at www.wikipedia.org

would be performed by many others in the ensuing decade.

Several reports of successful operations followed shortly thereafter. By year-end 1878, cholecystostomy had been performed by two additional surgeons, most notably in June by Theodor Kocher (1841–1915) (Fig. 1.3) (Table 1.1) who performed the first planned cholecystostomy, albeit using the two-stage technique, and William Williams Keen (1837–1932) a Philadelphia surgeon known for the first successful removal of a brain tumor, whose patient did not survive [8]. William Stewart Halsted (1852–1922) performed his first biliary tract operation, a cholecystotomy, upon his own mother in 1881 (Table 1.2) [8]. The cholecystostomy operation was popularized by the prominent Scottish surgeon Lawson Tait (1845–1899) (Fig. 1.4) who, working in Birmingham, England, did not perform his first until August 1879, but by 1889 had performed 55 such operations with but three deaths [8].

Karl Johann Langenbuch and the First Cholecystectomy

Not until 1882 was the first cholecystectomy performed. The surgeon was Carl J. Langenbuch (1846–1901) (Fig. 1.5) of Kiel, Germany, who had already performed the first nephrectomy for a renal tumor in 1877 [12, 13]. Langenbuch qualified in medicine at age 23, and was appointed surgeon to the Lazarus Hospital, Kiel, at age 27. Langenbuch noted that several mammalian species do not have a gallbladder, and concluded that human beings could also survive without this organ. Moreover, he believed that by creating gallbladder fistulae for gallstone removal, only temporary relief was afforded, and that the approach addressed the product of the disease, not the disease itself [9]. He devised the operation using the scientific method, by cadaver dissections over several years, and developed a method of surgical exposure by means of a T-shaped incision, the transverse limb of which was placed along the inferior margin of the liver, whereas the vertical component ran along the outer border of the right rectus abdominis muscle. The technique he developed involved ligation of the cystic duct with silk, dissection of the gallbladder from its liver bed, aspiration of the bile to prevent spillage, and only thereafter the transection of the cystic duct and removal of the gall bladder.

A 43-year-old male who had had repeated attacks of biliary colic and jaundice was selected as the index patient [12]. He had lost more than 35 kg body mass and was addicted to morphine. After 5 days of preoperative preparation (daily enemata), the operation was performed under strict asepsis and was carried out exactly as in the autopsy experiments; the gallbladder was chronically thickened and inflamed, and contained two cholesterol gallstones. One venous bleeder was ligated with catgut. Recovery was uneventful; the patient was afebrile and pain-free the next day, and was ambulatory by postoperative day 12. Two months later, the patient had regained 13.5 kg body mass.

Table 1.2 Vignettes in history referable to biliary tract disease

Alexander the Great (356–323 B.C.E): Historians have speculated that Alexander's terminal illness, at age 33 years, may have been acute cholecystitis complicated by peritonitis due either to gallbladder perforation or severe pancreatitis
William Stewart Halsted (1852–1922), in 1881, operated on his own elderly mother at her home in Albany, New York. She was described as desperately ill with jaundice, fever, and a palpable abdominal mass. He incised the mass, yielding pus and multiple gallstones. She recovered from surgery and the acute illness, but succumbed to calculous bile duct obstruction 2 years later
Halsted himself suffered from calculous biliary tract disease. He was hospitalized in September 1919 after a 5-to-6-year history of upper abdominal pain that was misdiagnosed as angina pectoris. For the prior 2 months he had suffered intermittent fever and jaundice. Cholecystectomy and common duct exploration for multiple common bile duct stones was performed on September 7, 1919. Profuse bile drainage from the wound and around the drainage tube postoperatively suggested a retained stone, but the drainage subsided 2 weeks after surgery, and he enjoyed well-being for 3–4 months before the pain and fever returned. He was finally readmitted to the hospital, gravely ill, in August 1922. George J. Heuer (1882–1950) and Mont R. Reid (1889–1943), both protégés of Halsted who had been among his favorite residents at Johns Hopkins, were summoned urgently to operate on Halsted from Cincinnati where they had been recruited earlier in 1922. They were successful in removing his single retained common bile duct stone, but he died on September 7, 1922, 16 days short of his 70th birthday, from pneumonia as a complication of cholangitis and surgery
Anthony Eden (Lord Avon), the youngest Foreign Secretary in British history, was before his affliction considered a possible successor to Churchill as Prime Minister. Eden underwent elective cholecystectomy on April 12, 1953 for chronic abdominal pain, gallstones, and prior episodes of jaundice. Although nothing was amiss according to the operative note, postoperatively he developed a biliary fistula and became jaundiced (serum total bilirubin concentration 15 mg/dL). At reexploration on April 29, there was found a subhepatic biloma. A T-tube was placed in the distal bile duct but it did not drain well; the proximal duct could not be identified. Eventually a sinogram along the drain tract found a communication with the common hepatic duct. After much political wrangling, the patient was transferred to Boston for surgery by Richard Cattell (1900–1964) of the Lahey Clinic. The third operation, on June 10, identified a biliary-duodenal fistula that was taken down. An end-to-side hepaticojejunostomy with enteroenterostomy was performed. The patient was well thereafter until 1954, but required reoperation by Cattell in April 1957 for stenosis of the right hepatic duct. He would remain ill episodically until 1970, when Cattell operated again for re-stenosis of the right hepatic duct. He would eventually be appointed Prime Minister in 1955, but was chronically and seriously ill at the time of the 1956 Suez crisis, his career and the course of history affected by a surgical error and calamitous consequences
President Lyndon Baines Johnson suffered an attack of biliary colic on September 7, 1965, as the Vietnam War was escalating. Evaluation by his Mayo Clinic physicians resulted in a recommendation for surgery. The President entered Bethesda Naval Hospital on October 7. The operation was performed the next day by George Hallenbeck and Donald C. McIlrath, both of the Mayo Clinic. Five hours later the President was able to stand. The next morning the President walked about his room. He returned to the White House on October 21

In his 1882 report, Langenbuch recommended cholecystectomy, after preliminary ligation of the cystic duct, as being less dangerous and more effective than cholecystotomy, but the naysayers were many and prominent [13]. Still prevalent was the notion that the gallbladder played an essential role in bile physiology. Leading the vitriol was Tait, famed for many advances but most notably salpingectomy as a life-saving intervention for ectopic pregnancy (which he opposed at first), who was vigorous in his condemnation of cholecystectomy rather than cholecystostomy (Tait being among the first to perform cholecystostomy in Europe). The debate was heated, and cholecystectomy was slow to be introduced. By 1886, only 33 gallbladder operations had been reported, with mortality of 27 %; of the 8 cholecystectomies, 5 had been performed by Langenbuch [13]. By 1890, 47 cholecystectomies had been reported by 27 surgeons, and by 1897, nearly 100 had been performed, albeit with a mortality rate of less than 20 %.

Choledochotomy

Although disputed and attributed variously to Ludwig Courvoisier (1843–1918) (Table 1.1), the London surgeon J.K. Thornton, and Herman Kümmell of Hamburg, Germany, the first

Fig. 1.4 Lawson Tait. Image in the public domain at www.wikipedia.org

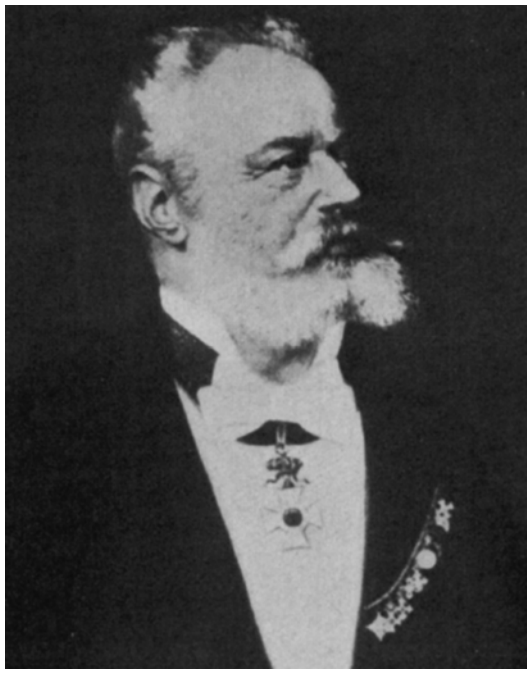

Fig. 1.5 Carl Langenbuch. Image in the public domain at www.wikipedia.org

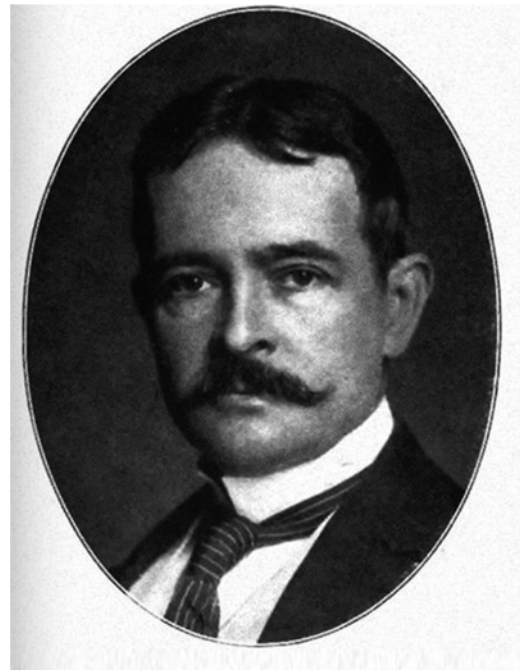

Fig. 1.6 Robert Abbe. Image in the public domain at www.wikipedia.org

choledochotomy is attributed most convincingly to Robert Abbe (1851–1928) (Fig. 1.6) [14], a native New Yorker who was the doyen of New York surgery at the turn of the twentieth century. The patient was a 36-year-old female, desperately ill with "blue-black" jaundice. Pus was drained, a bile duct calculus was removed, and the choledochotomy was closed with fine silk [15]. The patient was restored to good health. Abbe was a landmark contributor to the development of plastic and reconstructive surgery, and may have been the first surgeon to place after-loading catheters at surgery for radium treatment of an unresectable sarcoma [16], made possible by his friendship and collaboration with Marie and Pierre Curie, from whom he obtained a supply of radium. Radium exposure may have caused his eventual demise from aplastic anemia, which was staved off for several years by blood transfusions, itself an intrepid therapy of the day.

Hans Kehr (1862–1916) (Fig. 1.7), of Halberstadt and Berlin, Germany, introduced the T-tube (still in use, but called the Kehr tube in

Fig. 1.7 Hans Kehr. Image in the public domain at www.wikipedia.org

Europe) for drainage of the bile duct after choledochotomy [17, 18]. He was also instrumental in popularizing cholecystectomy as the operation emerged from controversy, refining the technique, and publishing in 1901 a monograph of his substantial experience of 433 laparotomies for gallstones. Kehr was well-trained. Among his teachers were Ernst von Bergmann (1836–1907) and Christian Albert Theodor Billroth (1829–1894). Bergmann was a pioneer of surgical asepsis who was first to introduce heat sterilization of surgical instruments. Billroth was the founder of modern abdominal surgery who, among numerous landmark achievements, introduced the concept of surgical audit and performed the first esophagectomy (1871), the first laryngectomy (1873), and (most famously), the first successful gastrectomy (1881) for gastric cancer. Kehr, working exclusively in small private clinics without a university appointment, performed his first cholecystectomy in 1890. A penchant for meticulous case documentation and his willingness to report his results led to international renown, although he is little known today outside of Germany. He developed numerous other biliary tract operations, including resection of common bile duct stricture and cholecystectomy for gallbladder carcinoma [18]. During his lifetime he performed more than 2600 biliary tract operations, and in 1913 published in Munich his classic two-volume *Die Praxis der Gallenwege-Chirurgie in Wurt und Bild* (The Practice of Biliary Tract Surgery in Words and Pictures), which laid a foundation for biliary tract surgery that lasted well into the modern era [18].

Biliary Endoscopy

In 1912, the brilliant but tempestuous Chicago surgeon John Benjamin Murphy (1857–1916) (Fig. 1.8) performed what was arguably the first biliary endoscopy by inserting an "electric" cystoscope into a cholecystostomy drainage tract [19]. Here in his own words [20] is what he saw and did: *It showed that a small stone was present in the hour-glass contraction zone*, *where the large stone had formerly been lodged. The cystoscope was pressed on this to the round ligament*; *a hook passed through the cystoscope to the stone. The stone was rotated and jammed against the edge of the cystoscope*, *and by this means it was extracted from its position. The drainage was removed at the end of five weeks. The gallbladder mucosa had resumed a smooth*, *glistening appearance*, *in contrast to the trachomatous appearance which* (sic) *had been present at the time of operation. The smooth condition of the gallbladder is our guide in removing the drainage tube*. The private journal in which this work was recounted [19] was the forerunner to *Surgical Clinics of North America*.

Murphy was an innovator who contributed greatly to the development of surgery [19]. He is credited with the first successful arterial anastomosis for the repair of a femoral artery transected by a gunshot wound. His eponymous "sign" of acute cholecystitis, inspiratory arrest during deep palpation of the right upper quadrant, remains in contemporary usage a century later. The Murphy anastomotic button was developed to facilitate cholecystoduodenostomy (at the time the preferred surgical treatment for acute cholecystitis)

Fig. 1.8 John Benjamin Murphy. Image in the public domain at www.wikipedia.org

without sutures. He developed it in the experimental animal laboratory that he maintained in a barn behind his house. The two halves of the brass button, each about one inch in diameter, were inserted into the hollow viscera to be anastomosed and held in place by purse-string sutures. When snapped together, the anastomosis was accomplished. In his 1892 report of three favorable cases using the invention [19], Murphy wrote: *It takes about as long to describe the operation as to perform it. The time occupied with the first lady on whom I operated was eleven minutes, from the entering of the peritoneal cavity until the closing of the same*. And further, as a measure of his audacity: *I decided to perform cholecystoenterostomy by my anastomosis button, which I had used for the first time on a dog six days previous*. The button became a commonly used method for intestinal anastomoses. It was the method of choice for such operations at the Mayo Clinic and elsewhere in the United States until the mid-1930s, and also adapted for vascular anastomosis, but not adopted. In a sense, the Murphy button was a forerunner of the modern end-to-end anastomosis (EEA) stapler [21].

Cholecystectomy in the Modern Era

Imaging

The twentieth century brought the introduction of imaging of the biliary tree, and numerous new and enhanced techniques almost to the present day. The era of plain radiography extended from 1895 to 1924 [22]. Sir William Osler, First Baronet (1849–1919) was unsure as late as 1897 as gallstones could be detected radiographically. The first report of X-ray visualization of gallstones occurred in 1900 in a presentation to the New York County Medical Society [23], but not without dispute. Unequivocal evidence would not come until 1910. The first percutaneous transhepatic cholangiogram was reported in 1922 using a air and a silver-containing contrast agent [22].

The era of contrast media extended from 1924 to 1960 [22]. It was known that phenolphthalein compounds were excreted by the liver and concentrated in bile. Working in St. Louis at the Washington University in 1924, Warren H. Cole (1899–1990), then a medical student, and Evarts A. Graham (1883–1957) (Fig. 1.9), the surgeon who performed the first successful pneumonectomy for bronchogenic carcinoma but at the time a surgical resident, succeeded in using IV tetrabromophenolphthalein cholecystography to visualize the canine gallbladder [24]. Serendipity played a role, in that the only animal in which visualization was successful had, in error, not been fed by the caretaker. Additional experiments confirmed the importance of an overnight fast. Successful visualization of the human gallbladder followed shortly thereafter, but using tetraiodophenolphthalein instead and in a lower dose they were able to visualize the gallbladder equally well while limiting the nausea, vomiting, and back pain that plagued earlier experiments. Eventually, sodium salts were found to be more soluble, and by 1925, tablets of sodium tetraiodophenolphthalein ushered in the era of oral cholecystography [22], By the 1950s the highly lipid-soluble iopanoic acid improved oral cholecystography further, but the modality is now of historic interest only.

Fig. 1.9 Evarts Graham. Image in the public domain at www.wikipedia.org

Fig. 1.10 Pablo Luis Mirizzi. Image in the public domain at www.wikipedia.org

The first intraoperative cholangiogram (IOC) was performed in 1931 by Pablo Luis Mirizzi (1893–1964) (Fig. 1.10), a surgeon who lived, was educated, served as Professor of Surgery at the National University, and died in Cordoba, Argentina [25]. He injected iodinated oil (lipodiol) at operation. It has been estimated that abnormalities of bile ducts are identified in 7–8 % of patients, although selection criteria are crucial to understanding the incidence, because some surgeons, but not all, recommend routine IOC during cholecystectomy. Mirizzi would also have named after him a syndrome of extrinsic common hepatic duct obstruction due to an impacted gallstone in Hartmann pouch, gallbladder infundibulum, or cystic duct, although his original conceptualization, ultimately proved incorrect, was of functional obstruction caused by a physiologic intraductal sphincter mechanism [25].

The period from 1960 to 1979 was an era of rapid technologic advancement [22]. Percutaneous transhepatic cholangiography using a sheathed needle was developed in 1962 by a group led by Frank Glenn (1899–1980) at Weill Cornell Medical College and The New York Hospital. Radionuclide imaging with HIDA (*N*-substituted 2,6-dimethylphenylcarbamoylmethyl iminodiacetic acid) was described in 1975; newer compounds that vary in the location and substitution of the phenyl ring now allow the gallbladder and biliary tree to be imaged even if the patient is jaundiced. Gray-scale ultrasound was introduced in 1970 and generally available by the early 1980s [25]. With improved probes allowing better beam formation and focusing, high-resolution, real-time sonography has become the technique of choice for the detection of gallstones.

The first clinical computed tomographic (CT) scan, of the brain, was performed on October 1, 1971 and announced publicly in 1972 by a group led by Sir Godfrey Newbold Hounsfield, CBE, FRS (1919–2004), an English electrical engineer who shared the 1979 Nobel Prize for Physiology or Medicine with Allan McLeod Cormack (1924–1988), a South African physicist, for his part in developing the diagnostic technique of X-ray CT [25]. While on a country outing,

Hounsfield imagined the possibility that one could determine the contents of a box by taking X-ray readings at all angles around the object. Applying this idea medically led him to propose what is now known as CT. At the time, Hounsfield was not aware of the work that Cormack had done on the theoretical mathematics for such a device. Hounsfield built a prototype head scanner and tested it first on a preserved human brain, then on a fresh cow brain from a butcher shop, and later on himself. The first CT brain scan was performed on a cerebral cyst patient at Atkinson Morley Hospital in Wimbledon, London, United Kingdom. In 1975, Hounsfield built a whole-body scanner, which technology became widely available by the early 1980s with numerous technical improvements over the ensuing 30 years.

Magnetic resonance imaging (MRI) was invented by Paul C. Lauterbur (1929–2007), an American chemist, in September 1971; he published the theory behind it in March 1973, and developed a way to generate the first MRI images, in 2D and 3D, using gradients [25]. In 1973, Lauterbur published the first MRI image and the first cross-sectional image of a living mouse in January 1974. In the late 1970s, Sir Peter Mansfield (1933–), an English physicist, developed a mathematical technique that achieved image acquisition in seconds rather than hours, and produced clearer images. The first MRI body scan of a human being was taken on July 3, 1977, and the first clinically useful image of a patient's internal tissues using MRI was obtained on August 28, 1980, which identified a primary chest neoplasm, an abnormal liver, and bone metastases. Magnetic resonance cholangiopancreatography (MRCP) was introduced in 1991. Lauterbur and Mansfield were awarded the 2003 Nobel Prize in Physiology or Medicine. The Nobel citation acknowledged Lauterbur's insight of using magnetic field gradients to determine spatial localization, a discovery that allowed rapid acquisition of 2D images. Mansfield was credited with introducing the mathematical formulae and developing techniques for efficient gradient utilization and fast imaging.

The Decrescence of Open Cholecystectomy

Open cholecystectomy, despite the initial resistance to its adoption, became the "gold standard" for a century [26]. At its zenith, the operation was successful and reasonably safe, although the subcostal incision used most commonly caused substantial morbidity, including pain and pulmonary dysfunction. Charles McSherry, who with Bjorn Thorbjarnarson was part of the group at The New York Hospital-Cornell Medical Center in New York City led by Glenn, the foremost American biliary surgeon of the era, summarized the Cornell single-center experience from 1932 to 1984 [26]. There were 14,232 patients operated on for nonmalignant biliary tract disease, with 237 postoperative deaths (30-day mortality), a rate of 1.67 %. Cholecystectomy was performed in 10,749 patients (60 deaths, 0.08 %). Among those, surgery was performed for chronic cholecystitis in 8910 patients with a mortality rate of 0.04 %, whereas the mortality rate was 1.20 % among the 1839 patients who underwent surgery for acute cholecystitis. Cholecystostomy was performed in 599 patients with a mortality rate of 10 % (60 deaths). Common bile duct exploration was performed with cholecystectomy or cholecystostomy in 2226 patients with 89 deaths (4 % mortality), whereas operations for stricture or miscellaneous conditions were performed in 284 patients with a mortality rate of 7.40 %.

Retained common bile duct stones were (and are) problematic after cholecystectomy. The incidence of common duct stones in the presence of gallstones is estimated to be 12–15 %, and increases with the duration of symptoms antecedent to surgery, and is higher in patients with acute cholecystitis. In the Cornell series, choledochotomy alone to search for stones (endoscopic retrograde cholangiopancreatography [ERCP] had been introduced only in the latter part of the reporting interval) was performed in 374 patients, with 21 deaths (5.61 %) [26]. Intraoperative cholangiography misses common duct stones in 1–2 % of imaging studies (e.g., small stones may

be misinterpreted as air bubbles introduced during instillation of contrast).

Ephemeral therapeutics were introduced to manage retained bile duct stones, or to avoid the morbidity of surgery altogether. After choledochotomy, a T-tube of 16F diameter was placed to facilitate threading of a Dormia basket down the tract to extract retained stones as an interventional radiologic procedure (if the common bile duct was too small to accommodate a tube of that size, the intraductal portion of the tube was shaved down to an appropriate dimension), a procedure introduced by the Argentine surgeon Mazzarello in 1972 [8].

Attempts to dissolve bile duct stones began in the 1950s by Best and Hicken, but their efforts were abandoned owing to severe pain and irritation. The concept was reintroduced in 1972 by Lawrence Way and John Englebert Dunphy (1905–1981) of San Francisco, who instilled a solution of cholic acid [8]. Methyl tert-butyl ether engendered transient latter interest for chemical dissolution [27], but also had to be instilled by needle cholecystotomy or via T-tube. Extracorporeal shock wave lithotripsy (ESWL) [28], although effective for nephroureterolithiasis, never succeeded as a therapy for gallstones because mobile gallstones were not a suitable target for the focused ultrasound pulse, stone fragments could escape containment by the gallbladder and result in common bile duct calculi, and recurrence of calculi was commonplace [29].

The First Laparoscopic Cholecystectomy

The clinics of the University of Erlangen, Germany, contributed substantially to the development of minimally invasive biliary tract manipulation [30]. The Erlangen clinic was in the vanguard of the development in the 1970s of ERCP and endoscopic papillotomy using diathermy. The first laparoscopic cholecystectomy on September 12, 1985, is credited to Erich Mühe [31] (Fig. 1.11), formerly an assistant in the surgical clinic, who was stimulated by those around

Fig. 1.11 Erich Mühe. Image in the public domain at www.wikipedia.org

him and the pioneering work of Kurt Semm (Fig. 1.12), from Kiel, Germany.

Several technical innovations presaged the moment. The history of the development of laparoscopic surgery is beyond the scope of this chapter, but has been reviewed extensively [32]. Semm was instrumental, developing thermocoagulation, an electronic gas insufflator, and intracorporeal knotting and suturing. Prior to his performance of the first laparoscopic appendectomy on September 13, 1980 [33], closing the appendiceal stump using sutures, Semm had become skilled at numerous gynecologic laparoscopic operations. It took Semm several years to have his report published, owing to ignorance, shortsightedness, and perhaps envy on the part of editors and reviewers of several peer-reviewed journals.

Substantial contributions were also made by Walker Reynolds, Jr., who introduced into clinical practice a pistol-grip hemoclip applier and scissors developed by Edward Weck & Co., Research Triangle Park, North Carolina for Reynolds [34].

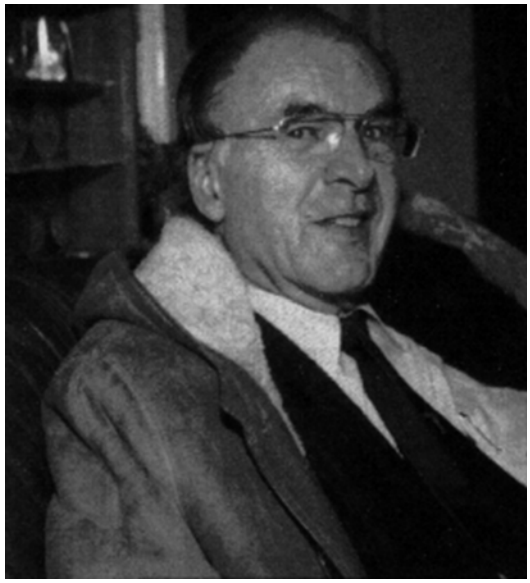

Fig. 1.12 Kurt Semm. Image in the public domain at www.wikipedia.org

Reynolds began to perform minimally invasive open cholecystectomies using the hemoclip applier and scissors via a vertical, right upper rectus abdominis muscle-splitting incision, retracting the muscle medially [35]. This lessened postoperative pain and allowed a quick recovery with a short postoperative hospitalization. In the 1990s, Reynolds confirmed by personal communication with Mühe that Mühe had utilized these devices. Mühe himself designed a new operative laparoscope called the "galloscope."

Mühe's Laparoscopic Cholecystectomy Technique

Mühe's description of his technique (ultimately gasless, using a single-incision technique) is as follows [36]: "*The first endoscope constructed and used by ourselves* ("*galloscope*") *had side-viewing optics, and an instrumentation channel with valves, a light conductor, and a duct for the establishment of continuous pneumoperitoneum by the Veress needle technique*; *the endoscope was introduced through the umbilicus into the peritoneal cavity. For the insertion, we used a sharp mandrin within a trocar sleeve. After removal of the mandrin, a trap valve was ejected from the inner wall of the tube to seal off escaping* CO_2. *When the gallbladder was removed under optical control through the endoscope, the top of the endoscope had to be taken off. However, the gallbladder could also be removed through the trocar sleeve. When this access route from the umbilicus or suprapubic abdominal wall to the gallbladder was used, a pneumoperitoneum was indispensable. Therefore, after the first six operations, we changed the method, and the remaining 88 patients were operated on using a simplified approach, namely laparoscopic cholecystectomy without pneumoperitoneum and without optical guidance. Using an access channel at the costal margin this served as a firm bone roof above the gallbladder, and neither a pneumoperitoneum nor optical guidance was necessary. Only one skin incision of 2.5 cm in length was required compared to at least 3 cm total length needed for three to four incisions when using a pneumoperitoneum* [36]." Mühe's laparoscope is shown in Fig. 1.13. Mühe performed 94 such procedures before another surgeon, Phillipe Mouret of Lyon, France, performed the first video-laparoscopic cholecystectomy in 1987 [33]. As in the early aftermath of the first open cholecystectomy, criticism was harsh; Mühe was even denied admission to the German Surgical Society upon his first application [33].

Technical Refinements

Unfortunately, laparoscopic cholecystectomy is associated with a higher incidence of bile duct injury than open cholecystectomy. There is a steep learning curve associated with the safe performance of laparoscopic cholecystectomy, but the risk is ever-present even for experienced surgeons. The incidence of laparoscopic common bile duct injury has been estimated to be 0.5 %, more than twice as high as with open operation [17]. Technical errors are usually at fault; most commonly, the common bile duct is mistaken for the cystic duct and clipped or even divided.

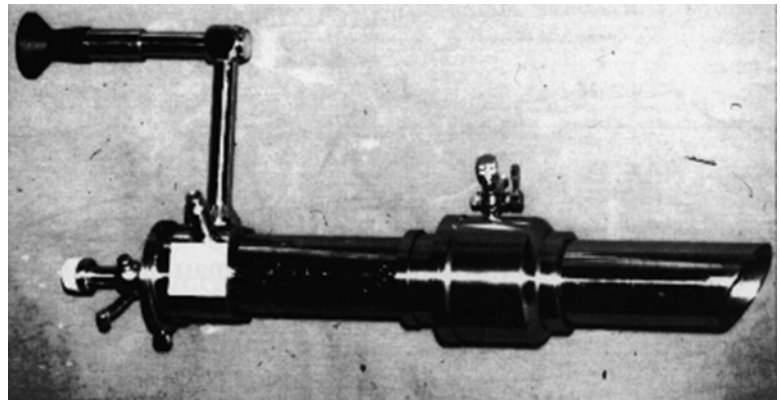

Fig. 1.13 Erich Mühe's "galloscope." Image in the public domain at www.wikipedia.org

Application of clips to a short cystic duct may inadvertently encroach on the common bile duct, resulting in stricture. Also, bleeding in Calot triangle that is clipped or coagulated indiscriminately may lead to injury.

The historic evolution and management of bile duct injuries is beyond the scope of this work, but has been reviewed extensively in the literature [37, 38]. However, technical refinements have made laparoscopic cholecystectomy safer. Notable is the description by Steven Strasberg in 1995 of the *critical view of safety* (CVS) [39]. To achieve the CVS, Calot triangle is cleared initially of fat and fibrous tissue. The distal gallbladder is then dissected from the cystic plate (gallbladder fossa) down to the junction of the gallbladder and cystic duct, demonstrating that only the cystic duct and cystic artery remain attached to the gallbladder, both of which should be visualized circumferentially. Once the CVS is achieved, the duct and artery can be occluded and divided in standard fashion, and the gallbladder detached and removed.

Laparoscopic Common Bile Duct Exploration

Laparoscopic common bile duct exploration was first reported in 1991 by Joseph B. Petelin of Shawnee Mission (Kansas City), Kansas, using a transcystic duct technique [40]. Among the first 22 patients, 21 attempts were successful and one resulted in open conversion. Subsequently, others have developed techniques for laparoscopic common bile duct exploration via direct choledochotomy. When performed, the common bile duct is usually closed primarily, which has been recognized to be safe and effective for many years.

Petelin has been a major contributor to the development of laparoscopic abdominal surgery, developing the first sets of curved laparoscopic surgery instruments in 1989, enabling operations of greater complexity to be performed. In that same year, he developed the technique of percutaneous cholangiography. Also attributed to Petelin are the first laparoscopic splenectomy, the first laparoscopic pancreatic cyst-gastrostomy, and the first laparoscopic gastrojejunostomy, all in 1991.

Laparoscopic Cholecystectomy in the United States

J. Barry McKernan and William B. Saye performed the first laparoscopic cholecystectomy in the United States on June 22, 1988 in Marietta, Georgia. Saye sutured the cystic duct and artery, but later they adopted the pistol-grip instruments to ligate the cystic duct and artery. Other American surgeons among the first to perform laparoscopic cholecystectomy in 1988 were Eddie J. Reddick and Douglas O. Olsen of Nashville, Tennessee, who also adopted the pistol-grip hemoclip applier and scissors to ligate and divide the duct and

artery. Saye and Reddick were among the primary teachers of the laparoscopic cholecystectomy technique in the United States, including to this writer. Laparoscopic cholecystectomy was a milestone in the development of surgery in the United States, not only on its technical merits, but also by accelerating the nascent shift to outpatient surgery, fostering an era of rapid change.

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Normal Biliary Anatomy and Pathophysiology of Gallstones

2

Caroline Maloney and Jared Huston

Embryology

During the fourth week of gestation, a bud arises off of the ventral wall of the primitive foregut, which eventually forms the duodenum. The liver diverticulum initially breaks into cranial and caudal portions—the cranial portion becoming the intrahepatic bile ducts and the caudal portion forming the gallbladder and cystic duct. The cranial diverticulum extends into the septum transversum mesenchyme and induces the formation of endothelium from the mesenchymal cells. The ductal cells then follow the development of the connective tissues of the portal venous system.

By the fifth week of intrauterine life, the cells between the liver bud and the remaining foregut proliferate and begin to form a primitive bile duct (Fig. 2.1). A distinct gallbladder bud forms off of this bile duct, and the connection between the two forms the cystic duct. The ventral pancreatic bud forms adjacent to these structures. By the sixth week, the ventral pancreatic duct rotates 180° posterior and medially to join the dorsal pancreatic bud. The duct of Wirsung (located in the ventral pancreatic bud) joins the common bile duct and empties into the duodenum via the ampulla of Vater. The duct of Santorini (located in the dorsal pancreatic bud) may fuse with the duct of Wirsung or may drain into the duodenum separately at the minor papilla, as seen in pancreas divisum [1, 2].

It is widely believed that the common bile duct becomes occluded with epithelial cell proliferation as it elongates, and by the end of the fifth week of development begins to recanalize moving distally toward the gallbladder, which remains solid until week 12. Failure of recanalization has been implicated in the pathogenesis of biliary atresia. However, some studies have failed to demonstrate the process of recanalization in human embryos [3]. As such, many aspects of biliary system development in utero remain unclear.

Anatomical Considerations

The biliary system functions to transport and store bile produced by hepatocytes in the liver. The gallbladder is the primary organ for bile storage, and it is located on the undersurface of the liver between segments IV and V (Fig. 2.2). Cantlie's line, which extends from the gallbladder fossa to the inferior vena cava, traditionally divides the liver into right and left lobes.

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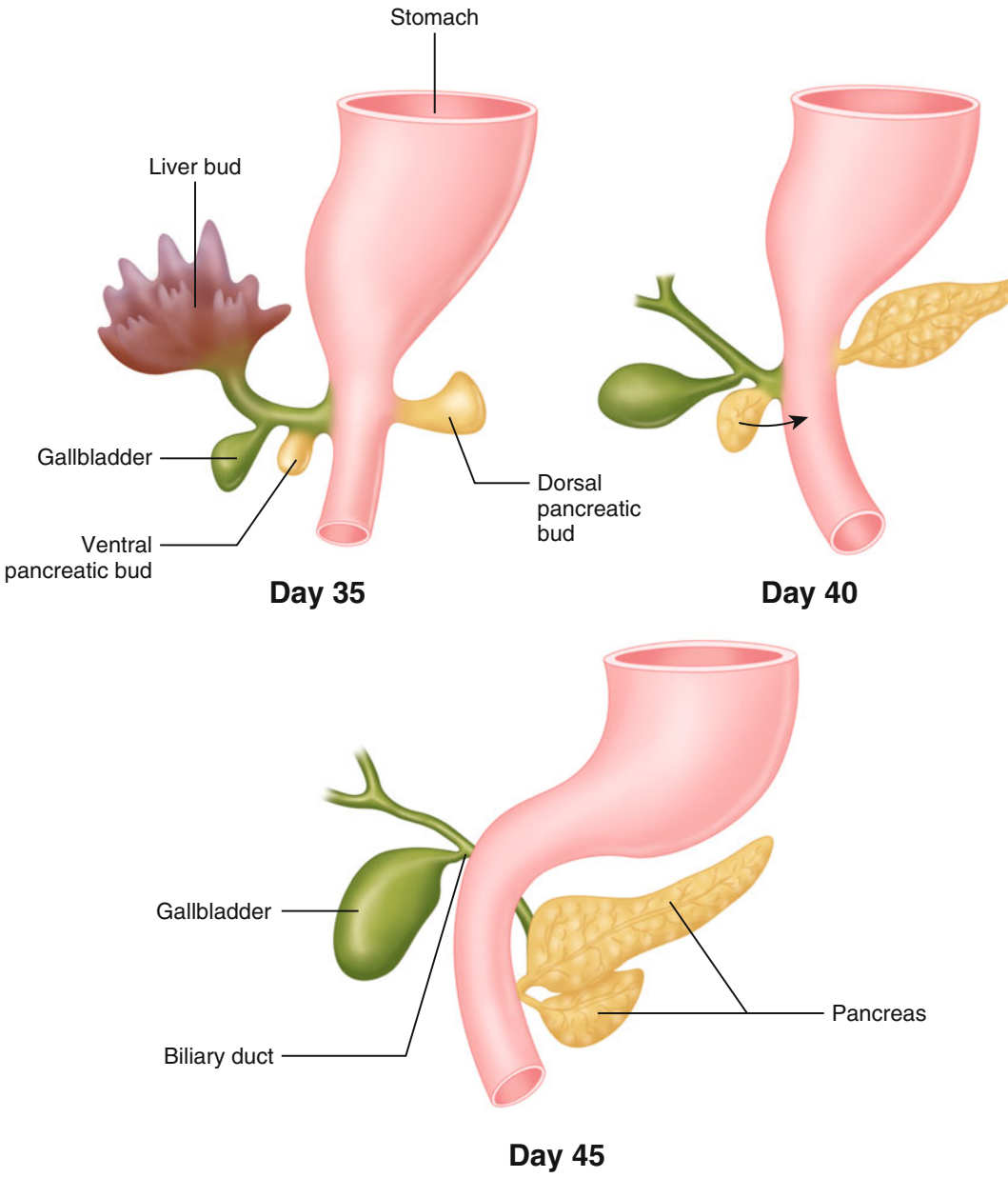

Fig. 2.1 Embryonic development of the bile ducts, gallbladder, and pancreas

The gallbladder is normally 7–10 cm in length and typically contains 30–60 mL of bile, although it is capable of storing up to 300 mL when maximally distended. The gallbladder is composed of a fundus, body, infundibulum, and neck. The fundus contains the majority of smooth muscle, which accounts for the organ's contractile function, while elastic tissue in the body affords distensibility. The infundibulum, often referred to as Hartmann's pouch, is an enlargement of the gallbladder between the body and neck. Dilatation of Hartmann's pouch may result from the presence of gallstones and can obscure the cystic duct and alter the anatomy during a laparoscopic cholecystectomy [4]. The infundibulum and gallbladder neck secrete

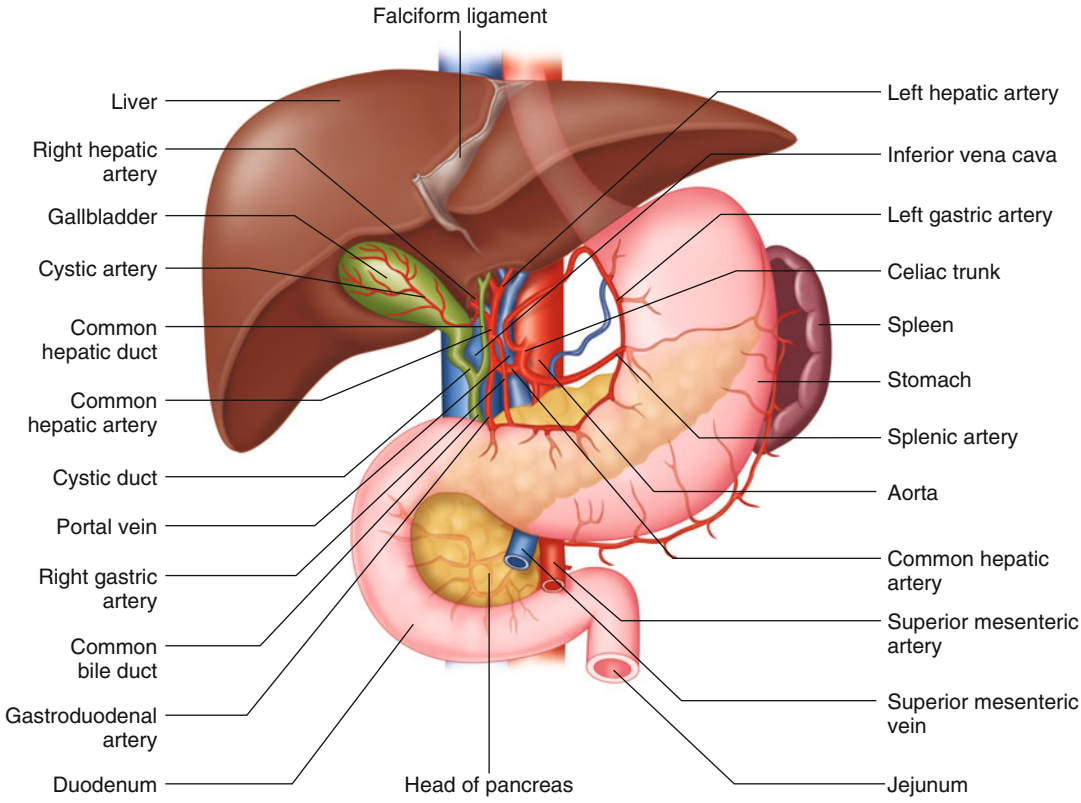

Fig. 2.2 Anatomy of the gallbladder and extrahepatic biliary system

mucus, which protects the gallbladder wall from the caustic nature of bile. The neck of the gallbladder is contiguous with the cystic duct, which joins the common hepatic duct to form the common bile duct. Within the neck of the gallbladder, the spiral valves of Heister act to prevent gallstones from falling into the common bile duct. The gallbladder is enveloped by a thin layer of visceral peritoneum, which is absent posteriorly where the gallbladder contacts the liver bed. Venous and lymphatic drainage of the gallbladder occurs here.

The junction of the right and left hepatic ducts forms the common hepatic duct. The common hepatic duct is about 1–4 cm in length and 4 mm wide. It lies anterior to the portal vein and just to the right of the common hepatic artery. The common bile duct is 7–11 cm long and 5–10 mm in diameter. It is divided into three portions: the supraduodenal, retroduodenal, and pancreatic portions. It courses in the hepatoduodenal ligament lateral to the proper hepatic artery and anterior to the portal vein. It then passes behind the first portion of the duodenum and moves laterally away from the portal vein and hepatic artery. The lowest portion of the common bile duct curves behind the head of the pancreas and can join the pancreatic duct before entering the second portion of the duodenum at the ampulla of Vater 10 cm distal to the pylorus (70 % of the time). In 20 % of cases, the common duct and pancreatic duct join within the duodenal wall, while in the remaining 10 % of patients these structures open into the duodenum separately. The sphincter of Oddi is composed of smooth muscle and surrounds the ampulla, maintaining continence of biliary drainage into the duodenum.

In contrast to the liver, which obtains a substantial portion of oxygen delivery from the portal venous system, the biliary system is supplied entirely by arterial blood flow. The inferior-most aspect of the common bile duct receives blood

from small vessels derived from the posterosuperior pancreaticoduodenal and the gastroduodenal arteries, which anastamose and travel along the medial and lateral walls of the duct (traditionally referred to as 3 o'clock and 9 o'clock). These vessels are at risk for disruption when dissecting close to the duct wall. The supraduodenal duct is perfused by the cystic artery, most commonly derived from the right hepatic artery. The common hepatic artery branches from the celiac axis to give off the proper hepatic artery which ascends alongside the anterior-medial aspect of the portal vein branches to form the right and left hepatic arteries. The right hepatic artery then dives beneath the common bile duct after which it gives off the cystic artery. The cystic artery is often found within the bounds of the triangle of Calot bordered by the cystic duct inferiorly, the common hepatic duct medially, and the liver margin superiorly. The cystic artery may often be found posterior to Calot's lymph node, which drains the gallbladder and is often enlarged in cholecystitis. Venous drainage of the biliary system follows the architecture of the bile ducts, with the veins generally coursing below the ducts [5].

The gallbladder is supplied by both sympathetic and parasympathetic innervation via the celiac plexus and the vagus nerve, respectively. At the level of T8 and T9, the preganglionic sympathetic chain receives afferent sensory information from the gallbladder, liver, and bile ducts, transmitting the pain of biliary colic. The parasympathetic supply of the gallbladder is derived from the hepatic branch of the vagus nerve. The cholinergic branches also release neurohormonal signals such as vasoactive intestinal peptide, somatostatin, and substance P, which act to modulate contraction and relaxation of the gallbladder wall and the secretion of bile.

Anatomic Variants

Common variations in biliary anatomy often contribute to inadvertent injuries during hepatobiliary surgery. The gallbladder itself can be buried within the parenchyma of the liver, referred to as an intrahepatic gallbladder. This can increase the risk of bleeding significantly, as injury to the liver parenchyma is more common during dissection. Duplication of the gallbladder, left-sided gallbladder, and congenital absence of the gallbladder are exceedingly rare conditions. Variation in the size of Hartmann's pouch can lead to obscuration of the cystic duct and increased incidence of common duct injury, as a short cystic duct may not be visible during lateral traction on the gallbladder [4].

Where the cystic duct emerges from the common bile duct is subject to great variability and is aberrant in 18–23 % of cases. Dissection of the cystic duct off of the common duct may increase the risk of injury to the latter. In 75 % of people, the cystic duct inserts into the middle one-third of the common bile duct, while it inserts into the distal third of the duct 10 % of the time. The typical pathway of cystic duct emergence is from the right lateral position; however, it may take other courses to join the gallbladder (Fig. 2.3). Around 1–2 % of patients have anomalous cysticohepatic ducts that empty into the cystic duct. Accessory bile ducts, observed in around 5 % of individuals, can arise from the right hepatic duct and insert directly into the cystic duct or join the common duct where it meets the cystic duct. This anomaly may lead to inadvertent clipping of the aberrant duct instead of the cystic duct during cholecystectomy [4].

Another common source of variation in biliary anatomy is the origin of the cystic artery and the presence of accessory hepatic arteries (Fig. 2.3). The cystic artery may have anterior or posterior branches to the gallbladder and are vulnerable to injury and subsequent bleeding if not recognized and ligated during cholecystectomy. In 90 % of patients, the cystic artery arises from the right hepatic artery; however, it can be seen arising from either the left or common hepatic, or the gastroduodenal artery (2–5 %). When this variant occurs, the cystic artery will cross anterior to the common duct. The cystic artery will course below the cystic duct in the event that it arises from the superior mesenteric artery. The right hepatic artery is often observed coursing behind the common duct and enters the liver high in Calot's triangle. The right hepatic artery may course very near the infundibulum of the gallbladder giving off a very short cystic artery, a

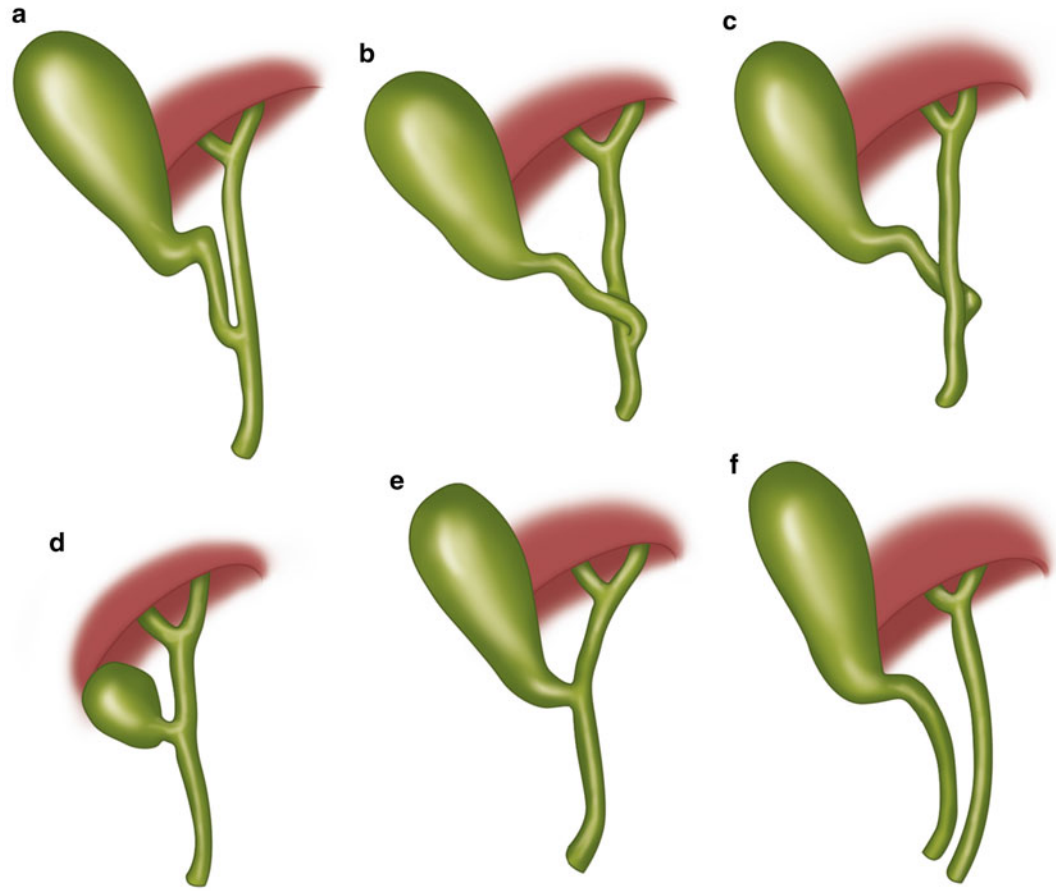

Fig. 2.3 Cystic duct variants. (**a**). Cystic duct lies parallel to the common bile duct (CBD). (**b**, **c**). Cystic duct crosses CBD and enters it on its left side. (**d**, **e**): Short cystic ducts. (**f**): Long cystic duct enters duodenum directly. There is no common bile duct, leaving only a common hepatic duct

variant referred to as Moynihan's or a caterpillar hump. The incidence of this variant may be as high as 50 % and can lead to the clipping of the right hepatic as it is mistaken for the cystic artery. In as many as 20 % of individuals, the right hepatic artery emerges from the superior mesentery artery. An accessory or second right hepatic artery emerging from the superior mesenteric artery is seen in 5 % of patients (Fig. 2.4) [6].

Physiology of the Biliary System

The liver normally produces about 500–1000 mL of bile daily. Bile travels from the hepatocytes into the surrounding biliary canaliculi, which converge to form bile ductules and then enter a portal triad composed of a hepatic artery, portal vein, and bile duct accompanied by lymphatics and vagus nerve branches. A hepatic lobule is composed of 4–6 portal triads. The bile ductules lie adjacent to the portal venule that communicates with the hepatic arteriole. The space of Disse separates hepatocytes from the sinusoidal space and facilitates the absorption of bile elements from the blood stream. After absorption, these elements are transported into the bile ductules and biliary tree, which is lined with tight junctions that prevent bile from refluxing back into the sinusoidal system. Bile flows retrograde through the common duct into the cystic duct to fill the gallbladder when pressure in the common bile duct increases due to tonic contraction of the sphincter of Oddi during fasting. The sphincter of

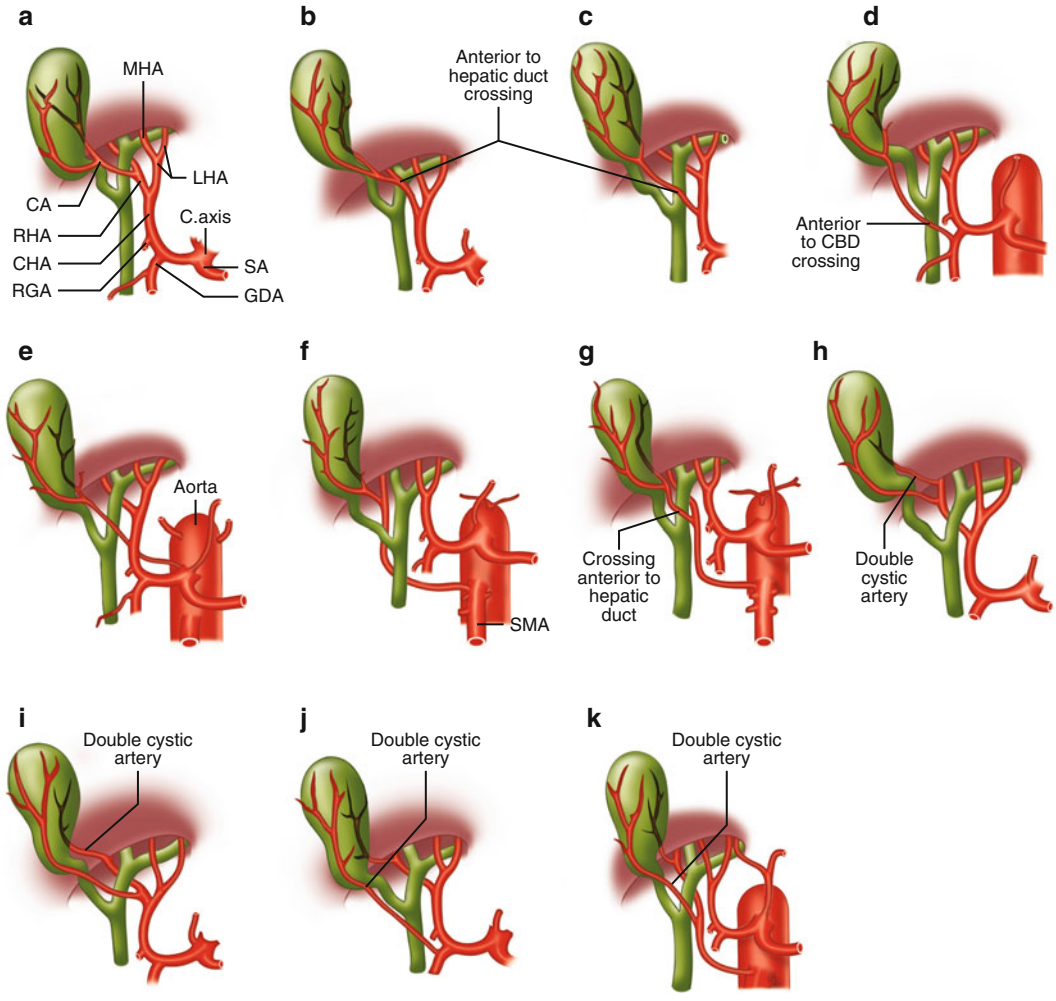

Fig. 2.4 Cystic artery anatomic variants. CA: Cystic artery. RHA: Right hepatic artery. CHA: Common hepatic artery. RGA: Right gastric artery. MHA: Middle hepatic artery. LHA: Left hepatic artery. C. axis: Celiac axis. SA: Splenic artery. GDA: Gastroduodenal artery. CBD: Common bile duct. SMA: Superior mesenteric artery

Oddi has a resting pressure of about 13 mmHg above the pressure measured in the duodenum. The interstitial cells of Cajal regulate its contraction, which occurs at a rate of 4 per minute.

Secretion of bile is stimulated through neurogenic, humoral, and chemical pathways. When a meal is consumed, vagal tone increases and sympathetic splanchnic tone decreases. Vagus nerve stimulation and distention of the gastric antrum cause gallbladder contraction and sphincter of Oddi relaxation. After eating, hydrochloric acid, proteins, and fatty acid entering the duodenum stimulate the release of secretin, which increases bile production. Cholecystokinin release causes gallbladder contraction and simultaneous relaxation of the sphincter of Oddi, allowing for ejection of 50–70 % of the gallbladder's contents. Vasoactive intestinal protein (VIP) and somatostatin decrease bile secretion and inhibit gallbladder contraction.

The two major functions of bile include excretion of cellular metabolites and toxins filtered out of blood by hepatocytes and emulsification of intestinal intraluminal fat to facilitate systemic absorption. Bile is composed of water, electrolytes, bile salts, bile pigment, and lipids, including cholesterol and phospholipid. Biliary pH is slightly alkaline, while concentrations of sodium, potassium, chloride, and calcium are similar to plasma. The two bile salts are cholate and chenodeoxycholate, which are derived from cholesterol

breakdown in the liver. Bile salts are conjugated with taurine or glycine and excreted by hepatocytes into bile through an ATP-dependent process. Bile salts facilitate the formation of micelles, which aid in the digestion and absorption of fats in the small intestine. Due to the amphipathic nature of bile salts, the hydrophilic regions aggregate and maintain contact with the surrounding environment, while the hydrophobic regions in the center of the micelle sequester fatty acids. Micelle formation is critical for the absorption of fat-soluble vitamins and many essential lipids. Bile salts also serve to eliminate cholesterol and other toxins from the body. Bile pigment, mainly bilirubin, is a breakdown product of hemoglobin and myoglobin from the destruction of red blood cells. It is transported from the bloodstream bound to albumin and enters the hepatocyte. Here, it is conjugated with glucuronic acid by the enzyme glucuronyltransferase, creating the water-soluble direct bilirubin. Direct bilirubin is then secreted into bile for excretion into the small intestine and colon. Colonic bacteria then deconjugate and metabolize bilirubin into urobilinogen, which is eliminated in stool or reabsorbed and ultimately eliminated in urine.

Approximately 95 % of bile salts are absorbed by the terminal ileum and colon and recycled through the mesenteric venous system back to the portal venous system in a process called the enterohepatic circulation. While the total amount of bile salt secretion into the gastrointestinal tract is about 12–36 g each day, the liver only produces 0.2–0.6 g of new bile salts each day, as the remaining is reclaimed through enterohepatic recycling. In the small intestine, bile salts are first unconjugated by bacterial bile salt hydrolase to form deoxycholate and lithocholate and then reabsorbed. Approximately 400–800 mg of bile salts reaches the colon each day and is ultimately excreted [7].

Natural History of Gallstone Formation

The production, storage, and secretion of bile are highly regulated. As such, any factor that disrupts this natural equilibration can induce gallstone formation, including increased saturation of bile with one of its components, altered concentrations of bile in the gallbladder, and gallbladder dysfunction.

To efficiently store bile produced by the liver, the gallbladder must first concentrate it approximately tenfold by absorbing water and sodium chloride. Additionally, the gallbladder secretes glycoproteins and hydrogen ions, which decreases the normally alkaline pH of bile and renders calcium more soluble. Concentrations of components in bile must be balanced to maintain a pure solution. Gallstones form when these concentrations are unbalanced. Cholesterol stones, the most common type of gallstones, are seen with excess cholesterol secretion that cannot be incorporated into micelles with bile salts. This leads to precipitation or nucleation of cholesterol salts and the formation of stones containing >70 % of cholesterol with some bilirubin and calcium. These stones are usually yellowish and range from hard to soft depending on the content of calcium. Pure cholesterol stones are rare and usually result in a single large stone.

In contrast, secretion of excess calcium-bilirubinate leads to the formation of black pigmented stones, which are usually small, brittle, and spiculated. This is often seen in hemolytic disorders such as sickle cell anemia and hereditary spherocytosis, where there is a large amount of conjugated bilirubin entering bile. A proportion of conjugated bilirubin will be deconjugated in the gallbladder by beta-glucuronidase produced by bacteria. In hemolytic states, this proportion is higher and a higher proportion of insoluble unconjugated bilirubin will precipitate with calcium to form black stones [7, 8]. This process is also observed in patients with Crohn's disease and cirrhosis. Patients with Crohn's disease have decreased absorptive capacity for bile salts, especially in the terminal ileum. As a result, they have a higher proportion of biliary calcium and unconjugated bilirubin. The cause of gallstones in cirrhosis may result from increased hemolysis due to hypersplenism or hepatocyte destruction and decrease the ability to conjugate bilirubin [9].

Brown gallstones form when there is dysfunction in gallbladder motility resulting in bile stasis and subsequent bacterial overgrowth. *E. coli*

produces beta-glucuronidase that deconjugates a higher proportion of the soluble direct bilirubin into indirect bilirubin, which then precipitates out of solution. Brown gallstones are often seen in developing countries with a higher incidence of parasitic infection causing biliary stasis. In the United States, biliary strictures can lead to brown stone formation in the gallbladder and common bile duct.

Conditions resulting in decreased gallbladder contractility induce biliary stasis and are implicated in stone formation. This is seen in biliary dyskinesia, prolonged fasting and iatrogenic causes including total parenteral nutrition and octreotide administration [10, 11].

There are several patient characteristics that are independent risk factors for the development of gallstones. Native North and South Americans are much more likely to develop gallstones than other populations. This is likely due to a combination of dietary and genetic factors. The incidence of cholelithiasis is 2–3 times higher in women and is expected to occur in as many as 50 % of women by age 75 compared to only 25 % of men. This is most likely due to the presence of estrogen, which increases the liver's removal of cholesterol from blood and deposits it into bile. Estrogen is also thought to promote the nucleation of cholesterol crystals out of micelles [12]. In fact, several studies have been performed to examine the relationship between gallstone formation and hormone replacement therapy with estrogen and progesterone in postmenopausal women. It appears that women who take hormone replacement therapy are 2–3 times more likely to develop gallstones and undergo cholecystectomy [13]. Additionally, pregnant patients are at increased risk for cholelithiasis due to the fact that estrogen increases cholesterol in bile and progesterone decreases gallbladder contractility [14].

Obesity, metabolic syndrome, and diabetes mellitus also increase the risk of gallstones. This is presumed to be secondary to increases in liver synthesis of cholesterol due to increased activity of HMG-CoA reductase activity. This causes an increase in the percentage of cholesterol in bile causing supersaturation and precipitation of stones [15]. Interestingly, rapid weight loss and bariatric surgery can also predispose patients to the development of gallstones. Rapid weight loss causes net excretion of cholesterol into bile, and fat-restricted diets can lead to decreased gallbladder contractility and stasis [16]. Diabetes is often associated with increased levels of cholesterol, although decreased intestinal and gallbladder motility due to autonomic dysfunction may also contribute to gallstone formation.

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The Diagnosis of Acute Cholecystitis

3

Bradley M. Dennis, Geoffrey E. Wile, and Addison K. May

Introduction

Acute cholecystitis is an inflammatory condition of the gallbladder resulting from a spectrum of pathophysiologic processes. While the diagnosis of AC is frequently straightforward, in some settings it can be quite complex. Acute cholecystitis is most commonly the result of acute obstruction of the cystic duct by biliary stones or cholelithiasis, termed calculous cholecystitis. Acute cholecystitis may also occur in settings in which obstruction of the cystic duct by stones is not the etiologic process, thus classified as acalculous cholecystitis. Occasionally, acute cholecystitis may develop in the setting of chronic inflammation and scarring of the gallbladder (chronic cholecystitis) altering common radiographic findings and confounding the diagnosis of acute cholecystitis. Both calculous and acalculous acute cholecystitis may progress to gangrenous cholecystitis with an elevated risk of free perforation and perioperative complications.

The diagnosis of most cases of typical calculous acute cholecystitis can usually be achieved with a high degree of accuracy with the combination of clinical presentation and diagnostic imaging. The signs and symptoms that suggest a diagnosis of acute calculous cholecystitis are due to one of the two pathophysiologic processes (1) contraction of the gallbladder against obstruction to biliary outflow causing biliary colic and (2) inflammation of the gallbladder that occurs secondary to the obstruction. As the condition progresses, the symptoms typically evolve. As the process becomes more severe and prolonged, contraction of the gallbladder and symptoms of biliary colic subside and symptoms of local inflammation predominate. As the severity progresses further, systemic symptoms advance. However, the signs, symptoms, and laboratory changes produced by the inflammatory process of acute cholecystitis are nonspecific and other inflammatory conditions involving organs in the right upper quadrant of the abdomen can mimic cholecystitis. Processes that may mimic acute cholecystitis and should be considered and excluded from the differential diagnosis include hepatitis, pancreatitis, or peptic ulcer disease. Additionally, establishing the diagnosis in certain patient populations may be more complex and difficult. Critically ill patients with acalculous acute cholecystitis and patients with comorbid diseases that alter the signs and symptoms of

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acute inflammation, such as those with diabetes or immunosuppression may be more difficult to diagnose. A delayed diagnosis of acute cholecystitis may lead to increased morbidity and mortality due to progression to gangrenous cholecystitis, perforation, and resultant increased operative complexity.

Historically, the diagnosis of acute cholecystitis was based almost solely on clinical findings. Chief among these was the Murphy's sign [1]. Unfortunately, many patients will not present with this clinical finding. Sensitivity of the Murphy's sign for acute cholecystitis is highly variable. Moreover, there is no one biochemical marker specific for acute cholecystitis. Fortunately, the advent of and subsequent improvement in various imaging modalities has aided the evaluation of the biliary tract. Ultrasonography (US), computed tomography (CT), and hepatobiliary scintigraphy are now commonly available and used in the diagnosis and evaluation of patients with right upper quadrant (RUQ) pain. Magnetic resonance imaging (MRI) is also used in selected patients and in some cases may provide additional functional information when hepatobiliary contrast is utilized. To address the variable physical exam findings, lack of a specific laboratory test, and the emergence of imaging technology, objective diagnostic criteria for the diagnosis of acute cholecystitis were established by an international consensus conference in 2007 and subsequently validated (termed the Tokyo Guidelines) [2, 3].

The Tokyo Guidelines

In 2003, the Japanese Society of Hepato-Biliary-Pancreatic Surgery, along with the Japanese Biliary Association and the Japanese Society for Abdominal Emergency Medicine formed a working group to develop guidelines for the management of cholangitis and cholecystitis. In 2006, an International Consensus Meeting was held in Tokyo, Japan. From this meeting came the Tokyo Guidelines for the Management of Acute Cholangitis and Cholecystitis. The so-called Tokyo Guidelines (TG13) was subsequently revised in 2013 to reflect the increasing importance of diagnostic imaging [4, 5].

Table 3.1 Diagnostic criteria for acute cholecystitis, according to Tokyo Guidelines[a]

• *Local symptoms and signs of inflammation* – Murphy's sign – Pain or tenderness in the right upper quadrant – Mass in the right upper quadrant
• *Systemic signs of inflammation* – Fever – Leukocytosis – Elevated C-reactive protein level
• *Imaging findings* – A confirmatory finding of acute cholecystitis on imaging (US, CT, or HIDA)
Suspected diagnosis The presence of one local sign of inflammation and one systemic sign of inflammation
Definite diagnosis The presence of one local sign or symptom, one systemic sign, and a confirmatory finding on an imaging test **Must rule out acute hepatitis, chronic cholecystitis, and other acute abdominal diseases

[a]Data are from Takada et al. and Hirota et al.

Diagnostic criteria described in the Tokyo Guidelines consist of three components: (A) local signs of inflammation, (B) systemic signs of inflammation, and (C) imaging findings of acute cholecystitis (see Table 3.1). Local signs of inflammation are predominantly limited to physical exam findings of right upper quadrant inflammation. These findings include positive Murphy's sign and RUQ mass, pain or tenderness. As severity progresses, systemic signs of inflammation also progress. Systemic signs of inflammation included in the guidelines are fever, leukocytosis, and elevated C-reactive protein (CRP). While transmural inflammation of the gallbladder may involve adjacent liver parenchyma and produce a mild elevation in liver function tests, such abnormalities do not significantly aid in establishing the diagnosis. More than a mild elevation in liver functions tests should suggest alternative diagnoses such as hepatitis or coexisting cholangitis. Imaging findings of acute cholecystitis are the final, and most important, component of the Tokyo Guidelines. Included in this are findings on US, CT, and scintigraphy that are consistent with acute cholecystitis. Each of these imaging

modalities is discussed later in more detail. However, per the Tokyo Guidelines definitions, ultrasonographic evidence of acute cholecystitis consists of the presence of gallbladder wall thickening, pericholecystic fluid, or ultrasonographic Murphy's sign. A suspected diagnosis of acute cholecystitis should be considered when local signs of inflammation are present along with one systemic sign of inflammation. A definite diagnosis can only be confirmed with a suspected diagnosis plus an imaging finding of acute cholecystitis. However, prior to applying Guidelines criteria, other causes of right upper quadrant pain must be ruled out including hepatitis, pancreatitis, peptic ulcer disease, chronic cholecystitis, or other sources of abdominal pain. A recent validation study of the TG13 guidelines demonstrated a sensitivity of 91.2 %, specificity of 96.9 %, and an accuracy of 94 % [4]. However, limited published data are available to quantify accuracy of the Tokyo Guidelines when the presence of other disease processes may coexist or remain to be excluded or for clinical settings where any of the three components (local inflammation, systemic inflammation, or imaging) may be altered. Limitations of the Tokyo Guidelines include the underdiagnoses of patients with few systemic symptoms and the infrequent utilization of C-reactive protein in the United States [6].

Presentation

Symptom history is an important part of the diagnosis of acute cholecystitis as it can identify at-risk patients. It may also help to eliminate other options from the differential diagnosis. Gallstones or biliary sludge are the most common cause of acute cholecystitis due to cystic duct obstruction [7]. Risk factors for gallstones include advancing age, obesity, rapid weight loss, female gender, and elevated estrogen levels (pregnancy, parity, and estrogen replacement therapy). Other causes of cystic duct obstruction include parasites, masses, and foreign bodies. Acute cholecystitis without evidence of cholelithiasis is referred to as acalculous cholecystitis. This is a challenging diagnosis that is discussed later in this chapter.

Clinical presentation of patients presenting with acute cholecystitis most commonly includes right upper quadrant and/or epigastric pain, occurring in 72–93 % of cases of acute cholecystitis [8–11]. Often this pain is intermittent or may be described as coming in waves. This intermittent, crampy RUQ pain is referred to as biliary colic. Nausea and vomiting are also very common, occurring in 62–83 % of cases [8, 9, 12, 13]. Symptoms can frequently occur in the postprandial period, particularly after meals high in fat. Fevers are less common with only 10–30 % manifesting temperatures over 38 °C [12, 14, 15].

The physical exam finding most connected to the diagnosis of acute cholecystitis is the Murphy's sign. This exam finding was first described in 1903 by John B. Murphy as significant pain to palpation over the gallbladder in the RUQ. He noted "the most characteristic and constant sign of gall-bladder hypersensitiveness [sic] is the inability of the patient to take a full, deep inspiration, when the physician's fingers are hooked up beneath the right costal arch below the hepatic margin" [1]. Subsequent studies have demonstrated this finding to be a reliably specific test, but variable in sensitivity. Specificity of a Murphy's sign for the diagnosis of acute cholecystitis ranges from 79 to 96 % [3, 8, 16]. Inflammatory processes not caused by cholecystitis but that involve the visceral peritoneum overlying the gallbladder or inflammation of the liver capsule can produce findings consistent with a positive Murphy's sign. The sensitivity of a Murphy's sign is fairly low, reported as low as 20.5 % to as high as 65 % [3, 16]. Thus, its use as a diagnostic test can result in a high rate of false negative findings.

Laboratory Tests

For the diagnosis of acute cholecystitis, there is no biomarker that specifically correlates with gallbladder pathology. Markers of generalized inflammation in combination with other clinical and imaging findings can increase the reliability of the diagnosis of acute cholecystitis. Leukocytosis and elevated CRP are most commonly employed.

Mild leukocytosis (over 10,000 cells/μL) is suggestive of systemic inflammation. Higher WBCs are more likely to be associated with more severe disease like gangrenous cholecystitis. However, studies have not clearly delineated where the transition from acute cholecystitis to gangrenous cholecystitis occurs. White Blood Cell counts over 13,000, 15,000, and 17,000 cell/μL have all been associated with increased risks of gangrenous cholecystitis [17–21]. CRP is also present in conditions of systemic inflammation. Values over 3 mg/dL are consistent with inflammatory conditions. When elevated CRP is combined with positive ultrasound findings for acute cholecystitis, sensitivity is 97 % for acute cholecystitis, with 76 % specificity [22]. Similar to leukocytosis, higher elevations of CRP correlate with greater likelihood of the existence of gangrenous cholecystitis [21, 22]. Transmural inflammation of the gallbladder may involve adjacent liver parenchyma that may produce a mild elevation in gamma-glutamyltranspeptidase (GGT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin but such abnormalities do not significantly aid in establishing the diagnosis. Significant elevation in liver functions tests are not due to inflammatory processes predominantly involving the gallbladder as the organ is functionally separated from the liver. Significant elevation of transaminases or bilirubin should prompt evaluation of alternative pathology such as hepatitis or coexisting cholangitis.

Imaging

Significant advancements in the diagnosis of acute cholecystitis have occurred with improvements in imaging technology. The majority of cases of acute calculous cholecystitis can reliably be established in a straightforward fashion with the use of ultrasound or computed tomography. Less frequently MRI and/or Tc-HIDA scans may be used to aid in the diagnosis. Rarely, in certain complex settings, the diagnosis (or its exclusion) may remain uncertain despite these advances. Each test has particular attributes as described below.

Ultrasound

Ultrasound is probably the most frequently used diagnostic imaging modality for acute cholecystitis. It should be considered the first imaging option for all suspected cases of acute cholecystitis. Advantages of ultrasound are multiple. It is often immediately available in the Emergency Department and can be even brought to the patient's bedside. It is a relatively cheap study making it accessible to more hospitals and patients. Findings are not affected by elevated liver function tests. Ultrasound can visualize gallstones (Fig. 3.1), which can be difficult to identify using CT or HIDA scan, is quick and noninvasive, and does not expose the patient to ionizing radiation. There are a few clear limitations for ultrasound; it is well known to be operator dependent and gallbladder visualization can be limited by patient body habitus and by bowel gas between the ultrasound probe and the gallbladder.

While acute cholecystitis on ultrasound can have a variable appearance, there are a few findings that are considered indicative of AC. Findings include the concurrent presence of thickened gallbladder wall (≥5 mm), pericholecystic fluid, and a sonographic Murphy's sign. Other findings which may also indicate AC include gallbladder distention/enlargement, gallstones, debris echo or sludge, and gas within the gallbladder wall. A sonographic Murphy's sign is the finding of pain elicited by pressing on the gallbladder with the ultrasound probe during ultrasound exam. Because of the ability to accurately press over the gallbladder, the sonographic Murphy's sign can be used to differentiate between other causes of RUQ pain that may manifest with a conventional Murphy's sign (e.g., perforated duodenal ulcer). Gallstones, while considered the cause of about 90 % of acute cholecystitis cases, are not diagnostic of AC. They are frequently present in the non-inflamed gallbladder and can even be a cause of a falsely positive sonographic Murphy's sign.

Ultrasound has demonstrated good sensitivity in multiple studies. Meta-analysis by Keiwiet showed sensitivities ranging from 50 to 100 % with an overall sensitivity of 81 %. Specificities

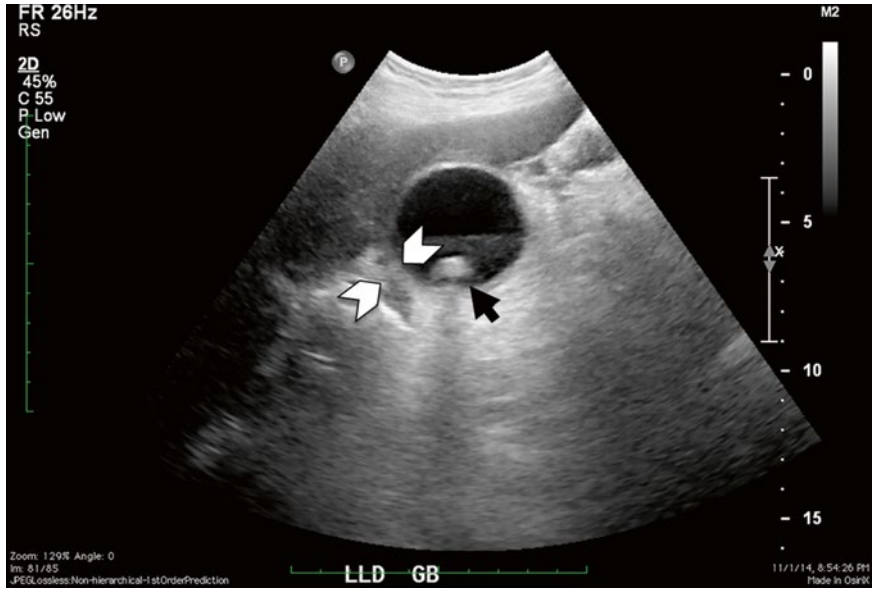

Fig. 3.1 US image showing a GB calculous (*arrow*) demonstrating posterior acoustic shadowing. Sonographic findings in AC include thickened gallbladder wall (between *white chevrons*), pericholecystic fluid, and a sonographic Murphy's sign. Gallbladder distention, gallstones, and debris echo or sludge are also frequently seen in AC

were shown to be a bit better with an overall specificity of 83 %, despite a range of 30–100 % [23]. Sonography by emergency department (ED) physicians has also proven to be reliable in the detection on acute cholecystitis. ED physician-performed US was shown in a study of 116 patients to have a sensitivity of 92 %, specificity of 78 %, and an 86 % accuracy when compared with radiologist-performed ultrasound [24]. More recently, 96 % sensitivity and 79 % specificity was noted on ED physician-performed US when compared to surgical pathology. Additionally, this study noted an 85.5 % rate of agreement when compared with blinded radiologist reading [25]. Sensitivities and specificities in head-to-head studies are comparable as well. In a study comparing the US diagnosis of AC by ED physicians and radiologists, similar sensitivities (87 % vs. 83 %, respectively) and specificities (82 % vs. 86 %, respectively) were reported [26].

In all of these studies, it is important to note that the ED physicians were trained or certified in ultrasonography. Also, while in these studies, the ability to detect acute cholecystitis was outstanding, the clinicians in these studies may have represented a particularly experienced and proficient sample. In light of that, the gold standard remains ultrasound interpreted by trained radiologist. However, in clinical settings with limited radiology availability, ED physician-performed ultrasound may be considered. Ultrasound is most effective when utilized, not in isolation, but in combination with other clinical and laboratory findings suggestive of inflammation. For patients with suspected acute cholecystitis, US plus elevated CRP showed a sensitivity of 97 % [22] for AC. The Tokyo Guidelines themselves are based on the idea of combining imaging findings of acute cholecystitis with clinical findings of inflammation.

Computed Tomography (CT Scanning)

CT scanning is a common imaging modality in patients with abdominal pain. It can differentiate other causes of RUQ pain. CT scanning is available in almost every hospital and has significantly decreased operator dependence compared to

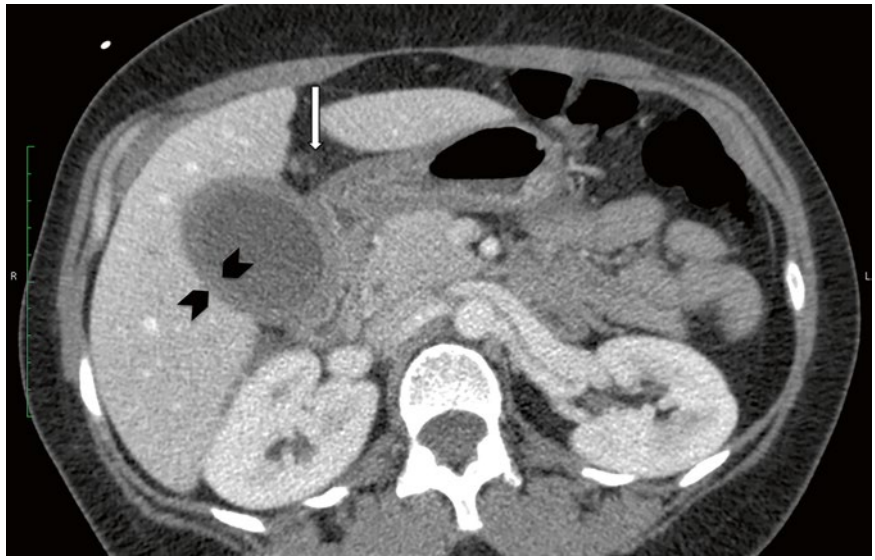

Fig. 3.2 Axial CT image of acute cholecystitis. Gallbladder distention, wall thickening (*chevrons*), and pericholecystic stranding (*white arrow*) are all visible and are findings consistent with AC

ultrasonography. Improvements in technology have led to faster imaging speeds with improved image quality and decreased artifact. Also, the increased anatomic coverage area imaged allows for broader diagnostic capabilities and can detect abdominal pathology outside the right upper quadrant. CT scanning also exhibits superiority over ultrasonography in detecting gastric and bowel pathology. In many centers, CT scanning can diagnose gall bladder disease before the symptoms localize to the right upper quadrant. However, these advantages come at the cost of increased radiation exposure and other side effects. Intravenous iodinated contrast exposure can potentially lead to anaphylaxis and some risk of renal impairment. Lastly, when compared with sonography, CT scanning is more expensive and requires technology that is not portable.

Findings of acute cholecystitis on CT scan (Fig. 3.2) are similar to those seen on ultrasound. Positive findings of the disease include gallbladder wall thickening >3 mm, pericholecystic fat stranding, and gallbladder distention [27]. Pericholecystic fluid, subserosal gallbladder edema, and high attenuation gallbladder can also be visualized, but less commonly [27]. Gallstones may also be visualized depending on the composition and size of the gallstones, but the presence of gallstones may often present in the absence of acute cholecystitis.

CT may not be an effective screening modality for acute cholecystitis. There is a paucity of data regarding the sensitivity of CT for AC diagnosis. In a comparative study with US in 117 patients, CT was shown to have 39 % sensitivity and 93 % specificity [28] and was significantly worse than US, which had a sensitivity and specificity of 83 % and 95 %, respectively. Negative predictive value was good for CT (89 %) but was still lower than US (97 %). The authors concluded that US is a better initial imaging study and that CT should be reserved for patients with a wider differential diagnosis and/or nonstandard symptomatology.

Hepato-Iminodiacetic Acid Scintigraphy

Hepato-Iminodiacetic Acid (HIDA) imaging is an attractive option for the diagnosis of AC as it is highly sensitive with good specificity. The modality is not operator dependent and it can often differentiate between acute and chronic

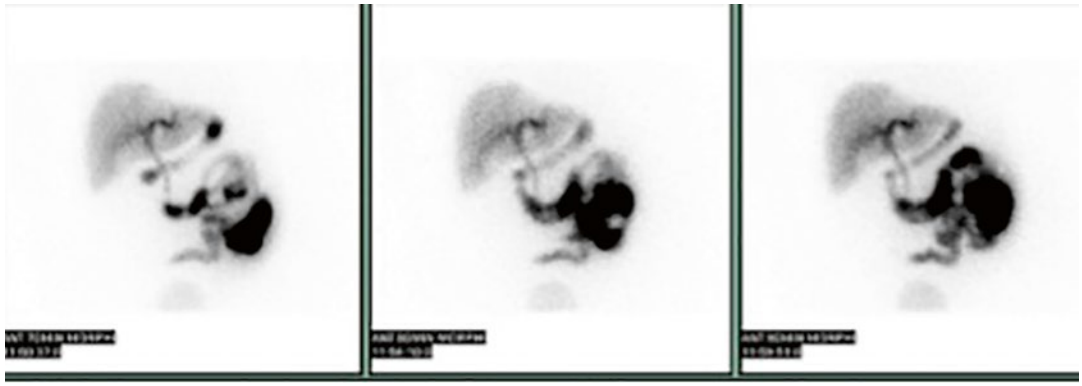

Fig. 3.3 HIDA scan showing no filling of gallbladder after delayed images. Failure to fill gallbladder with radiotracer after 60 min is abnormal but not diagnostic of AC. Findings consistent with AC include failure to fill within 3–4 h without morphine or within 90 min after administration of low-dose morphine at 60 min

cholecystitis, a feature that ultrasonography can often fail to do. Normal findings relate to the rapid filling of the gallbladder with radiotracer and passage into the duodenum which should occur within 30 min. Low sphincter of Oddi pressure can delay filling in some normal gallbladders but can be overcome by administering a low dose of morphine. Failure of the gallbladder to fill within 60 min is abnormal but not diagnostic of acute cholecystitis. The absence of any filling after 3 or 4 h delayed images qualifies as a diagnostic study (Fig. 3.3). Also considered a positive study is no filling after 90 min when morphine was administered at 60 min. These delayed images confirm no delayed filling of the gallbladder. This indicates cystic duct obstruction and is highly sensitive for AC. Chronic cholecystitis can also cause cystic duct obstruction, but much less commonly.

However, HIDA imaging also possesses some disadvantages. This study generally requires a period no oral intake for 3–4 h before the study. Then, the study itself can take up to 3–4 h to complete depending on how rapidly the radiotracer transits into the gallbladder. The first hour of the study is very labor intensive as it requires taking one radiographic image per minute for 60 min. The labor-intensive nature of the study often makes it unavailable outside of normal workday hours. Additionally, the study only gives information regarding the biliary tract. The accuracy of HIDA scanning is dependent on appropriate hepatic clearance and can be affected by altered liver function. Prolonged NPO status or parenteral nutrition can give false positives. Lastly, HIDA scanning exposes patients to ionizing radiation albeit at much lower doses than an abdominopelvic CT scanning and is still discouraged in pregnant females.

Meta-analysis incorporating 40 studies and nearly 4100 patients demonstrated an overall sensitivity of 96 % (95 % CI: 94–97 %) [23]. Further analysis showed that direct comparison to ultrasonography occurred in 11 studies with 1199 total patients. Sensitivity and specificity of scintigraphy in acute cholecystitis were both shown to be significantly higher ($p < .001$) than that of ultrasound (94 % vs. 80 % and 89 % vs. 75 %, respectively) [23]. Chatziioannou demonstrated that overall accuracy is higher with HIDA (92 %) than US (77 %) in a study of 107 patients with suspect AC who underwent both imaging modalities [29]. However, in combination, HIDA and US are exceedingly sensitive for diagnosing acute cholecysitis with a reported sensitivity of 97.7 % [30].

Magnetic Resonance Imaging

Previously, MRI was not a popular imaging modality for suspected acute cholecysitis. MRI was a long study that was expensive for patients and not readily available after hours at most

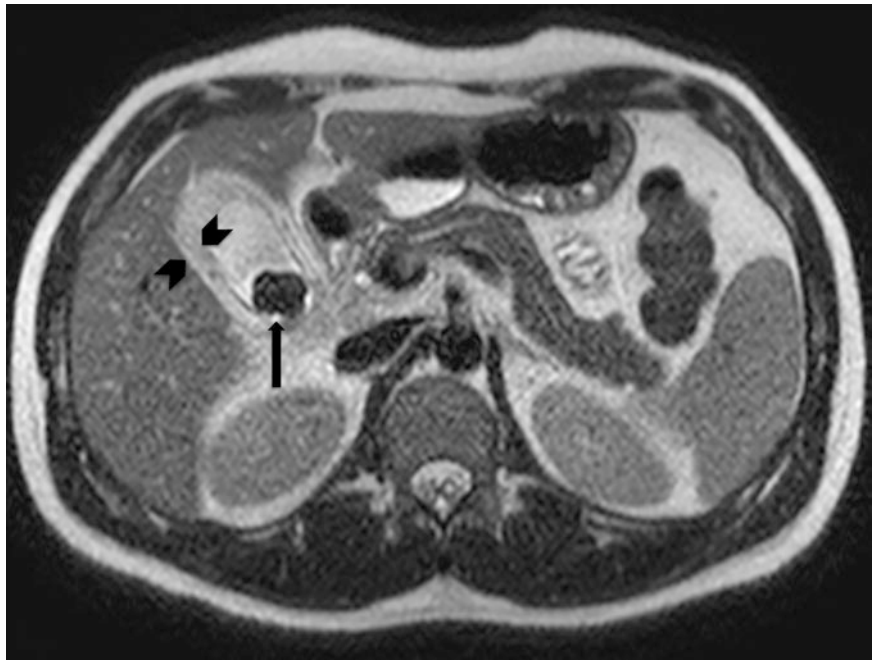

Fig. 3.4 T2 weighted MRI image without fat saturation showing cholelithiasis and acute cholecystitis. Gallstone indicated by *arrow*. Gallbladder wall thickening (between *chevrons*), gallbladder distention and pericholecystic stranding are common findings in AC

institutions. Additionally, many patients can develop discomfort or outright claustrophobia in the MRI scanner. Due to the danger of the magnet of the MRI machine, critically ill patients or those needing frequent access are not candidates for MRI scanning. Increasingly, however, concerns about radiation exposure have led to the reexamination of MRI as imaging option and MRI is safe in pregnancy. In other venues, MRI has become the imaging modality of choice for hepatobiliary, pancreatic, and pelvic pathology. Scanning protocols have been developed that can now complete an abdominal study in 15–30 min [31]. Sensitivity (85 %) and specificity (81 %) fall in between CT and US [23]. As with CT imaging, MRI findings of gallbladder wall thickening, pericholecystic fat stranding, and gallbladder distention are characteristic of acute cholecystitis (Fig. 3.4). Currently, MRI is most used for the detection of acute cholecystitis for those with ambiguity or a contraindication to one of the other modalities or those where additional information is required on hepatobiliary pathology.

Severity Assessment and Predicting Gangrenous Cholecystitis

Upon establishing the diagnosis of AC, determination of the severity of disease process aids in clinical judgment regarding the management of individual patients. The Tokyo Guidelines recommend the use of a three grade system: Grade I or mild AC occurs in a healthy patient with no organ dysfunction and mild inflammatory changes of the gallbladder; Grade II or moderate acute cholecystitis is present when any of several conditions are met—WBC > 18,000 cell/μL, palpable tender mass in the right upper abdominal quadrant, duration of symptoms longer than 72 h, or evidence of marked local inflammatory changes; and Grade III or severe AC is present when evidence of organ dysfunction is present [2]. While no significant prospective data provide information regarding the incidence of patients presenting with acute cholecystitis in the three severity categories, the large majority of patients appear to present as Grade I [6].

As the inflammatory process advances, acute cholecystitis may develop into gangrenous cholecystitis, with transmural inflammation, loss of mucosa, and necrosis of the gallbladder wall [21, 32]. Progression to gangrenous cholecystitis is associated with significantly greater requirement for conversion to open cholecystectomy, postoperative morbidity, and mortality when compared with uncomplicated acute cholecystitis and evidence suggests that this can be reduced by early diagnosis and treatment [33–36]. The incidence of gangrenous cholecystitis in patients with acute cholecystitis ranges from 2 to 41 %, but nearly half of cases of gangrenous cholecystitis are unsuspected preoperatively and no clinical or radiographic criteria consistently identify patients with this condition [19–21, 32, 34, 35]. As the gallbladder undergoes necrosis, local signs of inflammation such as a Murphy's sign diminish and may be completely absent. Identifying those patients at high risk of GC is important for early intervention. Several factors have been shown to be associated with gangrenous versus non-gangrenous cholecystitis in univariate and multivariate analysis including: Age, diabetes mellitus, heart rate, WBC, C-reactive protein, gallbladder wall thickness, and the presence of pericholecystic fluid [21, 32, 35]. Measurements and unadjusted odds ratio for each parameter are shown in Table 3.2.

Table 3.2 Preoperative risk factors for gangrenous cholecystitis

Parameter	Measure	Odds ratio[a]
Age	>45 years old	3.2[b]
	>50 years old	3.5[c]
Diabetes mellitus		2.8[c]
Heart rate	>90 beats per minute	2.8[b]
WBC	≥13,000 cells/μL	2.8[b]
	≥15,000 cells/μL	4.4[c]
C-reactive protein	>200 mg/dL	1.02[d,e]
Gallbladder wall thickness	>4.5 mm	3.2[b]

[a]Unadjusted value
[b]Wu, B. HPB. 2014; 16:801–806
[c]Fagan, S.P. Am J Surg. 200; 186:481–485
[d]Mok, K.W.J. Int J Surg. 2014; 12:649–653
[e]For each unit above 200 mg/dL

Two separate studies have developed predictive models for the presence of gangrenous versus non-gangrenous AC using similar but not identical variables [20, 35]. Nguyen and colleagues used diabetes mellitus, WBC, pericholecystic fluid, ALT ≥ 50 U/L, and alkaline phosphatase ≥ 200 U/L in a complex model to estimate the risk of gangrenous cholecystitis, generating an impressive area under the ROC curve of 88.9 % [20]. In a more recent study, Wu and colleagues developed a simple scoring system using only four factors to create a 0–5 point scale as shown in Table 3.3 [35]. Patients with a score of 0 had a 2 % risk of GC and patients with a score of 5 had a 65 % chance of GC, with the model achieving an area under the ROC curve of 0.77. Mok and colleagues examined C-reactive protein as a single marker and determined that CRP of ≤200 U/L had a 100 % negative predictive value to GC [21]. None of the studies have been validated in larger prospective studies and none have assessed the combined use of all measures determined to be independently related.

A few radiographic findings are suggestive of complicated gallbladder disease. These features are inconsistently found in advanced stage disease and are associated with low sensitivities but high specificities for complicated cholecystitis. One described finding is the so-called *rim sign* noted on HIDA (Fig. 3.6). The rim sign is the increased uptake of radiotracer in the liver adjacent to the gallbladder fossa combined with non-filling of the gallbladder itself [37]. This finding is present in about 25–35 % of cases of AC and has demonstrated a strong specificity for advanced gallbladder disease including gangrenous cholecystitis and even gallbladder perforation [38, 39]. CT, US, and MRI can identify changes suggestive

Table 3.3 Wu scale to differentiate gangrenous cholecystitis from acute cholecystitis

A score over 5 suggests gangrenous cholecystitis	
Age	≤45 = 0
	46 to ≤65 = 1
	>65 = 2
Heart rate	>90 bpm = 1
WBC	>13,000 = 1
Gallbladder wall thickness	>4.5 mm = 1

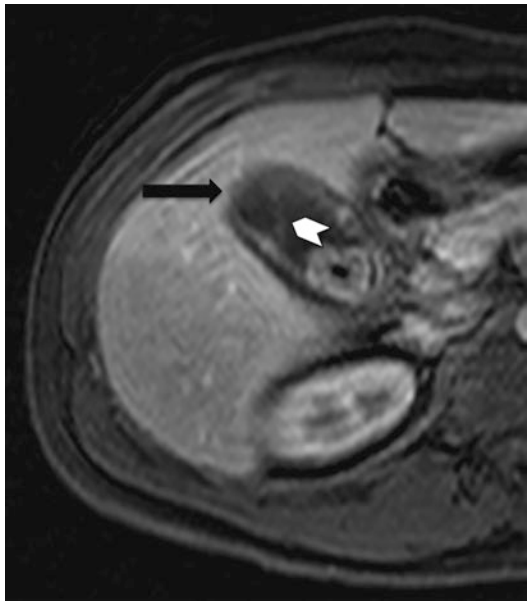

Fig. 3.5 T1 weighted axial image following contrast administration in patient with gangrenous cholecystitis. Chevron indicates an intraluminal membrane and *arrow* identifies a defect in wall enhancement

of complicated cholecystitis (Fig. 3.5), such as intraluminal membranes, gas in wall or lumen, and asymmetric wall thickening [40]. These features are somewhat nonspecific and can represent gangrenous cholecystitis, emphysematous cholecystitis, or even gallbladder perforation. Despite not being consistently found in advanced disease, the presence of any of these changes should heighten the suspicion of advanced stage gallbladder disease.

The Difficult Diagnosis

Certain patient factors and clinical settings can significantly confound and delay the diagnosis of acute cholecystitis, increasing the risk of complication. Unfortunately, limited data are available to quantify the diagnostic accuracy in these particular populations. Advanced age, immunosuppression, diabetes mellitus, preexisting neurologic impairment, and acalculous acute cholecystitis in the critically ill are all factors that may contribute to diagnostic dilemma and uncertainty.

For a variety of reasons, delays in diagnosis abound in elderly patients with acute cholecystitis [6, 41, 42]. Elderly patients have a greater frequency of presentation in which no Murphy's sign is present [41]. Physical examination and laboratory indexes may be in the normal range, fever may be more frequently absent and the only symptoms may be a change in mental status or decreased food intake [6, 41, 42]. As discussed above, age is an independent factor for the development of gangrenous cholecystitis. Thus, a high index of suspicion and an assertive approach to the diagnosis must be maintained. Similar to the elderly population, patients with immunosuppression, diabetes mellitus, or preexisting neurologic impairment may all have limited local signs and symptoms of acute cholecystitis. Blunting of the inflammatory response may allow progression to gangrenous acute cholecystitis without ever having right upper quadrant pain and tenderness and a more frequent progression to severe acute cholecystitis and sepsis [35].

Acalculous acute cholecystitis in the critically ill population is frequently difficult to diagnose with adequate certainty and may require drainage of the gallbladder to exclude its presence. Critically ill patients may have many confounding factors including multiple reasons for pain, fever, and leukocytosis. Critically ill patients may have no ability to corroborate findings while sedated, intubated, and/or unconscious in an intensive care setting. During critical illness, hepatic function may be altered and abnormal liver function assays occur unrelated to the presence of biliary tract pathology.

Although ultrasound, CT scanning, and HIDA scans (Figs. 3.6 and 3.7) play a significant role in the diagnosis of acalculous acute cholecystitis in the critically ill patient, an understanding of the physiologic changes that occur during critical illness and how these changes may alter radiographic findings is essential to appropriately interpreting each in this complex setting. During critical illness, particularly if the patient is fasted for a prolonged period, the gallbladder may passively fill with bile and become distended. The finding of gallbladder distension, therefore, may or may not have diagnostic significance. Additionally, the fluid resuscitation that is

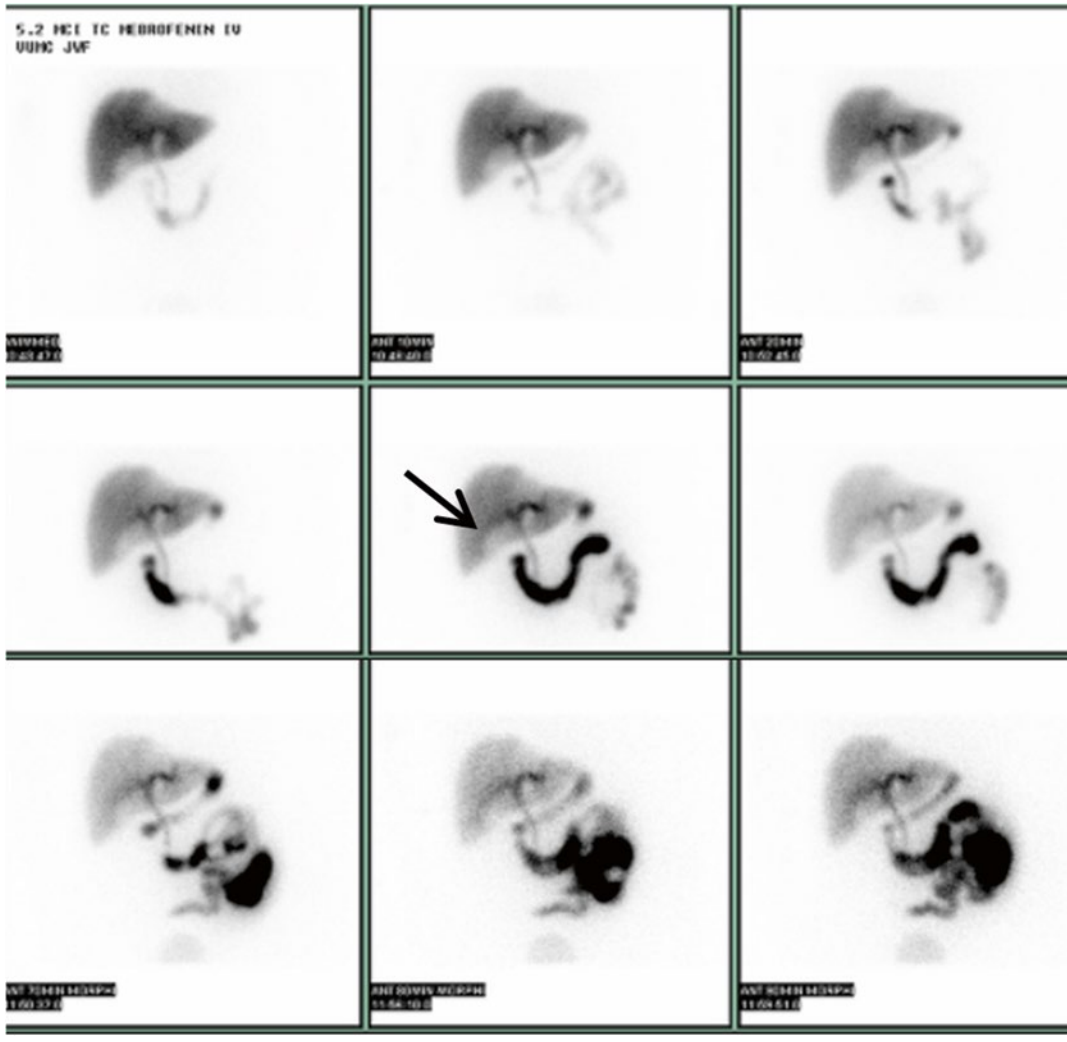

Fig. 3.6 Scintigraphy of patient with acalculous cholecystitis. Gallbladder does not fill at any point during the study. First six images are early images showing contrast transiting from the liver into the duodenum. The last three images are delayed images after the administration of low-dose morphine and show continued passage of contrast into the small bowel without filling the gallbladder. A rim sign (*black arrow*) is visible on multiple images in this series suggesting the possibility of advanced gallbladder disease

required to stabilize a critically ill patient and the catabolism of serum and body proteins may contribute to global body edema and ascites. Thus, the presence of gallbladder wall edema and pericholecystic fluid may not have diagnostic significance. The presence of a sonographic Murphy's sign is quite helpful in establishing the diagnosis but sedation, narcotics, incisional pain, and progression to gallbladder wall necrosis may all confound its detection or limit its presence. While an HIDA scan may be used to exclude acalculous cholecystitis, hepatic dysfunction and biliary stasis can limit the uptake and excretion of the radioactive material and thus not adequately image the biliary tree. Additionally, a significantly distended gallbladder may exhibit poor uptake, regardless of the absence of pathology. Thus, in critically ill patients with a distended gallbladder on imaging and without the ability to provide an appropriate clinical exam, percutaneous drainage may be necessary to establish the diagnosis.

Summary

Diagnosis of acute cholecystitis involves clinical, laboratory, and radiographic findings. TG13 guidelines provide a diagnostic algorithm that optimizes specificity and sensitivity in those patients with a history suggestive of possible acute cholecystitis. Physical exam and laboratory findings should suggest acute inflammatory processes. Imaging should start with RUQ ultrasound and include HIDA if inconclusive. For patients with atypical symptoms, CT may be a better initial imaging modality. The role of MRI is less clear, but may become more important as radiation exposure concerns grow. In select patient populations and certain clinical settings, diagnosis may be difficult or delayed. A high index of suspicion and an attentive approach in at-risk populations is required to limit delays in diagnosis and possible complications.

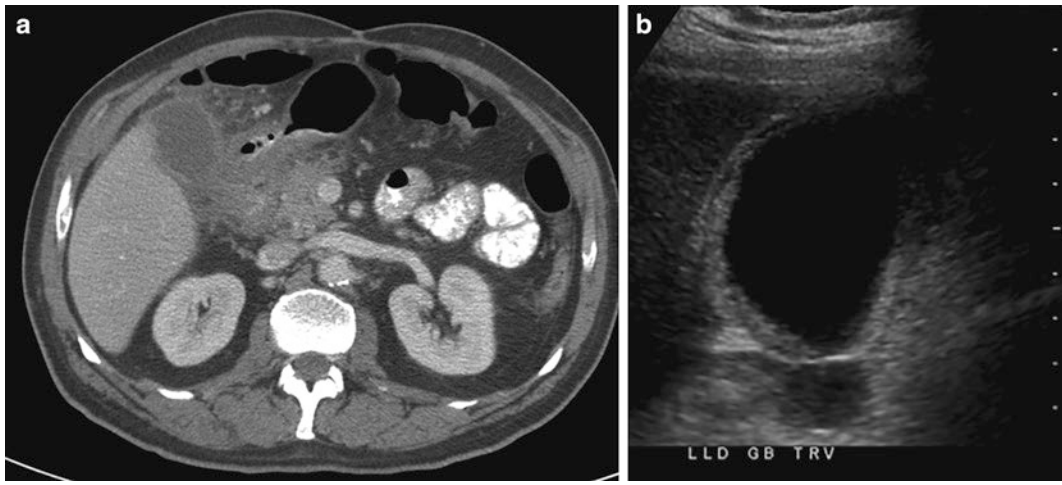

Fig. 3.7 Acalculous cholecystitis. CT demonstrates wall thickening and irregular enhancement of gallbladder. US shows wall thickening but no gallstones are seen

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The Use of Imaging in Gallbladder Disease

4

Christopher J. LaRocca, Torfi Hoskuldsson, and Greg J. Beilman

Introduction

Diseases of the gallbladder and biliary tree are frequently encountered problems in the medical community. Acute calculous and acalculous cholecystitis, symptomatic cholelithiasis, choledocholithiasis, gallbladder polyps, gallbladder wall calcifications, and gallbladder malignancies can all present unique diagnostic and treatment dilemmas.

In the United States, gallstones affect approximately 20–25 million adults [1]. Fortunately, most individuals do not become symptomatic from their cholelithiasis [2]. Despite this fact, gallstones are one of the most expensive digestive disorders with an estimated annual cost of approximately $6 billion [3]. Due to the prevalence of gallstones and the advent of laparoscopy, cholecystectomies have become one of the most commonly performed abdominal operations with over 750,000 completed annually [4]. It is notable that only 15–17 % of laparoscopic cholecystectomies are performed for acute cholecystitis [5, 6].

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Like many of the aforementioned conditions, acute cholecystitis can present many diagnostic difficulties for physicians, and there is an array of imaging modalities to help to confirm the findings of the history and physical exam. As it is not always clear which radiographic test is best for a particular clinical situation, the recently published Tokyo Guidelines have outlined severity criteria for acute cholecystitis and key imaging findings across different modalities to confirm the diagnosis [7].

Ultrasound

The initial test for the diagnosis of acute cholecystitis is currently abdominal ultrasound. This study has the advantage of being an inexpensive, widely available imaging modality that does not deliver any ionizing radiation. Structures of varying depth can be analyzed depending on the frequency of probe that is used. Additionally, its Doppler technology can provide information on vascular flow in the area of interest. Ultrasound's accuracy in diagnosing the presence of gallstones (Fig. 4.1) has been consistently reported to be greater than 90 % [8]. Imaging findings that suggest acute cholecystitis include: gallbladder wall thickening greater than 4 mm, pericholecystic fluid, cholelithiasis, sludge, and a sonographic Murphy's sign (Fig. 4.2).

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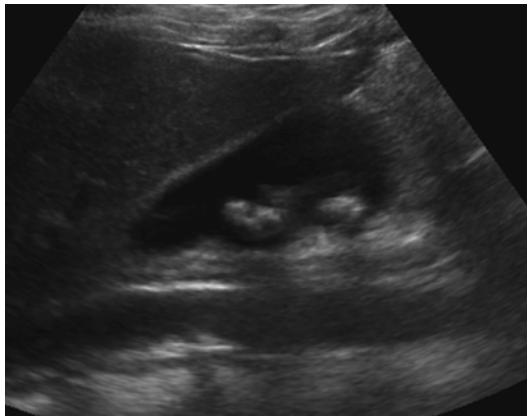

Fig. 4.1 Gray-scale ultrasound demonstrating cholelithiasis with no associated abnormal findings

Despite all of these advantages, there are still some drawbacks to using ultrasound as a diagnostic imaging technique. Importantly, the acquisition of images is operator dependent. Moreover, a number of patient and anatomical factors can obscure the signal and result in poor image quality. Two main issues are obesity and bowel/bone between the gallbladder and the transducer on abdominal wall. As with all imaging, findings must be placed in the appropriate clinical context. For example, gallbladder wall thickening is not unique to acute cholecystitis and can be seen in cases of cirrhosis and hepatitis [9]. Furthermore, gallstones can have a similar appearance to gallbladder polyps (Fig. 4.3). However, gallstones are mobile, whereas polyps are fixed structures. By simply rotating the patient and acquiring additional images, important clinical information can be obtained.

Depending on the series, the reported sensitivity and specificity of ultrasound for the diagnosis of acute cholecystitis have varied greatly [10–14]. However, a recent systematic review and meta-analysis reported them to be 81 % (95 % Confidence Interval (CI): 75–87 %) and 83 % (95 % CI: 74–89 %), respectively [15]. In a prospective study that analyzed the ultrasound findings of 497 patients suspected of having acute cholecystitis, the positive predictive value of gallstones in combination with a thickened gallbladder wall and/or a positive sonographic Murphy's sign ranged from 92 to 95 % [10].

Color Doppler can provide another potential information source to aid in clinical decision-making. One study showed that all patients with histologically proven acute cholecystitis had increased vascular flow in the distal two-thirds of the thickened gallbladder wall [16].

There is some controversy regarding which imaging modality is best for acute acalculous cholecystitis, as it can be difficult to clearly and definitively diagnose. Affected patients are often severely ill due to trauma, burns, sepsis, shock, or other postoperative complications. They cannot reliably participate in a physical examination and their laboratories values may be altered for other reasons. Compared to acute calculous cholecystitis, the pathology in these patients is likely a result of bile stasis and/or mucosal ischemia [17]. Ultrasound is easy to use, portable, and easily repeatable which minimizes logistical problems when dealing with critically ill patients. Therefore, ultrasound may make the most sense as the initial imaging modality for patients that cannot be easily transported to the radiology department.

Gallbladder wall thickness has been shown to be useful in diagnosing acute acalculous cholecystitis, with a wall thickness of greater than 3.5 mm having a specificity of 98.5 % [18]. Other criteria such as sludge, hydrops, and gallbladder distension have been cited as diagnostic criteria, but it is important to note that many intensive care unit patients have "abnormal" findings on ultrasound without having a diagnosis of acute acalculous cholecystitis [19, 20]. Multiple studies have shown a specificity of greater than 90 % for the diagnosis of acute acalculous cholecystitis by ultrasound, but the sensitivities have varied more widely and have been reported as low as 30 % [21–23].

In summary, due to its low cost, ease of use, and availability in many clinics and emergency rooms, the vast majority of patients with suspected acute cholecystitis undergo ultrasound as their initial imaging modality [11]. For clinical situations where the diagnosis is not entirely clear, it may be useful or necessary to pursue additional imaging studies.

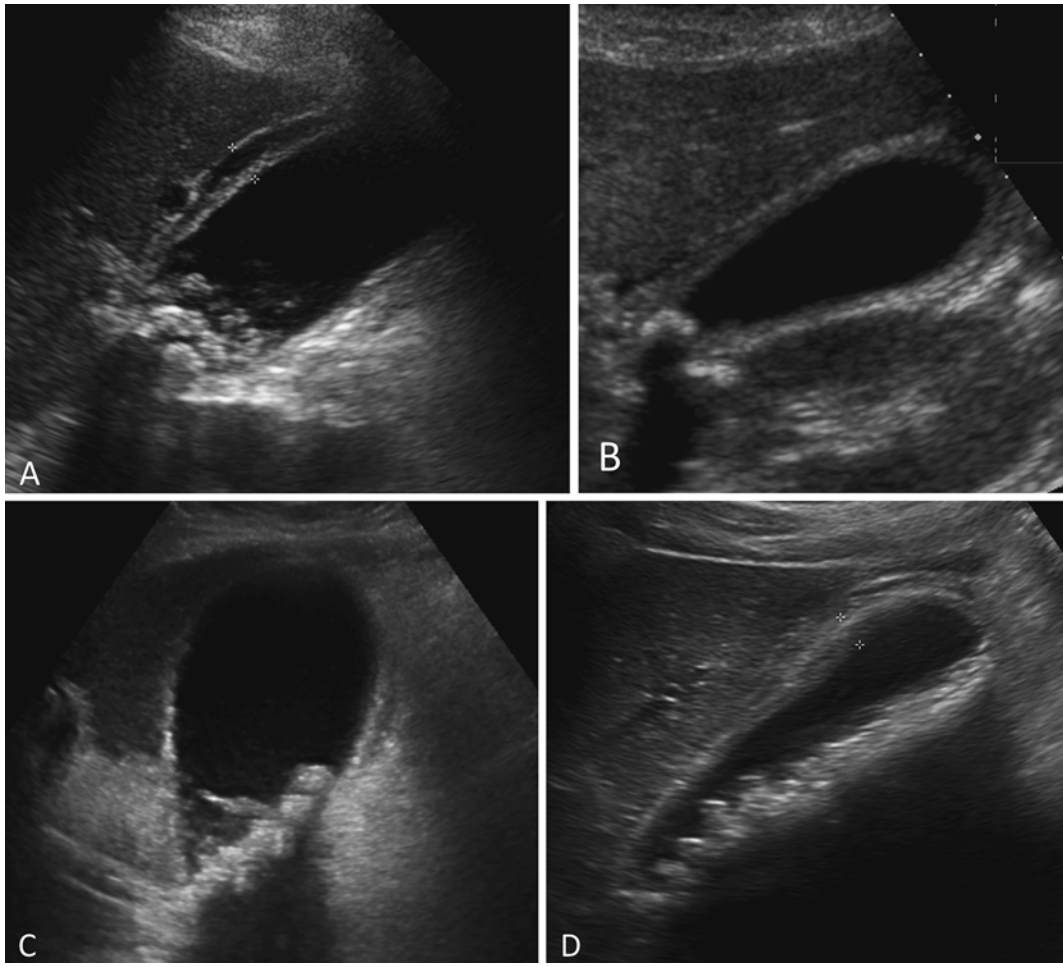

Fig. 4.2 Gray-scale ultrasound of the gallbladder with related abnormal findings. (**a**) Cholelithiasis and gallbladder wall thickening up to 8 mm. (**b**) Gallstone lodged in the gallbladder neck with associated wall thickening. (**c**) Cholelithiasis, thickened gallbladder wall, and pericholecystic fluid. (**d**) Cholelithiasis, sludge, pericholecystic edema, and mild gallbladder wall thickening

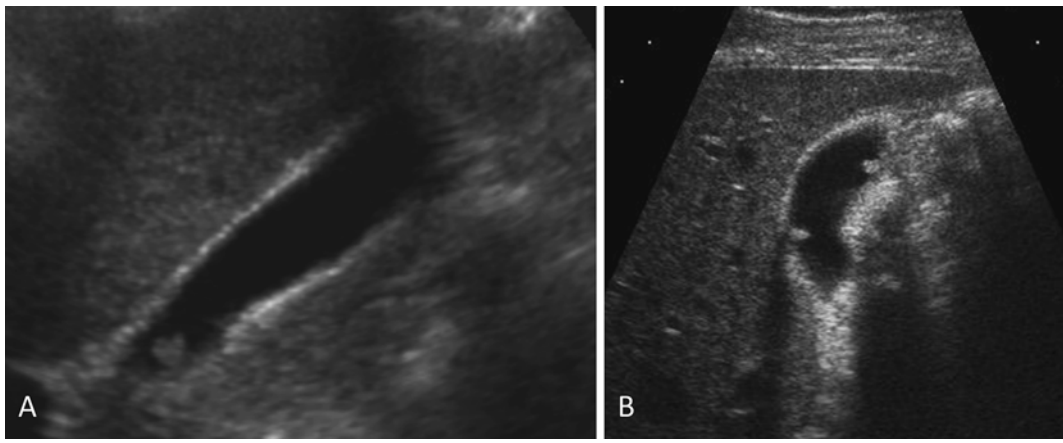

Fig. 4.3 Gray-scale ultrasound of the gallbladder demonstrating polyps. (**a**) Single polyp in the gallbladder neck. (**b**) Multiple polyps located throughout the gallbladder

Cholescintigraphy

Cholescintigraphy using technetium-99 m (^{99m}Tc) labeled hepatobiliary iminodiacetic acid (HIDA) is another commonly used imaging technique to confirm the diagnosis of acute cholecystitis. The radiolabeled agent is given intravenously after which it is extracted by the hepatocytes in the liver, secreted into the bile canaliculi, flows through the bile ducts and into the gallbladder, and then passes into the intestines [24]. The gallbladder usually begins to fill approximately 10 min into the study and is often completely filled by 30–40 min; however, up to 60 min is considered normal [25].

The classic finding of acute cholecystitis on a HIDA scan is persistent non-filling of the gallbladder, even on delayed imaging (Fig. 4.4) [25]. Additionally, increased radiotracer uptake in the liver parenchyma adjacent to the gallbladder fossa, known as the "rim sign," has been shown to be a predictor of acute cholecystitis [26, 27]. False-positive test results do occur and are frequently seen in individuals who have been fasting for a prolonged time period (greater than 24 h) or who have received parenteral nutrition [28, 29].

Morphine (which stimulates contraction of the sphincter of Oddi and increases pressure in the biliary tree) augmented cholescintigraphy has been touted as a way to decrease the false-positive rate and improve diagnostic accuracy [30]. Cholecystokinin, with its ability to stimulate gallbladder contraction and lower sphincter of Oddi pressure, has been used to increase the diagnostic accuracy as well [31].

Cholescintigraphy has been consistently reported to have a higher sensitivity and specificity than ultrasound for the diagnosis of acute cholecystitis. In the aforementioned systematic review and meta-analysis, the sensitivity and specificity were 96 % (95 % CI: 94–97 %) and 90 % (95 % CI: 86–93 %), respectively [15]. While cholescintigraphy may have a higher diagnostic accuracy compared to ultrasound, the modality does have some limitations that have historically precluded its adoption as the initial imaging study of choice in patients with suspected acute cholecystitis. These issues are mostly logistical as nuclear medicine personnel are typically unavailable to perform the study on evenings and weekends. Comparatively, in many larger centers, ultrasound technicians are present 24 h per day, including weekends. Additionally, a HIDA scan takes longer than an ultrasound to complete, provides information limited to the biliary system, and exposes the patient to radiation, thereby limiting its attractiveness in pregnant patients.

As mentioned previously, the diagnosis of acute acalculous cholecystitis is a difficult clinical problem. While ultrasound often may be the preferred modality, cholescintigraphy should not be overlooked as a valuable tool to aid in the diagnosis. Some authors even have advocated its role as the initial imaging modality [32]. Reported sensitivities have ranged from 67 to 100 %, and specificities have been reported from 38 to 100 % [21–23, 33]. There have been concerns of increased false-positive rates in critically ill patients, but morphine augmentation has helped to alleviate this issue [23, 33].

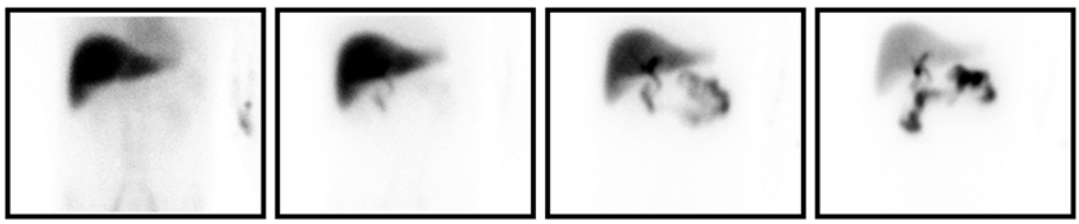

Fig. 4.4 HIDA scan consistent with cholecystitis. Shown from left to right are the images acquired at 5, 15, 30, and 60 min following radiotracer injection. Even at late time points, there was non-filling of the gallbladder

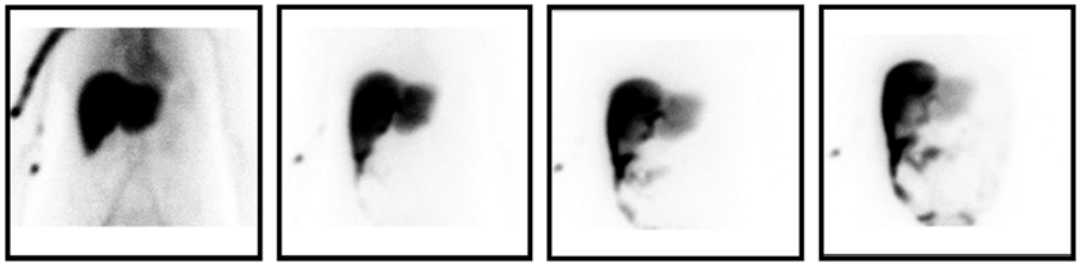

Fig. 4.5 HIDA scan demonstrating a post-operative biliary leak following cholecystectomy. Shown from left to right are the images acquired at 5, 15, 30, and 60 min following radiotracer injection. By the final time point, there continues to be evidence of tracer uptake at the level of the liver which extends down into the right paracolic gutter

HIDA scans are also useful in the postoperative setting to aid in the diagnosis of complications. Following cholecystectomy, there is an approximately 0.5 % risk of bile duct injury [34, 35]. For clinically significant bile leaks that go unrecognized at the time of surgery, patients are often discharged shortly thereafter and then present days later. Their symptoms can include abdominal pain and/or distension, nausea, vomiting, and possibly fevers. Initial imaging studies such as an ultrasound may demonstrate a fluid collection in the gallbladder fossa. HIDA scans are a useful and sensitive tool for determining if the fluid is biliary in nature (Fig. 4.5) [36, 37]. Additionally, obtaining delayed views are crucial to avoid missing bile leaks, especially when the initial images appear normal [38]. Furthermore, complete absence of emptying of the tracer from the liver may indicate a complete biliary obstruction as present with an inadvertently ligated common bile duct. Importantly, this study lacks the ability to pinpoint the exact site of the bile leak.

Consequently, cholescintigraphy is a useful imaging tool that can provide valuable information in multiple clinical settings related to biliary tract disease. However, the ability to perform the study may be limited by the availability of qualified personnel and the time necessary to acquire images.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) technology has advanced greatly in recent years. However, MRI is still not considered a routine initial imaging study for patients with suspected acute cholecystitis. MRI is a costly exam that is less readily available when compared to ultrasound. The study time is also greater in length, although there have been reports of protocols for acute abdomen imaging that are as quick as 15 min [39, 40].

One clear benefit of MRI is that it does not deliver any ionizing radiation, which makes it a particularly useful tool in the evaluation of pregnant patients with right upper quadrant pain (Fig. 4.6) [41]. Additionally, MRI's excellent tissue contrast provides high-resolution images of the biliary anatomy which allows for improved recognition of choledocholithiasis when compared to other imaging modalities (Fig. 4.7) [42].

Imaging findings on MRI that are suggestive of acute cholecystitis include: pericholecystic high signal, a thickened gallbladder wall, and an enlarged gallbladder [43, 44]. Multiple studies have demonstrated that MRI is equivalent to or slightly better than ultrasound in diagnosing acute cholecystitis [44, 45]. One study used the HASTE sequence (ultrafast protocol for image acquisition) with no additional contrast material to analyze the pericholecystic signal, and found that it yielded a diagnostic accuracy of 89 % [46]. While there are certainly fewer studies available to analyze MRI's role in diagnosing acute cholecystitis, a recent meta-analysis demonstrated a sensitivity of 85 % (95 % CI: 66–95 %) and a specificity of 81 % (95 % CI: 69–90 %) [15].

Magnetic resonance cholangiopancreatography (MRCP) has become one of the main diagnostic imaging modalities for the investigation of the biliary tree and pancreatic ducts, as well as

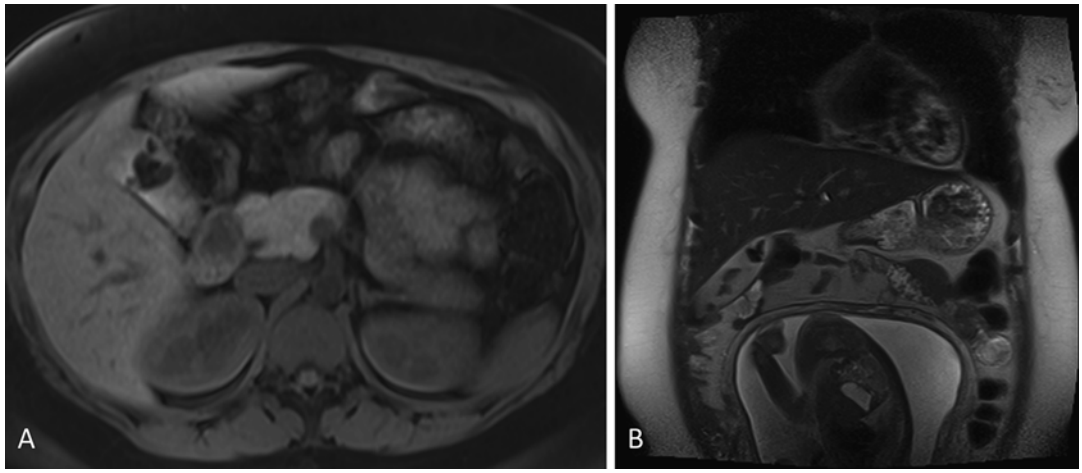

Fig. 4.6 MRI scan of a pregnant female who presented with right upper quadrant pain and was found to have cholelithiasis. (**a**) Axial T1-weighted image. (**b**) Coronal T2-weighted image

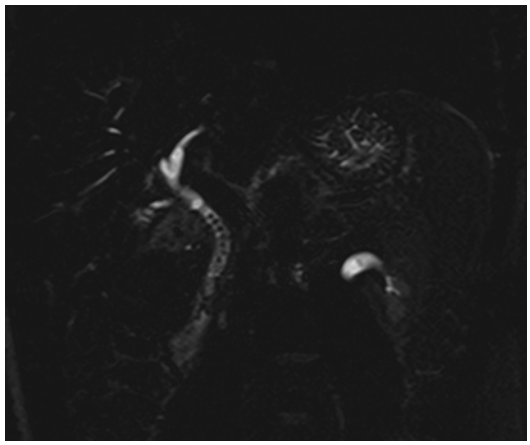

Fig. 4.7 MRCP of a patient presenting with elevated liver function tests. Coronal T2-weighted images demonstrated choledocholithiasis and mild ductal dilatation

the body and tail of the pancreas. This study is useful for investigating biliary obstruction (due to choledocholithiasis, stricture, or malignancy), anatomic variants of the biliary anatomy, the pancreatic ducts, and potential postoperative complications following hepatobiliary surgery [47–49]. Some studies have even suggested MRCP is equivalent to endoscopic retrograde cholangiopancreatography (ERCP) for the diagnosis of choledocholithiasis [50, 51]. MRCP has been demonstrated to have a sensitivity of 84 %, a specificity of 94 %, a positive predictive value of 91 %, and a negative predictive value of 93 % for the diagnosis of choledocholithiasis [52].

Therefore, while MRI has been shown to effectively diagnose acute cholecystitis, its cost, time consumption, and limited availability have prevented its widespread adoption as a first-line imaging modality for that disease process. However, with improved MRI technology and the advent of MRCP, high-resolution images of the hepatobiliary system greatly assist clinicians in the diagnosis and treatment complex biliary and pancreatic pathology.

Computed Tomography

Computed tomography (CT) has become one of the most widely used imaging modalities in modern medicine. This technology is readily available and of moderate cost, but does have the downside of exposure to ionizing radiation. Also, CT scans are less accurate than ultrasound at diagnosing cholelithiasis with a reported accuracy of just under 90 % and a sensitivity of 79 % [53].

Signs of acute cholecystitis on CT scans include: gallbladder distension, wall thickening, pericholecystic fluid and fat stranding, and mucosal hyperenhancement (Fig. 4.8) [54]. Reactive

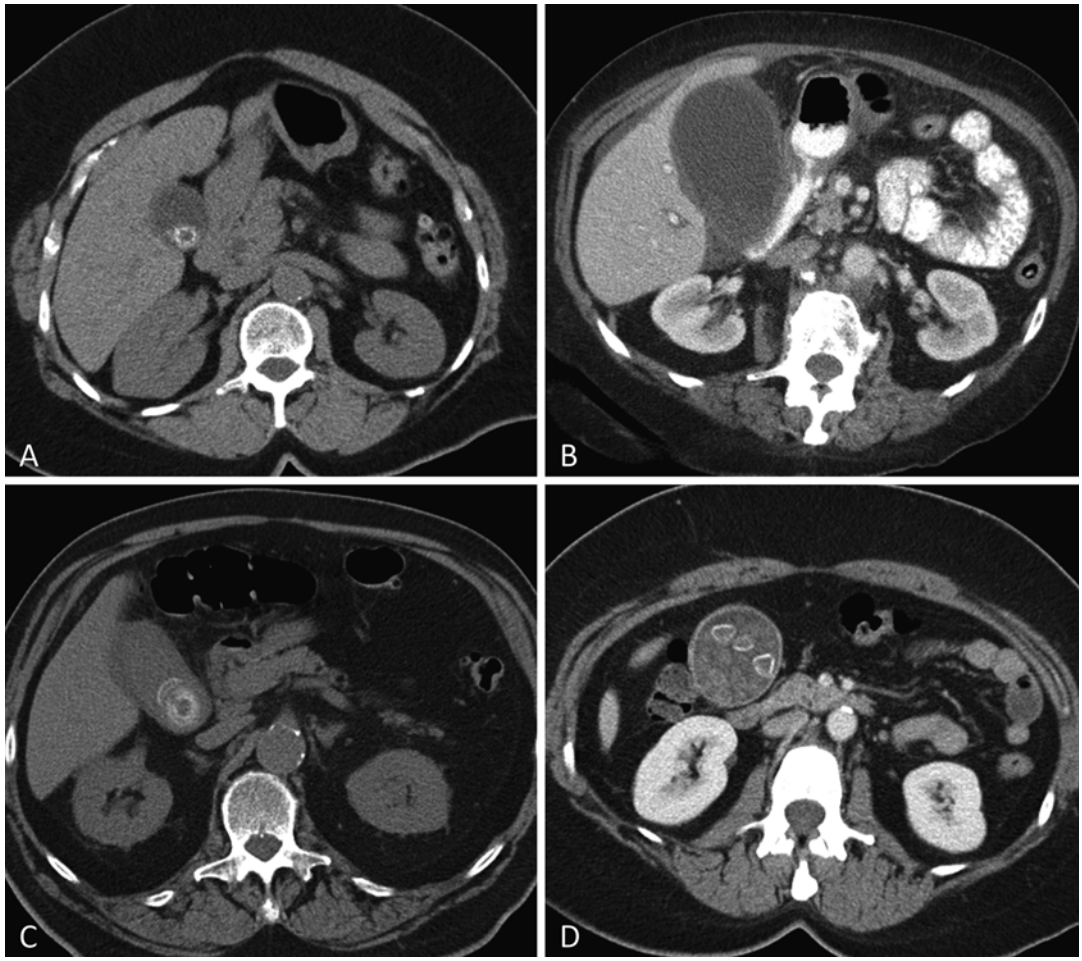

Fig. 4.8 Axial images from CT scans of patients presenting with right upper quadrant pain. (**a**) Cholelithiasis. (**b**) Thickened gallbladder wall and pericholecystic edema. (**c**) Large gallstone within the gallbladder lumen and associated pericholecystic fluid. (**d**) Gallbladder lumen filled with gallstones

hyperemia resulting in enhancement of the area of liver parenchyma adjacent to the gallbladder fossa may be present as well [54, 55]. Additionally, a tensile gallbladder fundus which displaces the abdominal wall may be a useful imaging sign to diagnose acute cholecystitis, especially in the disease's early stages (Fig. 4.9) [56].

For the diagnosis of acute cholecystitis, CT scans have been shown to have a range of sensitivities from 39 to 92 % and a specificity range of 93–99 % [57, 58]. One study reported a positive predictive value of 50 %, and a negative predictive value of 89 % [57]. In more complex clinical situations, CT scans have been shown to have a sensitivity of 96 % for the diagnosis of acute gangrenous cholecystitis, and key imaging findings include an irregular or absent gallbladder wall, gas in the wall or lumen, intraluminal membranes, or a pericholecystic abscess (Fig. 4.10) [58]. Also, CT is the most sensitive and specific imaging modality for identifying gas within the gallbladder lumen or wall [59] and has been reported to have up to a 100 % sensitivity for diagnosing emphysematous cholecystitis [60].

Given the accessibility of this technology, there has been some evidence to suggest an overuse of CT scans in evaluating patients with gallbladder disease, especially with presentation during off-hours [61]. However, it should be noted that CT imaging can provide important

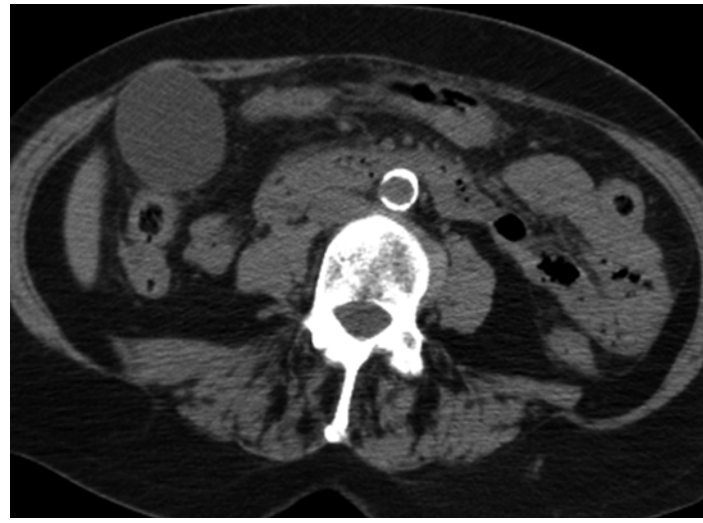

Fig. 4.9 CT scan demonstrating a distended gallbladder displacing the abdominal wall (tensile gallbladder fundus sign)

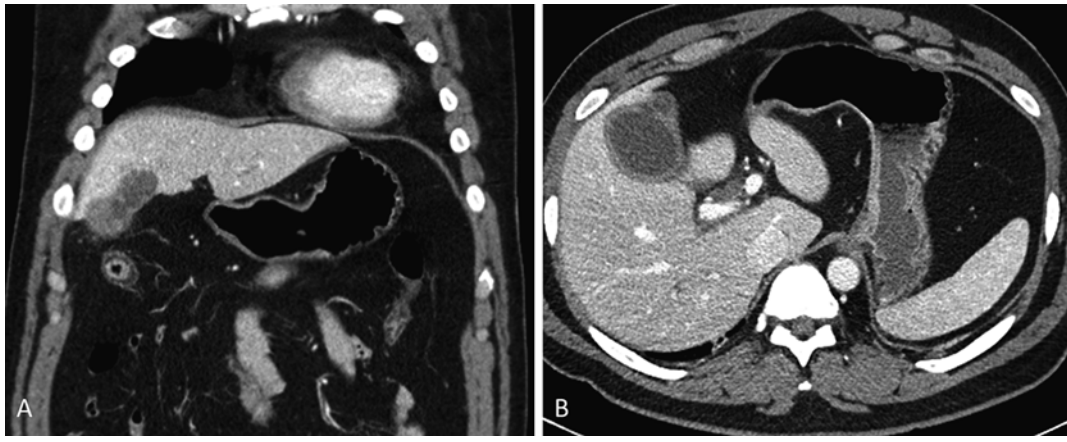

Fig. 4.10 CT scan demonstrating gangrenous cholecystitis. (**a**) Coronal image demonstrating focal mucosal loss of the gallbladder fundus with associated abscess extending into the liver parenchyma. (**b**) Axial image showing gallbladder wall thickening, pericholecystic fluid, and the area of focal gallbladder wall disruption

information when the clinical situation is unclear or a more complex diagnosis is being considered. CT scans are widely available and are most useful for patients with atypical presentations or when symptoms include areas of the abdomen outside of the right upper quadrant.

Intraoperative Cholangiography

Intraoperative cholangiography (Fig. 4.11) is performed in approximately 30 % of all cholecystectomies [62]. Clear preoperative indications for the procedure include: jaundice,

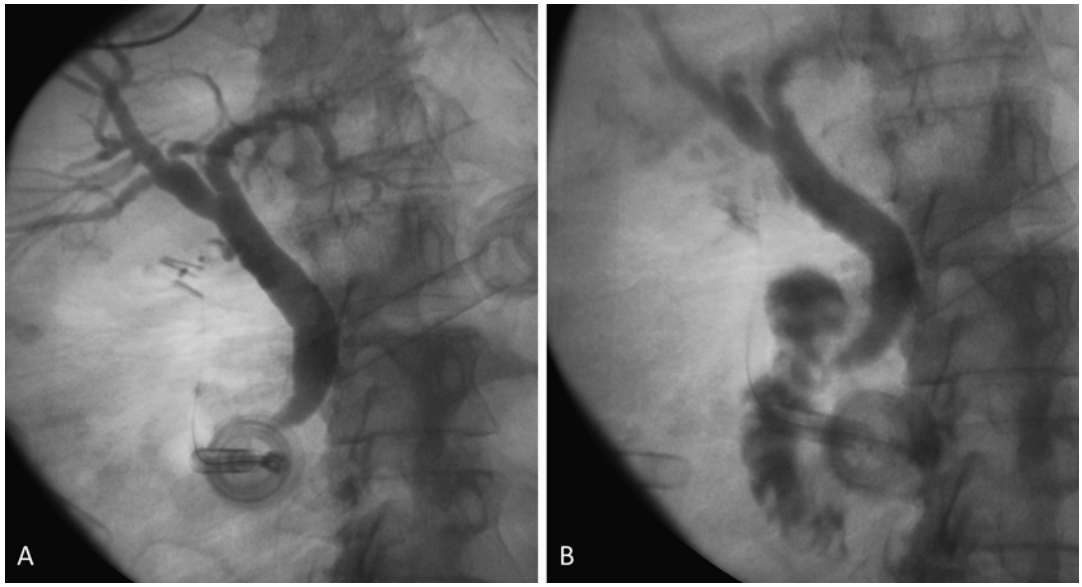

Fig. 4.11 Intraoperative cholangiogram during laparoscopic cholecystectomy. (**a**) Initial image demonstrated no filling defects, although there was tapering of the distal common bile duct near the papilla. (**b**) Glucagon administration was necessary to allow for contrast flow into the duodenum

elevated liver function tests and/or pancreatic enzyme levels, and ductal dilatation or choledocholithiasis seen on imaging studies [63]. There has been a great debate in the literature regarding the use of routine intraoperative cholangiography. Those surgeons in favor of this practice have argued that it results in a lower rate of biliary tract injury during cholecystectomy, an increased degree of intraoperative detection of common bile duct stones that can be treated at the time of initial surgery, and is a tool for surgical education [64]. Many other surgeons perform cholangiography only in select patient scenarios. Recent studies have suggested that there is limited, if any, benefit to performing routine intraoperative cholangiography with every cholecystectomy [65, 66]. There have even been reports of higher rates of bile duct injuries for surgeons who routinely perform cholangiography as compared to those who only do so selectively [67]. While this debate is likely to continue, the fact remains that intraoperative cholangiography can provide critical information about biliary anatomy that can be used to guide surgical therapy.

Percutaneous Cholecystostomy

The complication rate associated with performing a laparoscopic cholecystectomy for acute cholecystitis increases with the severity of the episode as well as the age of the patient. In patients who are poor surgical candidates, percutaneous placement of a cholecystostomy tube has been advocated as a temporary measure (until cholecystectomy can be performed) or as a definitive procedure [68]. It is performed under ultrasound or CT guidance, and it can be done by either a transabdominal or a transhepatic approach. The data on percutaneous cholecystostomy tubes are mixed with some studies suggesting their ability to be used as a first-line treatment for acute cholecystitis without interval cholecystectomy and others suggesting a role only when there are prohibitive operative risks [69–72]. In either case, percutaneous cholecystostomy tube placement will continue to be one treatment option for patients who are precluded from undergoing surgery on account of other medical comorbidities.

Endoscopic Drainage

Advances in endoscopy have allowed for increased access to the biliary tree and gallbladder for a variety of diagnostic and therapeutic procedures. Over the recent years, endoscopic approaches to gallbladder drainage have been reported with increasing frequency. These types of approaches are particularly useful in patients who are poor surgical candidates and who may have a contraindication to a percutaneous procedure. One option is to access the gallbladder through the transpapillary route and leave either a nasobiliary tube or a stent in place (Fig. 4.12). Alternatively, there are reports of transmural drainage through the distal antrum or the duodenum (Fig. 4.13).

A systematic review combined data from multiple retrospective studies on naso-gallbladder drainage to achieve a pooled technical success rate of 81 % and a clinical response rate of 75 % [73]. Similarly, for endoscopic transpapillary gallbladder stenting, the technical success rate was 96 % and the clinical response rate was 88 % [73]. A recent prospective, randomized controlled trial (designed as a non-inferiority study) demonstrated that the technical and clinical success of endoscopic guided transmural gallbladder drainage was comparable to that of percutaneous transhepatic gallbladder drainage [74].

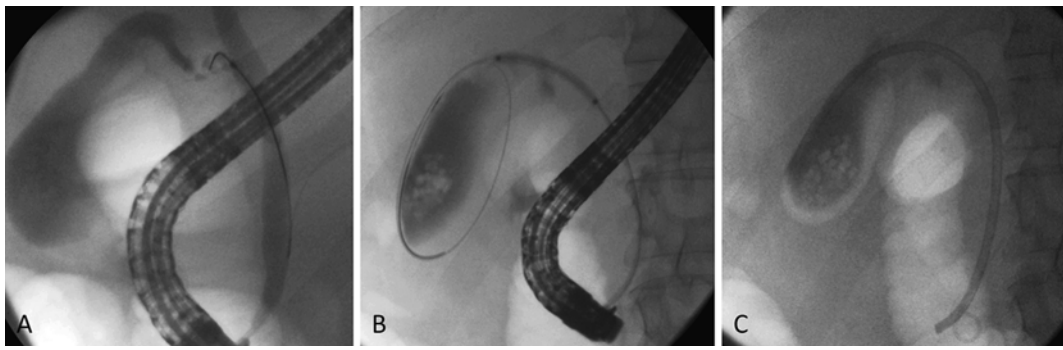

Fig. 4.12 Transpapillary gallbladder drainage in a 40-year-old male with a history of end-stage liver disease who presented with acute cholecystitis. (**a**) During ERCP, there was evidence of a cystic duct obstruction due to a gallstone. (**b**) Dilation of the cystic duct using a 4 mm balloon catheter. (**c**) Successful placement of a transpapillary ten French stent

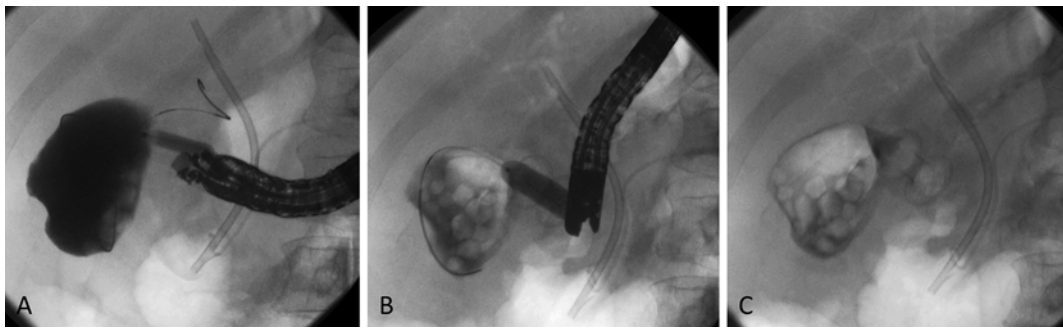

Fig. 4.13 Transduodenal gallbladder stent in a 70-year-old male with metastatic colon cancer who while receiving palliative chemotherapy developed acute cholecystitis. (**a**) Endoscopic ultrasound-guided transduodenal needle puncture with wire placement and subsequent balloon dilation of the tract. (**b**) Balloon dilation of the stent lumen. (**c**) Transduodenal lumen apposing covered metal stent within the gallbladder. *Note*: A common bile duct stent was also placed due to a biliary stricture

Endoscopic approaches for biliary tree access have undergone numerous advances in recent years and serve as an excellent therapeutic option for patients who are not able to undergo a surgical procedure.

Conclusion

Cholelithiasis and acute cholecystitis are common conditions that clinicians and surgeons encounter daily in practice. The recent advances in diagnostic imaging have provided numerous options to aid in the delivery of patient care. For most instances of acute cholecystitis, ultrasound still remains the initial diagnostic imaging of choice. HIDA scans play an important role in diagnosis, especially when the initial ultrasound is equivocal. Additionally, they are useful in the postoperative setting to investigate biliary leaks. MRI and MRCP provide high-resolution images of the hepatobiliary system with excellent tissue contrast. As MRI scanning becomes more ubiquitous and less expensive, this modality may have an increased role in the diagnosis of acute cholecystitis. CT scans are most helpful when the diagnosis of acute cholecystitis is unclear, or when there are additional symptoms outside of the right upper quadrant. CT scanning also has clinical utility when there is concern for complications of cholecystitis such intra-abominal abscess, gallbladder perforation, and gangrenous or emphysematous cholecystitis. By tailoring the selection of radiographic images to the individual patient scenario, clinicians can maximize diagnostic utility and mitigate unnecessary costs and radiation exposure.

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The Use of Routine and Selective Intraoperative Cholangiography

5

Joshua D. Person and Lillian S. Kao

Introduction

Routine versus selective use of intraoperative cholangiography (IOC), or radiographic imaging of the biliary tree, during laparoscopic cholecystectomy remains controversial. Introduced in 1937 by Mirizzi, IOC is primarily used to detect choledocholithiasis or common bile duct stones and to define biliary anatomy. Proponents of routine IOC argue that its use prevents common bile duct injury (CBDI) [1, 2]. Although the incidence of CBDI currently is approximately 0.3–0.5 % [3, 4], CBDI is associated with worsened functional status, reoperations, readmissions, and short- and long-term morbidity including biliary strictures, mortality, and costs [5–8]. In addition, CBDI is associated with increased malpractice, particularly when diagnosis is delayed [9–11]. In contrast, proponents of selective IOC argue that routine IOC use does not prevent CBDI and that its interpretation is unreliable [12]. Additional arguments include that IOC prolongs the length of laparoscopic cholecystectomy, has associated complications, and can yield false positive results leading to unnecessary studies and procedures [12].

There is wide variation in the use of IOCs. In an analysis of a clinical registry, the Society of American Gastrointestinal and Endoscopic Surgeons Outcomes Initiative database, approximately 50 surgeons entered the majority of over 3200 laparoscopic cholecystectomy cases between 1999 and 2005; IOC was used in 71 % of the cases [13]. While this percentage is relatively high, these data represent a small sample of surgeons with a special interest in laparoscopic surgery. A survey was performed of a larger population of surgeons randomly selected from the membership of the American College of Surgeons. Of 4100 surgeons queried, 44 % responded, of whom 27 % stated that they routinely performed IOC while 91 % stated that they performed IOC in greater than 75 % of cases [14]. Routine users were less likely to be academic surgeons and had more favorable opinions regarding the effectiveness of IOC. Selective users tended to be low volume surgeons defined as performing less than 20 laparoscopic cholecystectomies per year. Both of these studies utilized self-reported data. In an analysis of Texas discharge data, IOC use demonstrated significant variability, ranging from 2.4 to

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99.4 % of cases among surgeons and 3.7–94.8 % of cases among hospitals [15]. This population-based dataset analysis demonstrates the variability of IOC use in the community.

Based on the models created from the Texas discharge data, 21 % and 26 % of the variation in IOC use were explained based on surgeon and hospital factors, respectively [15]. There are multiple factors at both of these levels, as well as at the patient level, which are postulated to influence the use of IOC. Surgeon-specific factors include their belief in the strength of evidence for the effectiveness of IOCs in preventing CBDIs, their skill and experience in performing laparoscopic cholecystectomies and in interpreting IOCs, and their preferences. Hospital-specific factors include the availability of adjunctive methods for evaluating the anatomy (i.e., ERCP), availability of fluoroscopy, time and cost to perform IOC, system-level guidelines or mandates for IOC use, and culture. Patient-specific factors associated with increased use of IOC include increased age, diagnosis (gallstone pancreatitis or choledocholithiasis), lesser severity of disease, and socioeconomic factors such as Hispanic race and insurance [15].

Technique

There are several methods for performing IOC during laparoscopic cholecystectomy. One method for IOC that does not require any special instruments is cystic duct cannulation. A clip is placed across the gallbladder/cystic duct junction, and a small transverse cystic ductotomy is made just below the clip. Through a 1–3 mm subcostal incision a guiding sheath such as an angiocatheter is advanced through the skin towards the ductotomy. A cholangiocatheter is advanced through the sheath and into the cystic duct for 5–6 mm and secured with a clip (Fig. 5.1). Prior to insertion, the catheter should be flushed to ensure there is no introduction of air bubbles into the biliary tree that could be misinterpreted as choledocholithiasis. After the catheter is secured, bile should be aspirated from the catheter to confirm the intraductal position and the catheter should be flushed with saline to confirm there is no leakage around the catheter. The operating room table is placed in 30° Trendelenburg position and rotated to the right. The C-arm fluoroscope is covered with a sterile drape and advanced into position over the right upper quadrant. A radiopaque contrast material is injected consisting of an iodinated contrast dye mixed with saline in a 25–30 % solution; a noniodinated compound can be used for those with iodine allergy.

There are several commercially available devices that can be utilized to facilitate cholangiography. The Olsen Cholangiogram Clamp (Karl Storz Endoscopy, Culver City, California) is an instrument that can be used to grasp the cystic duct and allows passage of a 4- to 5-French ureteral catheter into the cystic ductotomy (Fig. 5.2). This instrument can be passed through either the subcostal or the epigastric port and therefore does not require an additional incision for introduction of a cholangiocatheter. As an alternative to IOC via a cystic ductotomy, imaging of the biliary system can be performed via a catheter inserted into the gallbladder. The Kumar Pre-View Clamp (Nashville Surgical Instruments, Springfield, Tennessee) is a locking grasper placed across the gallbladder fundus with a channel through which a catheter with a 1.25 cm 19 gauge needle can be passed and advanced into the Hartmann's pouch of the gallbladder for contrast injection (Fig. 5.3) [16]. The clamp can be introduced into the abdomen via the subcostal port. This method has a theoretical advantage of not requiring an incision in any ductal structures. Thus, this may be preferable in patients with a short cystic duct or where the ductal anatomy is unclear. However, this method may not be feasible when there is a stone obstructing the neck of the gallbladder or the cystic duct unless the stone can be dislodged.

There has only been one randomized trial comparing the Olsen to the Kumar clamp for IOC. There were no differences between the two clamps in terms of success rate in obtaining the IOC, the mean IOC time, or surgeon perception of the ease of using the clamps [17].

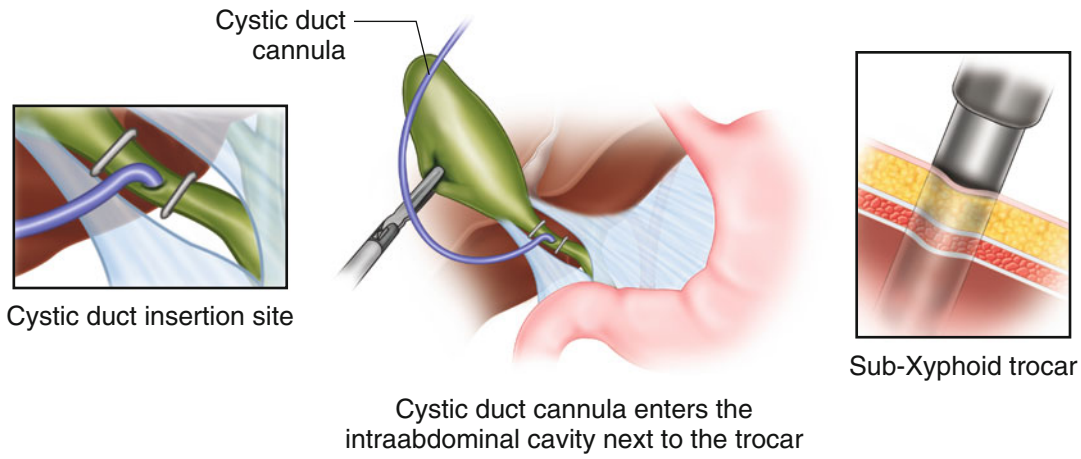

Fig. 5.1 A catheter is introduced into the abdomen through a separate subcostal stab incision via an angiocatheter or sheath. A clip is placed at the gallbladder/cystic duct junction and a ductotomy made in the cystic duct through which the cholangiocatheter is advanced

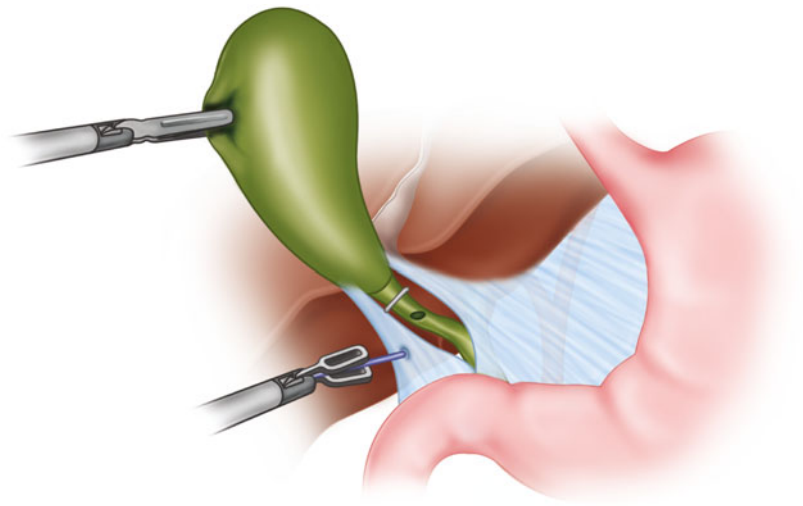

Fig. 5.2 The Olsen clamp can be placed through either the mid-subcostal or the epigastric port. A clip is still placed at the gallbladder/cystic duct junction, but no additional clip is necessary to hold the catheter in place. The catheter is threaded through a channel in the clamp and is held in place via the clamp on the cystic duct

However, the trial only included 59 laparoscopic cholecystectomy cases and surgeons had greater familiarity with the Olsen clamp. Given the relative advantages and disadvantages of each method, it is important for surgeons to learn and become proficient with each method in order to be able to perform IOCs across different presentations of acute cholecystitis or other biliary disease.

Once the cystic duct or gallbladder fundus has been cannulated, then fluoroscopy can be performed. During the initial infusion of con-

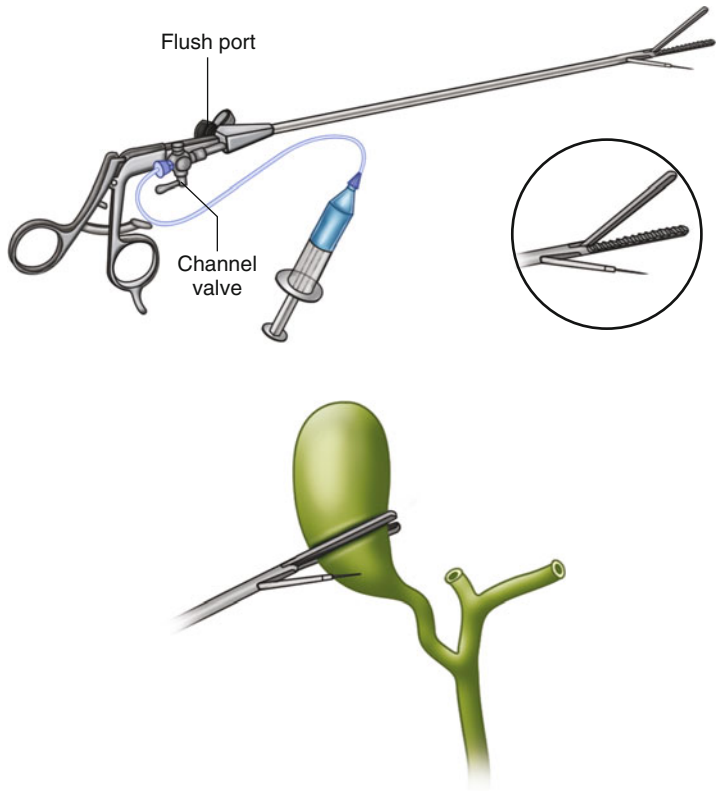

Fig. 5.3 (**a**) Kumar Pre-View Clamp has a channel through which the cholangiocatheter with a needle can be advanced into the Hartmann's pouch of the gallbladder. Contrast can be injected via the cholangiocatheter. (**b**) The clamp can be applied across the fundus to prevent contrast from flowing retrograde into the gallbladder

trast, 3–5 mL of dye is injected and the cystic duct/bile duct junction is observed. Attention should be paid to the length of the cystic duct and whether or not it contains any stones. The angle of insertion of the cystic duct into the common or right hepatic duct and any anatomic abnormalities should be noted as they may increase likelihood of bile duct injury during cholecystectomy. As the dye is injected, the entire biliary tree should be visualized to the third level of the intrahepatic ducts. A normal cholangiogram should demonstrate standard intrahepatic and extrahepatic ductal anatomy without anatomical variations or ductal dilation; there should be normal tapering of the bile duct towards the sphincter of Oddi with prompt passage of contrast into the duodenum (Fig. 5.4). The biliary tree should be examined for any aberrant ductal anatomy that may cause a predisposition to a bile duct injury such as a short cystic duct, cystic duct insertion into the right or left hepatic ducts, an accessory right hepatic duct, or an accessory cystic duct.

Biliary ductal dilatation should prompt investigation for a cause of bile duct obstruction such as choledocholithiasis demonstrated by intraluminal filling defects, an extraluminal stricture, or non-filling of the duodenum. If the duodenum does not easily fill with contrast, there may be a distal obstructing common bile duct stone, biliary stricture, or spasm of the sphincter of Oddi. If sphincter spasm is suspected, 1 mg of glucagon can be infused intravenously to cause relaxation of the sphincter and the cholangiogram can then be repeated. If dye does not freely pass with this maneuver, a common bile duct stone or biliary stricture should be suspected.

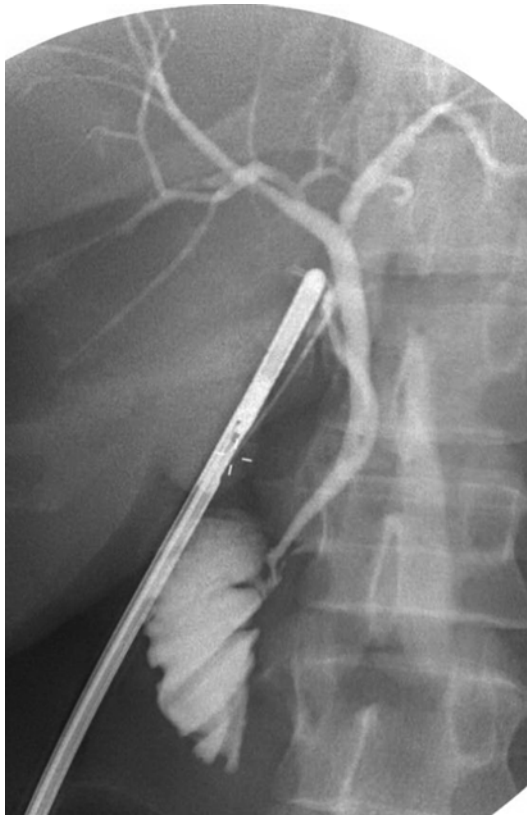

Fig. 5.4 A normal intraoperative cholangiogram showing filing of the intrahepatic and extrahepatic ducts, narrow tapering of the common bile duct, no filling defects, and emptying of contrast into the duodenum

Evidence for Routine Versus Selective IOC

IOC and CBDI

The primary reason for promoting routine IOC during laparoscopic cholecystectomy is the prevention of CBDI. Multiple cohort and case–control studies have examined the use of IOC. In 2002, 40 case series comprised of 327,523 laparoscopic cholecystectomies were analyzed [18]. The authors determined that there was an association between routine IOC use and a lower incidence of CBDI (0.21 % versus 0.43 %) and a higher rate of diagnosis at the time of initial operation (87 % versus 44.5 %). However, these data may be biased due to flaws in the study designs such as lack of standardized definitions for CBDI and selection bias in the performance of IOC.

Several randomized controlled trials of IOC have been performed. A systematic review of the literature performed in 2012 identified eight randomized trials comprised of 1715 patients [3]. The incidence of CBDI was 0.2 % including cystic duct avulsions, and the incidence of major CBDI was 0.1 %. A meta-analysis to combine the data from the trials was considered inappropriate because of the low number of injuries, the poor quality of the trials, and considerable heterogeneity between trials. The authors concluded that the evidence from randomized trials neither supported nor refuted the effectiveness of routine IOC to prevent CBDI.

Given the increasing availability of large administrative databases, advanced statistical methods have been used to better define the association between IOC and CBDI [2, 4, 12, 15]. In 2001, Flum et al. published one of the first studies using statewide data [2]. Using 1991–1998 Washington hospital discharge data, they identified 76 major CBDIs out of 30,630 laparoscopic cholecystectomies for an overall incidence of 2.5 per 1000 operations; the incidence of CBDI decreased over the time period from 3.2 to 1.7 per 1000 operations. The authors identified a statistically significant 1.7-fold increased relative risk of CBDI when IOC was not used. Furthermore, they determined that less surgeon experience and decreased surgeon frequency of IOC use were significant predictors of CBDI.

A more recent analysis used statewide Medicare data. In 2013, Sheffield et al. examined 2000–2013 Texas Medicare data to define the association between IOC use and CBDI [15]. The authors identified 280 CBDIs out of 92,032 patients for an overall incidence of 0.3 %; 40.4 % of cases used IOC. Using traditional statistical analyses, nonuse of IOC was associated with a statistically significant, 1.8-fold increased odds of CBDI. Using advanced statistical methods to adjust for unmeasured confounders, they determined that there was no longer an association between IOC use and CBDI.

How should these data regarding the effectiveness of IOC for preventing CBDI be reconciled?

The methodological limitations of case–control and cohort studies limit their utility, and the randomized trials were considerably underpowered to identify an effect of IOC on CBDI. The large database analyses provide significant advantages over these other study designs by providing more patients and therefore more power than all of the randomized trials combined. They also reflect "real-world" conditions rather than highly controlled circumstances as are present in randomized trials. Furthermore, use of advanced statistical methods can be used to infer whether or not a causal effect exists (i.e., whether use of IOC prevents CBDI) [19]. Nonetheless, limitations with these advanced methods must also be considered [20]. So, while the most recent evidence suggests that routine IOC is not an effective strategy for preventing CBDI, some caution should still be used in interpreting these results.

One unmeasured factor in large database analyses is the accuracy of individual surgeons in interpreting IOCs. Sanjay et al. evaluated IOC interpretation among 20 trainees and 20 fully trained surgeons [21]. They were asked to interpret 15 IOCs of normal anatomy as well as normal and abnormal variants of anatomy. Their accuracy was low for identifying normal anatomy and normal variants of anatomy, 45 % and 29.5 %, respectively. However, their accuracy for identifying abnormal anatomy was high at 95.5 %. There was no difference in accuracy based on trainee level or routine use of IOC. These findings are echoed by a case series of patients who had CBDIs; 43 % had IOCs and in two-thirds the injuries were not identified [22].

While the effectiveness of IOC to prevent CBDI has not been definitively proven, the cost-effectiveness of routine IOC to prevent CBDI has been debated. These cost-effectiveness analyses assume that IOC is an effective strategy. Even so, the answer regarding cost-effectiveness varies depending upon the estimated costs of IOC and the number of IOCs that need to be performed in order to prevent one CBDI. IOC is less cost-effective when the cost per IOC is higher and when the baseline risk of CBDI is lower (i.e., when performed by more experienced surgeons or during less complex cases) [2]. Using a cost per IOC of $122, Flum et al. estimated the cost of IOC per CBDI avoided was $87,100 (in year 2000 dollars) [2]. In contrast, using a cost per IOC of $700, Livingston et al. estimated the cost of IOC per CBDI avoided was $504,084 [23]. Using a cost of CBDI of $300,000 [23, 24], IOC is only cost-effective in preventing CBDI if the cost per IOC is low.

IOC and Suspected Choledocholithiasis

Another reason for performing IOC is to identify choledocholithiasis. While missed choledocholithiasis may result in recurrent episodes of biliary symptoms including complications such as gallstone pancreatitis or cholangitis, a systematic review of the literature suggested that the incidence of asymptomatic choledocholithiasis during laparoscopic cholecystectomy is only 4 % [25]. Furthermore, only 0.6 % of these common bile duct stones progress to symptoms. Another study where a catheter was left in place if common bile duct stones were found at IOC and imaging repeated in 6 weeks found that one-third of common bile duct stones passed spontaneously [26].

Multiple studies have been performed in order to identify predictors of choledocholithiasis given that preoperative risk stratification may alter the diagnostic and management algorithm in patients with symptomatic cholelithiasis or acute cholecystitis. The American Society for Gastrointestinal Endoscopy (ASGE) stratifies preoperative risk factors for choledocholithiasis into moderate, strong, and very strong and probability of choledocholithiasis into low, intermediate, and high risk (Fig. 5.5) [27]. For patients with a low probability of choledocholithiasis, they recommend laparoscopic cholecystectomy alone. For patients with a high probability of choledocholithiasis, they recommend ERCP. For patients with intermediate probability, there are multiple diagnostic and management strategies that are dependent upon local resources and expertise. These include preoperative endoscopic ultrasound (EUS) or magnetic resonance

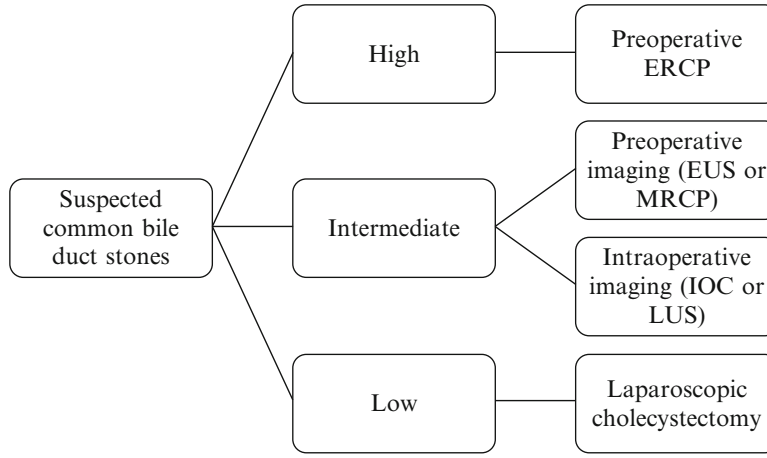

Fig. 5.5 Algorithm for managing suspected choledocholithiasis based on the presence of predictors. High suspicion is present if there is any strong predictor (common bile duct stone on transabdominal ultrasound, clinical ascending cholangitis, or bilirubin >4 mg/dL) or both strong predictors (dilated common bile duct on ultrasound defined as >6 mm and bilirubin 1.8–4 mg/dL). Intermediate suspicion is present if only one strong predictor or any moderate predictors are present (abnormal liver biochemical test other than bilirubin, age older than 55 years, and clinical gallstone pancreatitis). Low suspicion is present if no predictors are present. *ERCP* endoscopic retrograde cholangiopancreatography, *EUS* endoscopic ultrasound, *MRCP* magnetic resonance cholangiopancreatography, *LUS* laparoscopic ultrasound. From reference [27]

cholangiopancreatography (MRCP) followed by ERCP, laparoscopic cholecystectomy with IOC followed by common bile duct exploration or postoperative ERCP, and intraoperative laparoscopic ultrasound.

The cost-effectiveness of IOC to treat patients with suspected choledocholithiasis depends upon the probability of common bile duct stones. Urbach et al. performed a cost-effectiveness analysis comparing four strategies: preoperative ERCP followed by laparoscopic cholecystectomy, laparoscopic cholecystectomy with IOC and laparoscopic common bile duct exploration, laparoscopic cholecystectomy with IOC and postoperative ERCP, and laparoscopic cholecystectomy with expectant management [28]. Laparoscopic cholecystectomy with IOC and laparoscopic common bile duct exploration was the most cost-effective strategy, defined as the least cost per case of residual common bile duct stones prevented; this was true across probabilities of common bile duct stones. If the expertise is not available for laparoscopic common bile duct exploration, the authors recommended preoperative ERCP if the probability of common bile duct stones was greater than 80 %.

The cost-effectiveness of IOC in managing patients with suspected choledocholithiasis is derived in a large part from the high specificity of IOC. A prospective population-based study of over 1000 patients reported that IOC was feasible in 95 % of cases and had a sensitivity of 97 % and a specificity of 99 % for detecting choledocholithiasis [29]. With an incidence of 11 % of choledocholithiasis in that study, the negative predictive value was 99 % and the false negative rate was 1 %.

Brown et al. performed a decision and cost-effectiveness analysis in order to compare five strategies for treating suspected choledocholithiasis in patients with symptomatic cholelithiasis [30]. Using a specificity of 99 %, they determined that laparoscopic cholecystectomy with IOC followed by ERCP for positive findings was the most cost-effective strategy, defined as cost per hospital day, if the probability of choledocholithiasis was greater than 4 %. If the probability was less than 4 %, then laparoscopic cholecystectomy with

expectant management was more cost-effective. The cost-effectiveness of IOC decreased when the specificity was halved, largely due to a slightly longer length of stay. Furthermore, the cost difference was minimal between IOC with postoperative ERCP and preoperative ERCP when the probability of choledocholithiasis was high. This analysis is consistent with the findings of the Urbach analysis and with the ASGE guidelines [27, 28].

Ultimately, the decision to perform IOC for detecting choledocholithiasis versus laparoscopic cholecystectomy with expectant management or preoperative imaging with ERCP or an alternative modality depends upon multiple factors. These include the preoperative suspicion of choledocholithiasis; the specificity of IOC when interpreted by the operating surgeon; local resources in terms of the availability and timeliness of fluoroscopy, ERCP, or other imaging modalities; and local expertise in terms of performing laparoscopic common bile duct exploration.

Alternatives to IOC

Preoperative imaging of the biliary tree may be warranted if a patient has a high probability of choledocholithiasis or presents with cholangitis, biliary pancreatitis, or suspected periampullary stricture or neoplasm. Common preoperative imaging modalities include magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and endoscopic ultrasound (EUS).

MRCP is a diagnostic test which provides detailed anatomic images of the biliary tree and surrounding tissues which can delineate anatomic abnormalities, demonstrate choledocholithiasis, and assess for the presence of biliary or periampullary malignancies. Multiple studies have reported the utility of MRCP in detecting common bile duct stones preoperatively, including in the setting of acute cholecystitis [31]. MRCP may reduce the number of invasive procedures preoperatively, but is not cost-effective if used routinely given the low prevalence of clinically silent common bile duct stones [32].

In contrast to MRCP, which is solely diagnostic, ERCP is indicated when both diagnostic and therapeutic interventions are required, such as with ascending cholangitis, uncomplicated choledocholithiasis, or biliary pancreatitis with ductal obstruction. During ERCP, a side-viewing endoscope is advanced into the second portion of the duodenum and the Sphincter of Oddi is cannulated; contrast is injected as fluoroscopic images are obtained. Acute cholecystitis can be diagnosed by occlusion of the cystic duct. Choledocholithiasis can be diagnosed by the demonstration of filling defects in the hepatic duct or common bile duct. An endoscopic sphincterotomy can be performed with a sphincterotome, and various methods can be utilized to clear the bile ducts of stones including lithotripsy, balloon sweeps, and basket retrieval. If an extraluminal stricture is found, fine-needle aspiration can be performed to assess for the presence of malignancy. Biliary and pancreatic duct stents can also be placed. As already described, ASGE guidelines and cost-effectiveness analyses suggest that preoperative ERCP may be the preferred strategy when the suspicion for common bile duct stones is high [27, 28]. Furthermore, laparoscopic cholecystectomy with IOC followed by ERCP as necessary may be cost-saving in the setting of suspected choledocholithiasis [30], particularly if surgeons are not experienced in laparoscopic common bile duct exploration [28].

During EUS, an echoendoscope is advanced to the second portion of the duodenum and slowly withdrawn with visualization of the duodenal papilla, extrahepatic bile duct, cystic and hepatic ducts, and gallbladder. Endoscopic ultrasound is a modality that can be used as a screening tool immediately prior to ERCP in patients deemed to be moderate risk for choledocholithiasis. It has been reported to be accurate (97 %) with a positive predictive value of 98 % and negative predictive value of 96 % for the diagnosis of choledocholithiasis [33]. EUS allows for immediate endoscopic treatment of choledocholithiasis and helps to avoid unnecessary ERCP. When compared to ERCP alone, a strategy of EUS followed by ERCP detected 72 % of biliary anomalies and reduced ERCP-related complications by 60 % [34].

However, the cost-effectiveness of EUS is dependent upon physician expertise and the probability of choledocholithiasis.

While intraoperative imaging of the biliary tree is classically performed by IOC, there are alternative modalities which can be performed such as laparoscopic ultrasound (LUS) [35] or emerging technologies such as fluorescence cholangiography [36].

Laparoscopic ultrasound is performed after dissection of the Triangle of Calot and immediately prior to clipping of the cystic duct and artery. The operating room table is flattened and the field is irrigated with a sufficient volume of saline in order to submerse the common bile duct and provide a medium through which ultrasound waves can travel. The laparoscopic ultrasound probe is inserted through the epigastric port and the area of the common bile duct is scanned. Three rounded structures should be identified representing the common bile duct, the portal vein, and the hepatic artery. Doppler ultrasound is used to differentiate the vascular structures with flow and the CBD with no significant flow. The CBD can then be traced down to the duodenum and can be measured at its largest point. The presence of a CBD stone is demonstrated by the presence of a solid mass with an acoustic shadow within the CBD. Studies suggest that the accuracy of LUS for detecting choledocholithiasis is high; the sensitivity ranges from 92 to 95 % and the specificity ranges from 99 to 100 % [37–39]. The proposed advantages of LUS include a higher success rate than IOC, "noninvasiveness" (while laparoscopically inserted, it remains external to the ductal system), shorter operating time, no radiation exposure, and decreased costs [38, 39]. The disadvantages are that it requires expertise and requires a learning curve and may not adequately visualize the biliary anatomy in all cases [37].

Fluorescence cholangiography (FC) is performed by a method utilizing the intravenous injection of indocyanine green (ICG) before surgery [36]. ICG is a fluorophore that is excreted exclusively by the liver and binds to proteins found in bile. The excitation of protein-bound ICG by near-infrared light causes it to fluoresce, which allows the surgeon to delineate the biliary system. A specialized camera system illuminates the target with near-infrared light and filters the reflected wavelength that allows clear observation of the fluorescing ICG in the biliary tree. In addition, repeat injection upon viewing the critical view of safety can be used to confirm the arterial anatomy [40]. Several small studies have suggested that fluorescence cholangiography is safe and feasible, and it may have benefits over IOC. In a prospective study of 45 patients undergoing laparoscopic cholecystectomy, intraoperative fluorescence cholangiography could be performed in 100 % of cases (compared to IOC which could only be performed in 93 % of cases) [41]. Fluorescence cholangiography was cheaper and faster than IOC, and surgeons perceived it as easier to perform and at least as useful as IOC [42]. Similar results in terms of feasibility (95 % success with fluorescence cholangiography and 76 % success with IOC) and reduced time were obtained in another prospective study of 82 patients undergoing laparoscopic cholecystectomy [43]. Furthermore, in 20 of those patients where IOC was unable to be obtained, fluorescence cholangiography identified the biliary anatomy in 80 % of cases. Further trials are necessary to determine if outcomes are improved with use of fluorescence cholangiography versus IOC and whether fluorescence cholangiography should be performed routinely.

Conclusions

Significant variation exists in the utilization of IOC during laparoscopic cholecystectomy for gallstone-related disease including acute cholecystitis. Multiple factors account for this variation including but not limited to: conflicting evidence for the effectiveness and cost-effectiveness of IOC in preventing CBDI or complications for retained common bile duct stones, surgeon beliefs and expertise, and hospital resources. As newer noninvasive modalities evolve for evaluating the biliary system intraoperatively, the role of IOC may diminish over time. Nonetheless, in the current era, IOC still

has utility in some if not all cases of laparoscopic cholecystectomy such that surgeons should be fully trained on how to both perform and accurately interpret them.

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Management of Asymptomatic Gallstones

6

Nabeel R. Obeid and S. Rob Todd

Anatomy and Physiology

The gallbladder is an intra-abdominal organ that lies at the undersurface of the liver in the right upper abdomen. The primary functions of the gallbladder are to concentrate, store, and release bile into the gastrointestinal tract in order to facilitate absorption of lipids and certain vitamins. The composition of bile includes bilirubin, electrolytes, phospholipids, bile acids, proteins, and cholesterol. Bile concentration is mainly achieved by the active reabsorption of sodium and resulting passive diffusion of water through the gallbladder mucosa, which has a high absorptive capacity. This action alters the biliary concentration of cholesterol, consequently predisposing to crystal formation.

Bile is initially processed in the liver by conjugation and secreted into the hepatic ducts. The gallbladder then fills with bile due to the intermittent constriction of the sphincter of Oddi. This stored bile is then periodically drained through the cystic duct into the common bile duct and eventually into the duodenum. In order for this to occur, a coordinated action occurs with gallbladder contraction and simultaneous sphincter of Oddi relaxation. This action is promoted and activated by hormone regulation, primarily motilin and cholecystokinin, upon gastric emptying of a food bolus into the duodenum.

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Epidemiology

The most frequently encountered benign gallbladder pathology is cholelithiasis, or the presence of gallstones. Cholelithiasis remains common, with reports of up to 20 % of the adult population in the United States having gallstones [1]. However, this prevalence varies based on ethnic origin and gender. Among non-Hispanic Caucasians, 8.6 % of men and 16.6 % of women were found to have cholelithiasis on ultrasound imaging. Conversely, among Mexican–American men and women, the rates were 8.9 % and 26.7 %, respectively [2]. Furthermore, Native Americans have the highest prevalence of cholelithiasis in North America. As an example, 73 % of female Pima Indians over the age of 25 years were found to have gallstones [3].

Risk factors for the development of cholelithiasis are listed in Table 6.1. Age has been shown to be a key factor in the formation of gallstones, with those older than 40 years at an increased risk [4].

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Table 6.1 Risk factors for the development of cholelithiasis

Risk factors
Age
Female gender
Pregnancy
Obesity
Bariatric surgery due to rapid weight loss
Ileal resection
Hypertriglyceridemia
Cirrhosis
Ethnic groups
Pima Indians and other Native Americans
Hemolytic disorders
Sickle cell anemia
Hereditary spherocytosis
Medications
Ceftriaxone
Octreotide
Oral contraceptives
Gemfibrozil and other fibrate anti-hyperlipidemic agents
Gallbladder stasis
Diabetes mellitus
Total parenteral nutrition (TPN)

In addition to female gender, pregnancy status also plays a role. In a study comparing nulliparous vs. multiparous females, the prevalence of gallstones was found to be 1.3 % vs. 12.2 %, respectively [5]. Lastly, obese patients have been shown to have a higher rate of cholelithiasis [6].

Pathophysiology

Gallstone formation is directly related to the relative concentrations and solubility of bile contents, most notably cholesterol. Biliary "sludge" is a term used to describe a combination of cholesterol crystals, calcium bilirubinate, and mucin that congeals and acts as a precursor to stone formation. This sludge along with gallbladder dysmotility promotes the development of gallstones. Gallstones are classified as either cholesterol or pigment stones, and the particular classification depends on the relative cholesterol content. Cholesterol stones are composed mainly of cholesterol crystals as the name suggests and are due to an increased saturation of biliary cholesterol, a decrease in bile salts, and/or biliary stasis. Pigment stones can be further categorized as black or brown stones. Black pigment stones occur in those with conditions that result in high concentrations of unconjugated bilirubin. The primary composition of black pigment stones is calcium bilirubinate. Common etiologies include hemolytic disorders (e.g., sickle cell anemia) or changes in the enterohepatic circulation (e.g., Crohn disease, ileal resection, and cystic fibrosis). The third type of gallstone is the brown pigment stone, which results from hydrolysis of conjugated bilirubin or phospholipid by bacteria. This type of stone occurs in patients with infections of the biliary tract or strictures. Brown pigment stones have also been found as primary common bile duct stones.

Cholesterol stones comprise the vast majority of gallstones (75 %), especially in industrialized countries, with black pigment stones less frequently seen (20 %), and brown pigment stones being least common (5 %) [7]. Black pigment stones occur more prevalently in communities with higher frequencies of hemolytic disorders, and while rare in Western culture, brown pigment stones arise more commonly in Asian populations.

Several pharmacologic agents that are associated with the formation of gallstones have been identified. In children, intravenous ceftriaxone has been well documented, although the majority of patients remain asymptomatic [8–10]. In symptomatic patients, clinical improvement is generally seen with discontinuation of the medication [11–14]. Another drug known to contribute to gallstones is octreotide. Among its most common side effects is biliary tract pathology, including sludge or gallstone formation and ductal dilatation [15, 16]. Dysmotility of the gallbladder and decreased secretion of bile have been documented, even after administration of a single dose, and the risk of such side effects is proportional to the duration of therapy [17]. Lastly, gemfibrozil and other fibrate antihyperlipidemic agents have been associated with gallstones as the mechanisms of action of these agents increase cholesterol excretion through bile, promoting increased biliary cholesterol concentration [18].

Clinical Presentation

Cholelithiasis can be classified as asymptomatic or symptomatic. Asymptomatic patients are defined as those with known gallstones—usually discovered incidentally—but without associated symptoms, termed asymptomatic cholelithiasis. Patients are deemed symptomatic if they experience the typical pain related to gallbladder disease, often referred to as "biliary colic." The pain is described as constant, epigastric and/or right upper quadrant abdominal pain that usually resolves after several hours, occurs characteristically post-prandially, and is associated with nausea and vomiting [19].

As opposed to asymptomatic cholelithiasis, patients with symptomatic cholelithiasis are at an increased risk for developing complicated gallstone disease, including acute cholecystitis, choledocholithiasis and/or cholangitis, and gallstone pancreatitis. A randomized, prospective study showed that in patients with symptomatic cholelithiasis, 38 % per year experienced recurrent pain attacks and 2 % per year required cholecystectomy for significant biliary symptoms [20].

On the other hand, most patients with gallstones (up to 70 %) remain asymptomatic [21]. Of those with incidental (asymptomatic) gallstones, only 20 % will experience symptoms over a 15-year time point, and even then, their initial symptoms are normally biliary colic-type pain, rather than severe complications of gallstone disease [22]. Rarely does a patient with no symptoms experience complicated gallstone disease on first presentation. Risks for symptoms or complications from initially asymptomatic cholelithiasis are reported in the literature to be 1–4 % per year [23, 24]. Interestingly, one retrospective cohort analysis with propensity score matching found patients with coronary artery disease (CAD) to be significantly more likely to develop gallstone-related symptoms or complications than patients without CAD. The finding suggests that patients with CAD be monitored more closely than other patients with gallstone disease [25].

Diagnostic Imaging

Individuals with silent gallstones do not undergo routine diagnostic imaging for this condition since, by definition, they are asymptomatic and therefore are unaware of the presence of stones. As such, gallstones in those without symptoms are usually detected as an incidental finding on abdominal imaging done for unrelated reasons. Below is a summary of different modalities used to assess the gallbladder and biliary tract.

Plain Abdominal Radiographs

Plain films of the abdomen are of little use for evaluating the gallbladder and bile ducts. In very rare circumstances, one may be able to identify pneumobilia (air in the biliary tract), which can signify a cholecystoenteric fistula. Additionally, the majority of gallstones are not radiopaque, and therefore will not be visualized on plain radiographic imaging. Only occasionally will stones or the gallbladder wall be calcified enough to be seen on plain radiographs.

Transabdominal Ultrasonography

Ultrasonography is now considered the imaging modality of choice for evaluation of gallbladder or biliary tract pathology due to both its excellent sensitivity and specificity. The noninvasiveness, lack of radiation, relatively low cost, and ease of use add to its appeal. On transabdominal ultrasonography, gallstones appear as hyperechoic foci in the gallbladder lumen. Each stone carries an accompanying posterior acoustic shadow and lies in the dependent position due to gravity (Fig. 6.1). These characteristics help to differentiate gallstones from gallbladder polyps, which are also hyperechoic but are not in dependent positioning and do not contain a shadow. Limitations of ultrasonography include user technical proficiency, obese body habitus, and the presence of ascites.

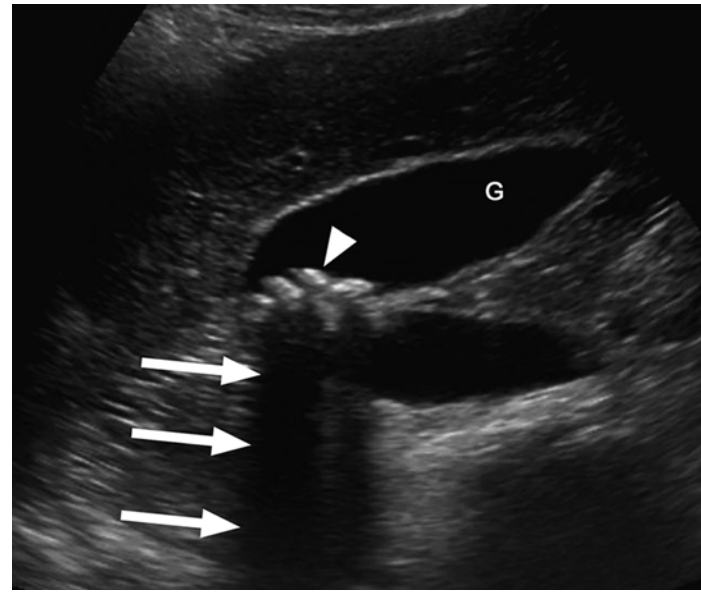

Fig. 6.1 Typical sonographic appearance of gallstones as hyperechoic foci (*arrowhead*) in dependent positioning within the gallbladder lumen (G), and associated acoustic shadowing (*arrows*)

While patients with asymptomatic cholelithiasis are not routinely screened, some populations warrant screening ultrasonography. These groups include New World Indians, such as Pima Indians, as well as in patients undergoing bariatric surgery, and in particular gastric bypass. However, numerous studies have shown minimal benefit for prophylactic cholecystectomy in bariatric surgery patients, and therefore some do not advocate routine imaging for these patients as is done for their nonobese counterparts [26–28].

Cholescintigraphy

Cholescintigraphy uses radiotracer material (hepatic 2,6-dimethyl-iminodiacetic acid—HIDA) in order to evaluate the liver, gallbladder, and biliary tree. With an HIDA scan, the tracer is taken up by the liver and excreted into the bile ducts. The primary use of this test is for the diagnosis of acute cholecystitis, signified by the absence of gallbladder visualization representing cystic duct obstruction from a gallstone. HIDA scanning is generally performed when ultrasound findings for acute cholecystitis are equivocal and has no role in determining the mere absence or presence of gallstones.

Computed Tomography

Computed tomography (CT) scan of the abdomen and pelvis is increasingly being performed for the evaluation of abdominal pain, especially in the Emergency Center setting. With this widespread use comes an increased incidence of cholelithiasis. Many of these patients present with a chief complaint that is non-biliary in origin and are found to have gallstones incidentally. For the assessment of cholelithiasis, CT scanning is less sensitive than ultrasonography, although radiopaque gallstones can be visualized if calcified (Fig. 6.2). The primary use for CT scanning as it relates to biliary pathology is to evaluate gallstone-related complications, including acute cholecystitis with abscess and pancreatitis.

Management

Surgical Therapy

The status of patient symptoms remains the most important factor in determining the appropriate management for cholelithiasis. Due to the increased risk for recurrent biliary colic or complicated gallstone disease, cholecystectomy is indicated in patients with symptomatic

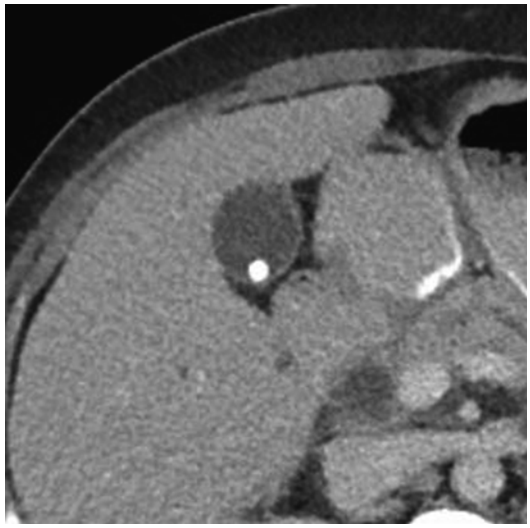

Fig. 6.2 CT scan finding of cholelithiasis, with a solitary, calcified gallstone

cholelithiasis. Additionally, cholecystectomy is indicated after an episode of complicated biliary disease (acute cholecystitis or gallstone pancreatitis) because there may be a 30 % chance of having a recurrence of complicated disease within 3 months [29].

Conversely, the low rates of symptoms or complications in those with asymptomatic cholelithiasis are outweighed by the risks of surgery and added costs. As such, current practice guidelines indicate that cholecystectomy is not indicated for routine patients with asymptomatic cholelithiasis [30–32]. These guidelines are based on the natural history of silent gallstones, although no randomized trial comparing cholecystectomy vs. nonoperative management for asymptomatic cholelithiasis has been performed [33]. Only in very special circumstances are the risks associated with surgery in asymptomatic patients outweighed by the risks of gallstone complications or gallbladder cancer, as described below.

Certain patients carry a higher risk of developing gallbladder cancer. The classic teaching has been that patients with a calcified gallbladder, known as porcelain gallbladder, required cholecystectomy for fear that the vast majority of these would become malignant. We now know that the rates of cancer development among patients with porcelain gallbladder are much lower, in the realm of 2–3 % [34, 35]. Nonetheless, prophylactic cholecystectomy is still recommended in such patients. Anomalous pancreatic duct drainage is another risk factor for the development of gallbladder cancer. Generally, patients will have pancreatic duct drainage into the common bile duct proximal to the normal peri-ampullary position. In patients with this anomalous drainage but without choledochal cysts, gallbladder cancer was the most common malignancy seen and is the main indication for prophylactic cholecystectomy [36]. Larger gallbladder adenomas, 1 cm or larger, are associated with a significantly increased risk for gallbladder cancer, and as such, these patients should undergo cholecystectomy [37, 38]. In addition, patients who have both gallbladder polyps and gallstones should undergo cholecystectomy regardless of polyp size, since cholelithiasis is a risk factor for gallbladder cancer in those with gallbladder polyps [39].

Some have advocated for prophylactic cholecystectomy in certain patient subsets due to the high incidence of cholelithiasis and associated gallbladder cancer. The most well-known example is the New World Indians, such as Pima Indians, who carry a very high likelihood of gallstone disease, arguing for prophylactic cholecystectomy even in asymptomatic individuals [40]. Diabetes, once considered an indication for prophylactic cholecystectomy due to its increased risk for gangrenous cholecystitis, is no longer considered to be an indication. It is now known that the rates of conversion from initially asymptomatic to symptomatic or complicated gallstone disease among diabetic patients are similar to their nondiabetic counterparts [41].

As mentioned above, hemolytic disorders are common etiologies for pigmented stones. Specifically, those with sickle cell anemia and hereditary spherocytosis are at greater risk [42–44]. Almost half of sickle cell patients have gallstones by the third decade of life and gallstone-related complications can induce a sickle cell crisis. Most clinicians therefore recommend that these patients undergo prophylactic cholecystectomy, either alone or at the time of

another abdominal procedure. A randomized study revealed that the laparoscopic approach to cholecystectomy resulted in shorter hospitalization and those patients receiving preoperative blood transfusion experienced less sickle cell events postoperatively [45].

In candidates for organ transplantation and those patients that are immunosuppressed, cholecystectomy is often recommended [21, 46]. The significant morbidity and mortality associated with acute cholecystitis and other gallstone-related complications in the setting of immunosuppression justifies prophylactic surgery in this patient cohort.

There is little debate that rapid weight loss following bariatric surgery results in a significantly increased incidence of cholelithiasis [47]. The argument for prophylactic cholecystectomy in patients undergoing bariatric surgery is that there is minimal associated increased risk or additional intraoperative time. Others advocate that the lack of added benefit precludes this practice and that such patients should therefore be treated in the same manner as nonobese, asymptomatic patients. One retrospective study with a median follow-up of 4 years found that post-bariatric patients underwent cholecystectomy for symptomatic cholelithiasis at a rate of 7.8 % and was highest among those undergoing Roux-en-Y gastric bypass (RYGB) as compared to adjustable gastric banding (AGB) or sleeve gastrectomy (SG) [48]. The strongest predictor for need for subsequent cholecystectomy was the amount of excess weight loss with the first 3 postoperative months. Given these findings, the authors of this study concluded that prophylactic cholecystectomy was not indicated at the time of primary bariatric operation. This topic remains without consensus opinion.

Cholelithiasis is relatively uncommon in the pediatric patient population. While not highly prevalent, patients with increased risk include those with obesity, hemolytic disease (as discussed above), cystic fibrosis, Crohn disease, and necessity of long-term total parenteral nutrition. In such patients, prophylactic cholecystectomy is warranted [49]. This selective approach is practiced by many, although one recent report recommends routine surgery for all pediatric patients found to have cholelithiasis, regardless of symptoms [50]. The main argument for this recommendation is that, unlike in the adult population, the first clinical sign of cholelithiasis in 25 % of the pediatric study group was a gallstone-related complication. Another study revealed similar findings, with an incidence of complicated gallbladder disease of 58 % among pediatric patients without initial symptoms [51].

Finally, gallstone size has been shown to be a factor for the development of gallstone-related complications like acute cholecystitis. Large gallstones, usually defined as 2–2.5 cm or greater, are considered an indication for prophylactic cholecystectomy to avoid such complications [21, 52]. Furthermore, the majority of patients with gallbladder carcinoma are found to have large gallstones, especially 3 cm or larger [53]. Hence, prophylactic cholecystectomy is indicated for the presence of large gallstones.

Nonsurgical Therapy

In general, patients with asymptomatic cholelithiasis should be managed nonoperatively. This usually means observation without the need for follow-up imaging or screening. The clinician has an obligation to educate patients regarding symptoms associated with gallstone disease that may arise in the future in order to seek medical care when appropriate.

In addition to observation and patient education, physical activity has shown to have a potential positive impact on the fate of gallstones. One large study compared the outcome of women who were seated for fewer hours per week with those seated for the majority of workdays, and found that those who spent less time seated were significantly less likely to undergo cholecystectomy [54]. Another study documented a threefold increase in symptomatic gallstones in men who watched a significant amount of television (more than 40 h per week) compared to those who spent much fewer hours doing so [55].

Nonsurgical therapy for the treatment of gallstones can be achieved with dissolution agents

like ursodiol. This class of medication is used to dissolve gallstones by decreasing cholesterol synthesis as well as the amount secreted, thereby reducing the cholesterol saturation in bile. Ursodiol should not be used routinely in all patients, as its primary use is for small, radiolucent, cholesterol stones in patients who are not ideal surgical candidates. The drug has multiple drawbacks in that the stone dissolution may take up to 2 years, the drug may not be well tolerated due to diarrhea or constipation, and stones may recur after cessation of the drug [56].

Ursodiol does have an indication in the bariatric population as well as for the prevention of cholelithiasis in post-bariatric patients with rapid weight loss. A meta-analysis of randomized, controlled trials found a significant decrease in cholelithiasis after bariatric surgery in those taking ursodiol compared with placebo (8.8 % vs. 27.7 %, respectively) [57].

In conclusion, a significant percentage of the adult population, particularly in Western societies, has gallstones. The vast majority of these patients are asymptomatic and can be managed expectantly without the need for cholecystectomy. Specific patient subgroups, including those with a higher risk for gallstone-related complications or gallbladder cancer, seem to benefit from prophylactic cholecystectomy.

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Surgical Management of Acute Cholecystitis

7

Katherine D. Gray and Govind Nandakumar

Indications and Introduction

Acute cholecystitis is a common surgical disease. The typical presentation is of persistent right upper quadrant pain with or without associated fevers. Liver enzymes may be mildly elevated, and patients will often have a leukocytosis. A right upper quadrant ultrasound classically will show an edematous gallbladder wall, pericholecystic fluid, and the presence of gallstones. Additional imaging modalities can be used to confirm the diagnosis if equivocal and are discussed in more detail elsewhere.

The definitive treatment for acute cholecystitis is cholecystectomy. In the healthy patient, little preoperative preparation is required. The patient should fast prior to operation to prevent biliary stimulation and in preparation for general anesthesia. Broad-spectrum antibiotics with activity against enteric organisms are initiated, as is fluid resuscitation. In patients with severe comorbidities or those who present with sepsis or cholangitis, preoperative stabilization is required. A percutaneous cholecystostomy tube may be a useful adjunct when patients are critically ill. In patients who can tolerate immediate operation, a recent multicenter, randomized trial describes significantly decreased morbidity, length of hospitalization, and total hospital costs for patients who undergo operation within 24 h of admission when compared to delayed cholecystectomy [1].

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Laparoscopy

Laparoscopic cholecystectomy is the gold standard for the treatment of acute cholecystitis. After some initial controversy, improving techniques, equipment, and surgeon comfort with laparoscopic cholecystectomy have made it the preferred operation for gallstone disease since it was recommended in 1993 by the National Institutes of Health in their consensus statement [2]. In 1998, a landmark study in the Lancet showed lower morbidity rates and decreased lengths of stay for patients undergoing laparoscopic treatment for gangrenous cholecystitis [3].

Multiport Approach

The typical approach to laparoscopic cholecystectomy employs a multiport technique. The patient is placed in the supine position, and one or both of the patient's arms may be tucked. The usual safety precautions are taken, including securing a safety belt across the legs of the patient, placement of an electrocautery grounding pad, and use of sequential compression devices. A Foley catheter is not required.

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The abdomen is prepped and draped in the usual sterile manner.

The abdomen is initially entered using a Veress needle or Hasson technique at an umbilical site with placement of a 10 mm trocar. Upon entry, the abdomen is insufflated with CO_2. A 10–11 mm subxiphoid port is placed which becomes the main working port for electrocautery and dissection. Two additional 5 mm ports are then placed at the midclavicular line just below the costal margin and in the lateral right upper quadrant (Fig. 7.1). Retractors are placed through the two subcostal ports to retract the liver and gallbladder superiorly and laterally. The camera is operated through the umbilical port, typically with a 30° scope. This allows visualization of the gallbladder, cystic artery, and cystic duct. If a distended gallbladder is encountered, a laparoscopic needle and syringe may be used to aspirate the gallbladder contents. This decompression improves exposure and allows the empty gallbladder sac to be safely grasped and manipulated throughout the operation. The aspirated bile can be sent for culture if desired.

Any inflammatory adhesions to surrounding viscera are then cleared, and medial and lateral hepatic attachments of the gallbladder are released.

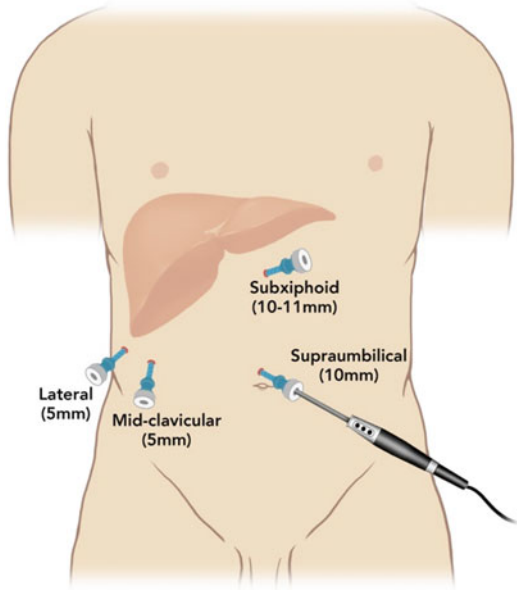

Fig. 7.1 Multiport trocar placement

The hilum is dissected clear of adherent tissue and adhesions using a blunt dissector and electrocautery hook. In the acutely inflamed gallbladder, the expected anatomy may be obscured by dense adhesions, edematous tissues, and the limited view of a laparoscope. Resultant misidentification of structures can lead to vascular or biliary injury. A technique developed by Strasberg in 1995 called the "critical view of safety" has been so effective in preventing intraoperative injury to surrounding structures that it is now incorporated into the standard dissection [4]. The triangle of Calot must first be skeletonized of adherent tissue. The gallbladder hilum is separated from the cystic plate. The critical view is then achieved with visualization of two (and only two) discrete structures entering the gallbladder: the cystic artery and the cystic duct (Fig. 7.2). If all of these criteria are met, then the surgeon can confidently proceed with transection of the cystic duct and the cystic artery.

After dissection of the cystic triangle, the cystic duct is clipped on the gallbladder side to minimize the potential for stones to migrate into the bile ducts during manipulation. At this point, if a cholangiogram is indicated or desired, the cystic duct is cannulated using a cholangiocatheter. Water soluble contrast dye can be injected and fluoroscopy performed to evaluate the biliary system. The cystic duct and cystic artery are then

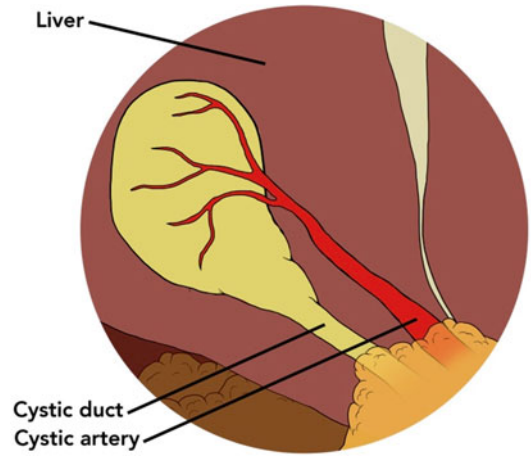

Fig. 7.2 Critical view of safety: two distinct structures are seen entering the gallbladder

clipped proximally and distally and divided. Electrocautery hook is used to separate the gallbladder from the liver bed, moving from the hilum to the fundus.

If dissection of Calot's triangle proves difficult, particularly in cases where gallbladder anatomy is obscuring the cystic triangle such as in Mirizzi's syndrome, a dome-down approach can be used. Similar to the technique used in open cholecystectomy, the cystic plate is divided superiorly at the fundus with dissection proceeding toward the ductal structures. Some experts claim a lower rate of converting to an open procedure and faster recovery with this approach [5–7].

In gangrenous or severely inflamed gallbladders, standard clips may be inadequate to control the cystic duct. Laparoscopic staplers can be used to divide either the cystic duct proper or the distal gallbladder. If a remnant gallbladder is left, the surgeon and patient must be aware of the risk of recurrence or incomplete control of infection. Alternatively, the cystic duct can be suture ligated using intracorporeal suture. Finally, an endoloop ligature can be used to control the proximal cystic duct.

Once successfully freed, the gallbladder is removed through the umbilical port using a specimen bag. The trocars are removed under direct supervision, and port sites are closed and dressed according to surgeon preference.

Postoperatively, the patient can tolerate a clear liquid diet, which is advanced as tolerated to a full diet. Pain control can be achieved with oral analgesics, and no further antibiotics are required. Even in the case of acute cholecystitis, the patient is routinely discharged on the first postoperative day.

Role of Intraoperative Cholangiogram and Ultrasonography

If indicated, intraoperative cholangiogram (IOC) is performed after identification of the cystic duct. The duct is clipped on the gallbladder side and scissors are used to create a small ductotomy. A small, 4–5 Fr catheter is introduced into the peritoneal cavity via angiocath beside a subcostal port and guided into the cystic duct lumen through this defect. Saline is used to prime the catheter prior to insertion to prevent accumulation of air bubbles. Images are obtained with a portable X-ray machine present in the operating room. These images are used to identify ductal stones or an enlarged common bile duct. If choledocholithiasis is identified, the surgeon may proceed with a common bile duct exploration laparoscopically or via laparotomy. It is also routine in many centers to complete the laparoscopic cholecystectomy as planned; the patient then undergoes postoperative endoscopic sphincterotomy and stone extraction. The cholangiogram may also be used clarify anatomy and ensure appropriate identification of structures.

IOC can be performed either selectively or routinely during laparoscopic cholecystectomy to evaluate for ductal stones. Selective use is indicated with a preoperative history of jaundice, pancreatitis, or enlarged common bile duct on imaging. Some surgeons choose to routinely perform IOC to decrease the incidence of occult retained stones and to confirm biliary anatomy with the intention of protecting against injury to the extrahepatic biliary tract.

However, the use of IOC for anatomic delineation is controversial. Large population-based studies from Sweden, Australia, and the USA have found IOC to be protective against biliary injury [8–10]. However, a recent multicenter retrospective analysis of almost 93,000 patients undergoing cholecystectomy showed no statistical difference in the number of common bile duct injuries when the data was controlled for confounding variables [11]. There is data to suggest that cholangiogram can successfully be used to diagnose bile duct injury at the time of operation [12, 13]. One study quotes a sensitivity of 79 % and specificity of 100 % for intraoperative diagnosis of common bile duct injury when IOC is routinely performed [12]. While IOC cannot be relied upon to prevent injury, it may confirm anatomy prior to transection of critical structure and allow for immediate diagnosis and repair of injury at the time of the primary operation.

As an alternative to cholangiogram, laparoscopic ultrasonography has shown initial success

for defining difficult anatomy [14]. In this technique, a 10 mm ultrasound probe is inserted through either the periumbilical or epigastric port. A transverse image is obtained of the portal triad in the hepatoduodenal ligament, and the probe is manipulated to visualize the extrahepatic biliary tract. Doppler signal can be used to differentiate vascular structures from biliary structures and can also identify ductal stones with an experienced operator. Despite these reports of success, laparoscopic ultrasound remains an uncommonly used technique.

Single Incision Approach

Single incision laparoscopic cholecystectomy (SILC) was introduced in 1995 by Navarra, 10 years following the introduction of the multiport cholecystectomy [15]. Surgical technique for SILC is not standardized and is not as popular as the traditional multiport operation. This technique can be performed using either one large access platform or a single skin incision with the insertion of multiple ports.

For single incision surgery, the patient is prepped in an identical manner as for a multiport operation. A 2.5 cm incision is made in the umbilicus and extended into the peritoneum. A platform device is inserted, and 4–5 trocars are placed within the platform (Fig. 7.3). The abdomen is insufflated, and the subsequent dissection is carried out in the same manner as described for multiport cholecystectomy. The primary difference in surgical technique is that electrocautery is held in the left hand and retraction is supplied by the right to prevent excessive crossing of instruments. The postoperative course is as previously described.

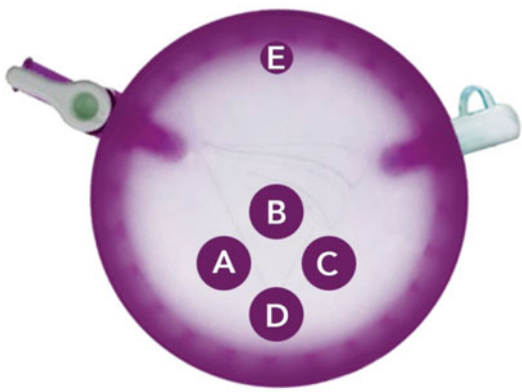

Fig. 7.3 Trocar placement in Single Incision platform. (**a**) Camera. (**b**) Dissector. (**c**, **d**) Retractors. (**e**) Angiocath insertion for cholangiogram

No large-scale randomized trials have been conducted to compare SILC to standard laparoscopic cholecystectomy. Initial meta-analyses of small, randomized trials and case series showed an increase in operative time and complications, especially biliary tract injuries [16–18]. However, a current meta-analysis that included almost 7500 patients found no difference in overall rates of complications or biliary spillage [19]. Routine cholangiogram can be successfully performed with SILC [20]. Additionally, a multicenter randomized trial of 200 patients with biliary colic found an increase in rates of hernia but no increase in overall or serious adverse events, with an improved self-reported cosmetic outcome [21].

As the surgical community has gained familiarity with the SILC technique, it is now being applied to patients with acute cholecystitis. There are series that report safety of SILC in acutely inflamed gallbladders when performed by experienced surgeons [22]. In a single-surgeon prospective series that has been accepted for publication from our institution, SILC was completed on all patients with an indication for cholecystectomy regardless of pathology. There was a slightly increased rate of conversion to multiport laparoscopy in acute cholecystitis when compared to noninflammatory disease but no increase in the rate of conversion to open cholecystectomy or in the number of serious complications.

Ultrasonic Dissection

The use of ultrasonic dissection devices such as the Harmonic (Ethicon) in laparoscopic cholecystectomy are gaining popularity. Ultrasonic scalpels take advantage of ultrasound waves at a frequency that cause coagulation, cutting, and

cavitation of tissues with minimal spread of injury [23]. They have the advantage of eliminating thermal injuries to surrounding structures that are seen with traditional electrocautery and can also be used to ligate the cystic artery and duct without the use of suture or clips [24]. Proponents cite shorter operating times, lower risk of bile leak, and faster recovery [25]. However, ultrasonic dissectors require special training and have a higher cost than traditional electrocautery and are not yet routinely used in laparoscopic cholecystectomy.

Salvage Operations

In some cases, anatomy is unfavorable or a patient is too unstable to proceed with planned laparoscopic operation. In this situation, the surgeon has the option of converting to an open procedure or performing a salvage operation. Salvage operations include subtotal cholecystectomy and cholecystostomy tube placement. They are used to avoid futile and dangerous attempts to dissect Calot's triangle in cases of severe inflammation, empyema, or fibrosis in which the anatomy is obscured [26, 27]. If performed laparoscopically, these procedures can avoid conversion to an open procedure and the associated morbidity [28].

Subtotal cholecystectomy (Fig. 7.4) is undertaken after attempts at traditional cholecystectomy have failed. The anterior wall of the gallbladder is opened, and bile and stones are suctioned out. If the cystic duct can be identified, it is suture ligated. If the cystic duct cannot be identified, it can be left to fibrose with a drain in place. The anterior gallbladder is resected leaving only the posterior wall adherent to the hepatic plate. The remaining mucosa is cauterized and a drain is left in the gallbladder fossa. Potential complications include increased risk of intra-abdominal abscess and surgical site infection, biliary leak, and the potential for undiagnosed gallbladder cancer in the ablated mucosa. Nonetheless, at least one recent comparison between subtotal and total cholecystectomy showed no increase in the number of postoperative complications, and no retained stones or recurrent acute cholecystitis at 42 months [29].

In cases of severe acute cholecystitis and intraoperative hemodynamic instability, the cholecystectomy may be aborted and a cholecystostomy drain placed across the wall of the gallbladder. Like percutaneous drains, this is a temporizing measure to drain the gallbladder to treat acute infection. An interval cholecystectomy is indicated once the patient has appropriately stabilized and infection is resolved, typically at a minimum of 6 weeks from the initial hospitalization.

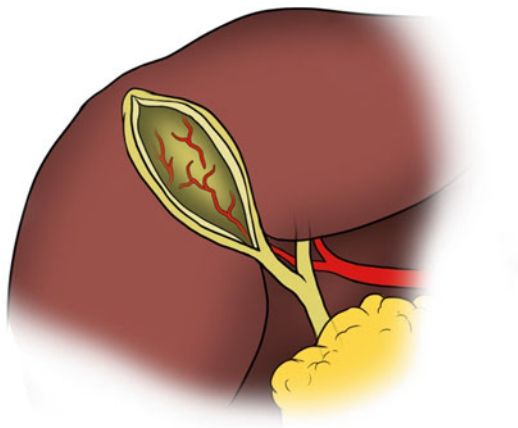

Fig. 7.4 Subtotal cholecystectomy. The anterior gallbladder is resected and the remaining mucosa ablated

Open Cholecystectomy

Early criticisms of laparoscopic cholecystectomy cited high complication rates when compared to the traditional open approach. In the past, early conversion to laparotomy was advocated in cases in which anatomy was obscured by inflammation. Operative techniques have been refined since that time to improve outcomes and exposure, and now the overall rates of surgical complications in laparoscopic cholecystectomy are superior to that of the open procedure [30]. In certain cases, however, it still remains necessary to convert from laparoscopic to open cholecystectomy. Indications include intolerance of pneumoperitoneum, severe inflammation or otherwise limited view, uncontrollable bleeding, malignancy, or suspected or confirmed biliary injury.

An open cholecystectomy is performed via an upper midline or right subcostal incision 2–3 cm inferior to the costal margin. The peritoneum overlying the gallbladder is incised 1 cm away from the liver edge. Adhesions between the inflamed gallbladder and adjacent viscera, most commonly duodenum and transverse colon, are identified and sharply divided. Dissection along the avascular plane between the gallbladder and the hepatic bed is carried from the fundus inferiorly using electrocautery. The cystic artery and duct are identified and individually clipped or suture ligated. The specimen is removed and the fascia and skin are closed in the usual manner.

As surgeons and trainees are gaining more experience with laparoscopy and techniques are becoming more sophisticated, many argue that there are few strict indications for conversion to open cholecystectomy. A Dutch retrospective review analyzed the severity of biliary duct injuries before and after conversion and found that of all injuries that occurred, open procedures produced more severe biliary injuries [31]. These authors propose that the increased severity of injury occurs because of inadequate training in open cholecystectomy in young surgeons.

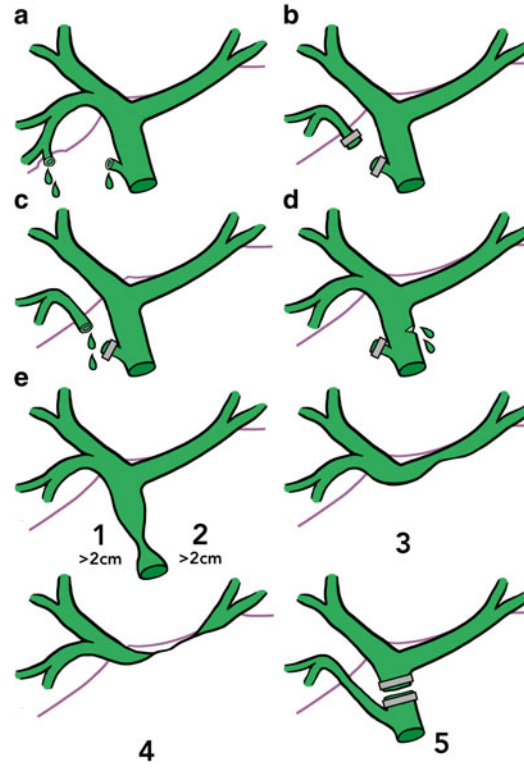

Fig. 7.5 Strasberg-Bismuth classification of bile duct injuries. (**a**) Cystic duct stump leak. (**b**) Transection of accessory duct. (**c**) Accessory duct leak. (**d**) Partial transection of any bile duct. (**e**) Complete transection of common bile duct, subdivided based on location of injury (1–5).

Complications

Complications of cholecystectomy include bile duct injury, bile leak, and retained stones. The associated clinical syndromes vary widely in timing and severity of presentation.

Bile Duct Injury and Bile Leak

Bile duct injury (BDI) is the most feared complication of cholecystectomy and is associated with significant morbidity and mortality. As techniques in laparoscopy have improved, the incidence of BDI has decreased dramatically. The exact incidence is unknown, but in recent laparoscopic series is reported to be as low as 0.1–0.3 % [32, 33].

Risk factors for biliary injury include obesity, advanced age, male sex, dense adhesions, and aberrant anatomy [34]. Multiple classification systems have been introduced in an attempt to guide management of BDI [35–37]. Perhaps most commonly used is the Strasberg-Bismuth classification system (Fig. 7.5). In this system, Class A injuries consist of a bile leak from the cystic duct or from a small liver duct in the gallbladder fossa. Class B injuries represent transection of an accessory duct, usually an aberrant right hepatic duct. Class C are bile leaks from an accessory duct. Class D is partial transection anywhere along the bile duct system, and Class E is a complete transection of the bile duct, subdivided based on location [37]. The type of injury helps determine the most appropriate method of repair.

Intraoperative diagnosis with immediate repair of BDI provides the best chance of a favorable outcome, but repair should only be undertaken by a surgeon with hepatobiliary experience [38, 39]. If the surgeon does not have the necessary hepatobiliary experience to complete an indicated repair,

an external drain and/or percutaneous transhepatic drain should be placed with transfer to an experienced center [39]. The stump of the transected portion of bile duct should not be clipped. This has been shown to produce duct necrosis and leakage of bile, and rarely produces appreciable dilation of the duct [40].

Very small accessory ducts <3 mm can safely be ligated if injured. Class D injuries can be repaired over a T-tube. However, transection injuries such as Class E injuries are almost always associated with a loss of tissue of the involved portion of the bile duct. Depending on the location of injury and the amount of duct that has been inadvertently resected, these injuries require a biliary-enteric repair, either an end-to-side Roux-en-Y choledochojejunostomy or hepaticojejunostomy. All of these repairs are subject to a high rate of stricture formation. This complication can be ameliorated by performing the anastomosis over a stent or T-tube and by reducing the amount of tension on the repair [41].

In the early postoperative period, patients will present with fevers, pain, and elevated liver function tests. Right upper quadrant ultrasound and CT scan will show biloma, bilious ascites, and/or a dilated biliary tract. Patients with a bile leak from the cystic duct stump can typically be managed with endoscopic stenting to decrease pressure in the biliary system and promote enteric drainage [42]. If major transection, ligation, or stenosis of the ductal system is recognized in the early postoperative period, these injuries are best managed with a staged approach to avoid complications from sepsis and biliary peritonitis [43]. Transhepatic biliary drainage is performed for decompression, as is intra-abdominal drainage if indicated. The patient then undergoes interval repair at 6–8 weeks after postsurgical inflammation is reduced.

Late postoperative complications often present with cholangitis or with progressive obstructive jaundice from stricture. Transhepatic biliary drainage is performed for decompression and anatomic elucidation. Endoscopic balloon dilatation and stenting are temporary repairs in all but the most comorbid patients. Definitive repair consists of biliary-enteric bypass as described above once septic complications are resolved [43].

Post-Cholecystectomy Ductal Stones

Patients may present with ductal stones following cholecystectomy. If these occur shortly following surgery, they are considered retained stones. These may have been seen at the time of surgery with intraoperative cholangiogram if performed. Those occurring months or years later are likely recurrent ductal stones and may be forming de novo. Management is with endoscopic sphincterotomy and stone extraction and rarely requires reoperation [44].

Drains

Intra-abdominal drainage after cholecystectomy is not indicated. A Cochrane review of drain placement in open cholecystectomy showed no protection against abdominal collections, biliary peritonitis, or abscess and is associated with a significantly higher risk of surgical site infection and pulmonary infection [45]. The data is similar for drainage after laparoscopic cholecystectomy [46].

Antibiotics

Open surgery for acute cholecystitis is associated with higher rates of surgical site infections than laparoscopic procedures. Additional risk factors include diabetes, prolonged operative time (>90 min in laparoscopy), preexisting biliary colic, increased age, and immunosuppression [47, 48]. Intraoperative bile spillage likely does not increase the rate of postoperative infection, although spilled gallstones have been associated with abscess formation in rare cases [49, 50]. *E. coli*, *Klebsiella spp.*, and enterococci are the most commonly isolated organisms from biliary infections. A single dose of cefazolin, cefoxitin, ceftriaxone, or ampicillin-sulbactam is recommended as antimicrobial prophylaxis for all patients undergoing cholecystectomy for acute cholecystitis. Alternative regimens for patients with beta-lactam allergy include clindamycin or vancomycin with Gram-negative coverage with gentamycin, aztreonam, or

a fluoroquinolone [48]. Administration of routine prophylactic postoperative antibiotics does not decrease rates of infectious sequelae [51].

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Robotic Cholecystectomy

8

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Introduction

Since the advent of laparoscopic cholecystectomy in 1985 by Prof. Dr. Erich Mühe of Germany, surgeons have continued to improve upon its safety, efficacy, and cosmetic results [1]. Minimally invasive surgery has become the gold standard for most thoracic and abdominal operations due to reduced postoperative pain, shorter hospital stays, and improved cosmetic outcomes. As surgeons have become more experienced and efficient with multi-port laparoscopic cholecystectomy (MPLC), the development of single-incision procedures has become a rapidly expanding field. Single-incision laparoscopic cholecystectomy (SILC) was first described in 1997 and, since then, many surgeons have demonstrated the procedure as safe option for cholecystectomy in patients interested in an improved cosmetic outcome [2].

However, difficult instrument maneuverability secondary to space constraints in SILC has lead to the introduction of single-site robotic cholecystectomy (SSRC)—this technology has been shown to reduce instrument collisions, improve retraction, and increase the overall ease of single-incision surgery [3]. Although most studies describing the safety, efficacy, and outcomes of single-incision cholecystectomy are based on the SILC operative platform, many of these findings are directly translatable to SSRC. Therefore, much of this chapter includes aspects of the SILC literature that are directly applicable to the SSRC procedure and its outcomes. Nevertheless, the overall aim of this chapter is to describe an efficient, reproducible single-site robotic cholecystectomy technique that surgeons can use as a guide to decrease operative time while maintaining safe standards.

Indications

Over 300 studies have described or analyzed SILC and SSRC, confirming their increasing popularity. While these studies have varying diagnostic inclusion and exclusion criteria, the indications for SILC and SSRC should be guided by the recommendations set forth by the 1992 National Institutes of Health Consensus Development Conference Statement on Gallstones and Laparoscopic Cholecystectomy [4]. The SSRC procedure itself should typically be reserved for surgeons with a high robotic skill level and patients who desire a nearly "scarless" procedure.

Most studies assessing the safety and efficacy of SILC and SSRC have been in patients with

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biliary colic or symptomatic cholelithiasis, while excluding acute inflammatory states, such as cholecystitis and pancreatitis, and patients with BMI > 35 kg/m^2 or prior upper abdominal surgery [5]. However, several recent SILC studies have included patients with acute cholecystitis: they observed a longer operative time and a potential increased risk for conversion to multiport, but there were no differences in complication rates compared to operations for noninflammatory gallbladder disease [6–10]. Only two SSRC studies have included patients with cholecystitis, but neither was powered to detect differences in outcomes between patients with cholecystitis and noninflammatory biliary disease. While larger prospective trials are needed to confirm the safety of SSRC in acute cholecystitis, both SSRC and SILC are feasible options for treatment, provided there is adequate visualization of vital structures.

In addition to cholecystitis, SILC and SSRC have been proven as safe operations to treat other forms of gallbladder disease. Several prospective randomized studies and meta-analyses defined their SILC inclusion criteria as patients with symptomatic cholelithiasis and have demonstrated safe outcomes with variable operative length and postoperative pain control [11–14]. Similarly, several studies have shown SSRC to be safe for patients with symptomatic cholelithiasis [15–20]. Other indications such as gallbladder polyps and biliary dyskinesia have not been specifically analyzed in the SILC or SSRC literature. Lastly, recent studies have suggested that using the robotic platform can safely be used in obese patients as well [17].

Relative Contraindications

Relative contraindications for the SILC and SSRC approaches are the same as those for MPLC, which are typically severe inflammatory disease states of the gallbladder including gangrenous cholecystitis, gallbladder empyema, perforated gallbladder, cholecystoenteric fistula, and Mirizzi syndrome. These conditions generally confer a more difficult operation secondary to obscured normal anatomy with conversion rates ranging from 35 to 75 %, depending on the condition [21–28]. Furthermore, most of these conditions often present as a severe illness, and are difficult to diagnose preoperatively secondary to imaging modality limitations. Risk factors for these conditions include increased age, marked leukocytosis, and a history of diabetes [21, 29–33]. Historically, these patients usually required percutaneous cholecystostomy or open cholecystectomy, but more recent reports in the literature have demonstrated that urgent MPLC is a safe alternative with improved outcomes and shorter hospital stay [34–38]. However, there are currently no reports of using SILC or SSRC in these patient populations; it is reasonable to initially attempt cautious dissection via single-incision approach, but the surgeon should have a lower threshold to convert to open to avoid inadvertent injury.

Several additional unique conditions warrant caution when considering SILC. Porcelain gallbladder is associated with a difficult dissection secondary to a brittle, calcified gallbladder wall, as well as an associated 7 % incidence of carcinoma [39]. While several studies have described the feasibility of using the MPLC approach for treatment of porcelain gallbladder, only one case report has described using SILC [40–42]; thus, the decision to pursue SILC or SSRC in such cases should be left to the discretion of a skilled minimally invasive surgeon.

Lastly, the pregnant patient with symptomatic gallstones must always be approached carefully. It has been well documented that laparoscopic cholecystectomy is most safe during the second trimester, without any increase in maternal–fetal morbidity [43–48]. On the other hand, first-trimester operations may have deleterious effects on fetal organogenesis, and third-trimester operations are technically limited by the enlarged uterus and may be associated with an increased rate of preterm labor [45]. Only one case report currently exists in the literature documenting success using SILC during pregnancy; thus, the approach must be used with caution in the appropriate clinical setting [49]. If the SILC or SSRC approach is used, we recommend careful port insertion to avoid uterine injury, low insufflation pressures (10–12 mmHg) to minimize pressure on the uterus, and left-lateral positioning to minimize caval compression.

Absolute Contraindications

The absolute contraindications to SILC are also similar to MPLC. These are typically patients who cannot tolerate general anesthesia secondary to severe comorbidities or have an acute critical illness. Patients in septic shock with hemodynamic instability are not candidates for the operating room, and instead require fluid resuscitation, IV antibiotics, ICU monitoring, and percutaneous cholecystostomy (PC) tube placement [50]. Despite non-operative management, the mortality rate in this patient population approaches 25 % [51, 52]. However, patients with calculus cholecystitis who achieve full recovery will have a 45 % risk of recurrence, and thus should undergo elective cholecystectomy if preoperative medical optimization is feasible [52, 53].

Several medical comorbidities may preclude a minimally invasive operation. Patients with severe chronic obstructive pulmonary disease can develop a severe respiratory acidosis because they are unable to clear excess carbon dioxide absorbed from pneumoperitoneum. Patients with congestive heart failure can experience an acute exacerbation from decreased venous return and increased systemic vascular resistance secondary to insufflation, particularly with an ejection fraction <20 % [54]. Severe liver dysfunction and refractory coagulopathy generally precludes any operation, including cholecystectomy, particularly in the setting of hypoalbuminemia. Furthermore, Child-Pugh class C cirrhosis is associated with a high mortality rate, and cholecystectomy should be avoided, potentially using percutaneous cholecystostomy for acute cholecystitis [55]. While laparoscopic cholecystectomy on Child-Pugh classes A and B have been shown to be safe, they are associated with higher conversion rates, longer operative times, bleeding complications, and overall higher morbidity [56–58].

Lastly, known gallbladder carcinoma is a contraindication to minimally invasive approach. Stage Ia gallbladder carcinoma, frequently found incidentally on resection, is the only cancer that can be managed by laparoscopic technique [59, 60]. However, stage Ib and above require a subsequent open operation with potential segment 4B/5 liver resection and portal lymphadenectomy [61–66].

Feasibility and Safety

As single-incision laparoscopic techniques have gained widespread utility in clinical practice, there have been many studies documenting the safety and feasibility of SILC [67–69]. This included several large meta-analyses of randomized control trials which each included over 500 patients [11–13, 70]. These studies concluded that SILC may have longer operative durations; however, complication rates did not increase, and patient satisfaction was improved compared to MPLC. Furthermore, the safety and feasibility of SILC has been also demonstrated in a community setting, which supports its use outside of academic tertiary care centers [67, 71]. Several studies also included patients with acute cholecystitis as part of the inclusion criteria and determined that there may be a slight increase in operative length and conversion to open in an acute inflammatory state; however, there were no increases in complications as compared to MPLC [6, 69]. The SILC technique has been proven to be a safe method for cholecystectomy, while being just as efficacious as MPLC for the treatment of benign gallbladder disease.

Technique

As with any operation, appropriate and reproducible technique is imperative for safety and efficiency. The following is the standard SSRC procedure that we use at our institution, which is based on similar principles used in SILC.

Patient Preparation and Surgeon Positioning

Upon application of sequential compressive devices and administration of appropriate preoperative antibiotics and subcutaneous heparin, the

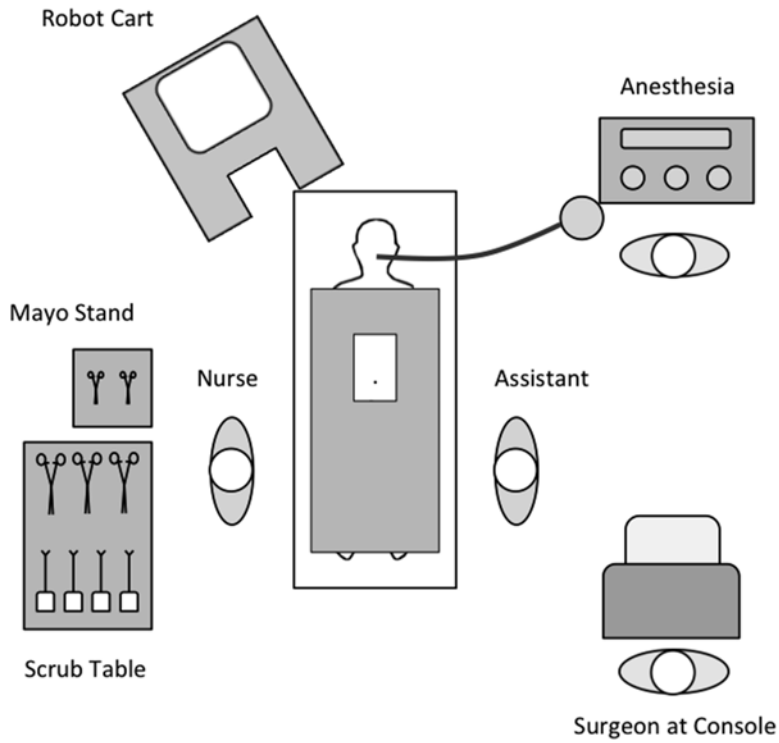

Fig. 8.1 Operating room setup. Organization of operating table, robot cart, scrub nurse and table, surgeon console, anesthesia, and surgical assistant

patient is placed in the supine position with both arms tucked. This positioning allows for adequate docking of the robot over the right shoulder, and room for the surgical assistant to stand on the patient's left once the peritoneal cavity is entered and the single-incision platform is set up (Fig. 8.1). If indocyanine green (ICG) is being used for real-time near-infrared fluorescent cholangiography (see detailed description below), it should be injected 30 min prior to incision. Lastly, during dissection, the patient should be in reverse Trendelenburg position to facilitate inferior displacement of the digestive tract away from the gallbladder and liver.

Incision, Port Placement, and Instrumentation

The patient's abdomen is prepped and draped in standard sterile fashion. The infra-umbilical crease is incised in a transverse, curvilinear fashion approximately 2–2.5 cm in length (Fig. 8.2a). The subcutaneous fat is dissected off the fascia to allow a 2.5-cm transverse fascial incision. The peritoneum is entered sharply and carefully to avoid intra-abdominal organ injury. The peritoneal cavity is swept with a finger to assess for intra-abdominal adhesions and ensure safe insertion of the multichannel umbilical port. Any local adhesions are lysed sharply to facilitate port insertion.

In order to place several instruments through a single infraumbilical incision, the multichannel *da Vinci*® *Single-Site*® port platform (Intuitive Surgical Inc., Sunnyvale, CA, USA) is utilized. The port is cylindrical with five lumens that provide access for two working instruments, a 8.5 mm 3D-HD endoscope camera, an assistant's accessory port, and insufflation adaptor (Fig. 8.2). The working ports cross at the abdominal wall (Fig. 8.2c), so that the right instrument is positioned on the left side of the operative field, and the left instrument is positioned on the right—this arrangement minimizes extracorporeal clashing of the robotic arms. The robotic console

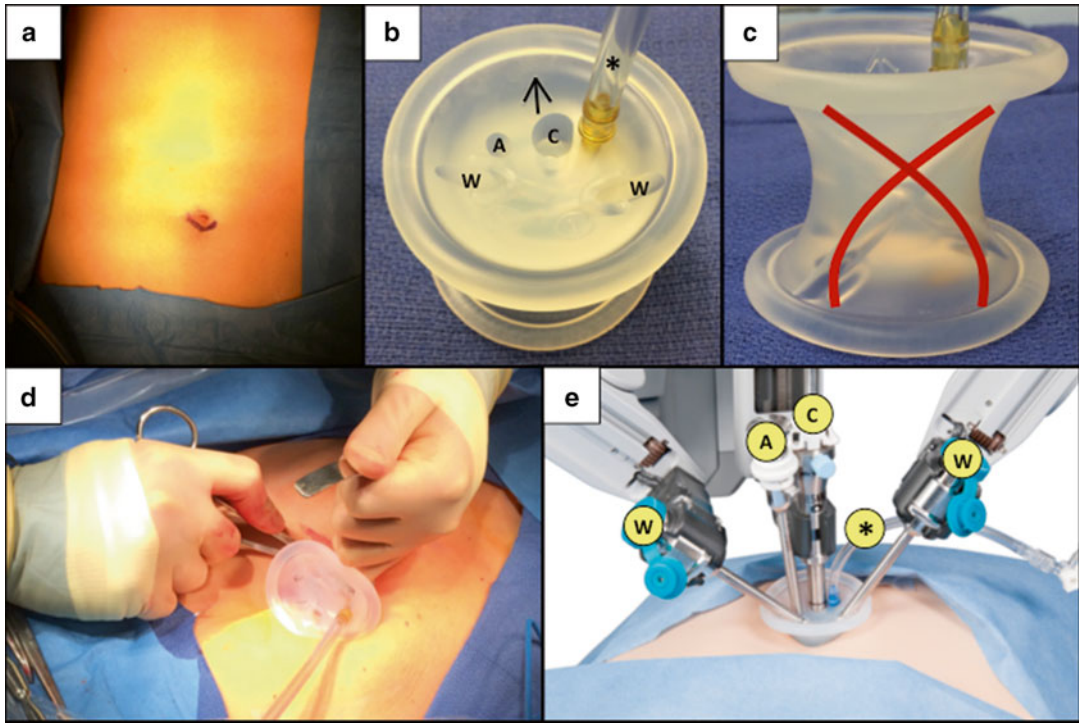

Fig. 8.2 Umbilical port. An infraumbilical curvilinear incision is made (**a**) for insertion of the *da Vinci® SingleSite®* port platform (**b**), whose working ports cross at the abdominal wall (*red lines*) (**c**). Using an S-retractor, the umbilical port is gently inserted with the *arrow* pointing toward the right upper quadrant (**d**). The robotic ports are then docked with their appropriate instrument arms (**e**). *©2015 Intuitive Surgical, Inc. W* working instrument port, *A* assistant's accessory instrument port, *C* camera Port, *Asterisk* insufflation adaptor

corrects for this switch in laterality so that the operating surgeon's right hand controls the "left extracorporeal" robotic arm, and the left hand controls the "right extracorporeal" arm. This configuration has been shown to improve single-site simulator task performance by eliminating instrument collisions, decreasing camera manipulations, and improving clutching efficiency [72].

After umbilical port placement, the abdomen is insufflated with CO_2 to 15 mmHg, and the camera and instruments are inserted under direct vision into the abdominal cavity. Specifically, a laparoscopic grasper is inserted through the accessory port by the assistant at the bedside for cephalad retraction of the gallbladder fundus. The "right extracorporeal" robotic arm (i.e., left intracorporeal instrument) is dedicated for the infundibulum grasper. The "left extracorporeal" robotic arm (i.e., right intracorporeal instrument) is designated for electrocautery (Covidien ForceTriad monopolar electrocautery platform, ValleyLab, Boulder, CO, USA), suction, and the clip applier.

Triangulation and Flexible Instrumentation

Both the SILC and SSRC techniques require the surgeon and assistant to control four instruments in a limited space through a 2.5-cm fascial incision. Thus, it is of utmost importance to employ the spatial principle of *triangulation of instrumentation* to maximize the operative field. The single-site platform allows the surgeon to direct instruments from a radial position extracorporeally towards an opposite point intracorporeally, thereby crossing the plane of visualization. This crossing vector is not conventional in multiport laparoscopy; however in SILC and SSRC,

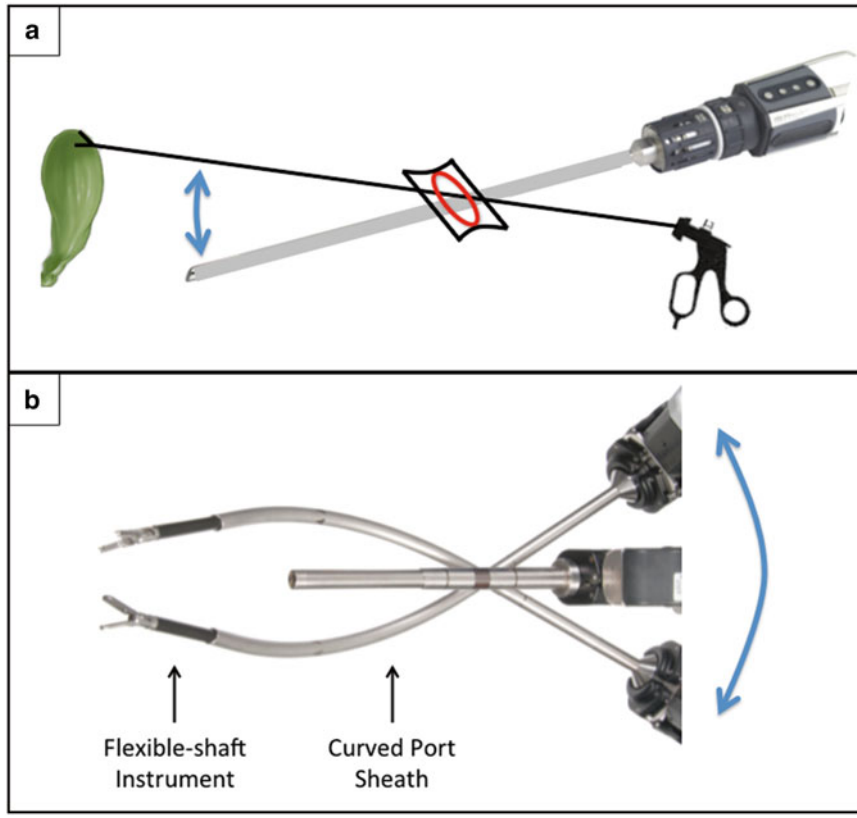

Fig. 8.3 Triangulation of crossing vectors. (**a**) Crossing vectors of the camera and fundal grasper maximize cephalad retraction and visualization of the gallbladder (*arrow*). (**b**) Crossing vectors of working port instruments maximize extracorporeal robotic arm range of motion (*arrow*); the curved port sheaths redirect the flexible instruments towards the operative field and minimize intracorporeal instrument collisions. ©*2015 Intuitive Surgical, Inc.*

it maximizes retraction in the opposite direction of port insertion (Fig. 8.3a). Specifically, a grasper is placed through the assistant's accessory port to grasp the fundus and retract superiorly, while the endoscope is inserted through the camera port and aimed inferiorly. This triangulation maximizes the angle of cephalad gallbladder retraction through the narrow umbilical incision while maintaining an unobscured view of the operative field.

To minimize instrument collisions, the two working port vectors are crossed at the abdominal wall. Rigid curved cannulas are inserted through the two working ports, through which flexible instruments will be placed (Fig. 8.3b). These crossing vectors maximize the extracorporeal robotic arms' range of motion, thereby reducing collisions. Additionally, due to the flexibility of the instruments, the rigid curved cannula allows for redirection of the radially oriented instruments back to the center of the operative field [73]. This minimizes intracorporeal instrument collision, provides adequate infundibulum retraction ("right extracorporeal" robotic arm), and facilitates electrocautery dissection ("left extracorporeal" robotic arm).

Approaches to Dissection

There are two main approaches to gallbladder dissection: anterograde (fundus-last) and retrograde (fundus-first). The retrograde approach is commonly used in open cholecystectomy as a safe method of dissection with the visual plane in the anterior–posterior direction. This allows a safe

dissection plane from the fundus toward the cystic duct by retracting the gallbladder away from the liver bed, particularly if there is marked cholecystitis obscuring the anatomy. The anterograde approach is the method of choice during minimally invasive procedures. This approach allows safe identification of Calot's triangle from the laparoscopic field of view, which is directed from the umbilicus in the caudal-cephalad plane.

The anterograde approach for SILC and SSRC is similar to MPLC. It begins with identification of the gallbladder and careful lysing of any adhesions preventing adequate visualization and exposure. The fundus is then grasped through the assistant's accessory port and retracted superiorly, using the *triangulation* concept as described above. Adhesions to surrounding structures, such as the duodenum and omentum, are then stripped away until the inferolateral aspect of the gallbladder is completely visualized.

Identification of Calot's triangle is the next critical step. This is achieved by careful retraction of the infundibulum using the "right extracorporeal" robotic arm and dissection using the "left extracorporeal" arm. The peritoneal reflection is taken down medially and laterally to allow for visualization of Calot's triangle. The surgeon can dissect with a Maryland forceps, electrocautery, or suction device when appropriate, until the cystic duct, common hepatic duct, and inferior border of the liver are identified. It is imperative to avoid bleeding, as this can obscure the visual field. Ultimately, a window around the cystic duct is created to allow the surgeon to visualize the isolated cystic duct and cystic artery entering the gallbladder. Of note, it is important to minimize the use of electrocautery near Calot's triangle to avoid thermal injury to the cystic and common hepatic ducts. The cystic duct and artery are each clipped and divided with two clips remaining on each of the in situ structures. The gallbladder is then dissected off the liver bed with electrocautery, being mindful to avoid an aberrant right hepatic artery.

In order to aid in anatomical identification during dissection, the robotic platform allows for near-infrared fluorescent cholangiography using ICG, a low-toxicity fluorescent dye containing sodium iodide that binds plasma proteins and is excreted exclusively in bile. When exposed to near-infrared light by the robotic endoscope, ICG emits light detectable at a peak wavelength of 830 mm, which illuminates the biliary tree and surrounding vasculature [74]. Specifically, three milliliters (mL) of ICG is injected intravenously 30 min prior to incision. Its peak absorption after excretion into the biliary tree occurs 45–60 min postinjection, which aids in identification of the cystic duct, CBD, common hepatic duct, and potential aberrant ducts. Additional 3 mL aliquots can be injected intraoperatively to properly identify surrounding vasculature (e.g., the cystic artery) within 45 s postinjection (Fig. 8.4).

Unlike traditional cholangiography, near-infrared fluorescent cholangiography allows the surgeon to evaluate biliary anatomy in real time without inserting catheters into the cystic duct, and can quickly assist in delineating biliary anatomy during dissection of Calot's triangle. Although contraindicated in pregnancy and patients with iodide allergies, this technique has been demonstrated as safe and effective for identifying biliary anatomy in both laparoscopic and single-site robotic cholecystectomy—specifically, it identifies the cystic duct, CBD, and common hepatic duct in 97–100 %, 83–100 %, 67–100 % of cases, respectively [75–78]. Moreover, it requires only a simple injection without implementation of a C-arm or exposure to radiation. Therefore, we recommend routine usage of real-time near-infrared cholangiography during SSRC only to aid during anatomical dissection; it is currently not indicated to evaluate for choledocholithiasis. If ICG imaging is negative during SSRC, proceed with careful dissection and employ traditional intraoperative cholangiography as indicated (see below).

A retrograde approach has been described as a safe alternative during laparoscopic cholecystectomy, usually performed in cases with severe inflammation and an inability to safely identify Calot's triangle [79–86]. This method may reduce the expected conversion-to-open rate without increasing the risk of injury to the biliary tree [79, 83]. It has also been described as a

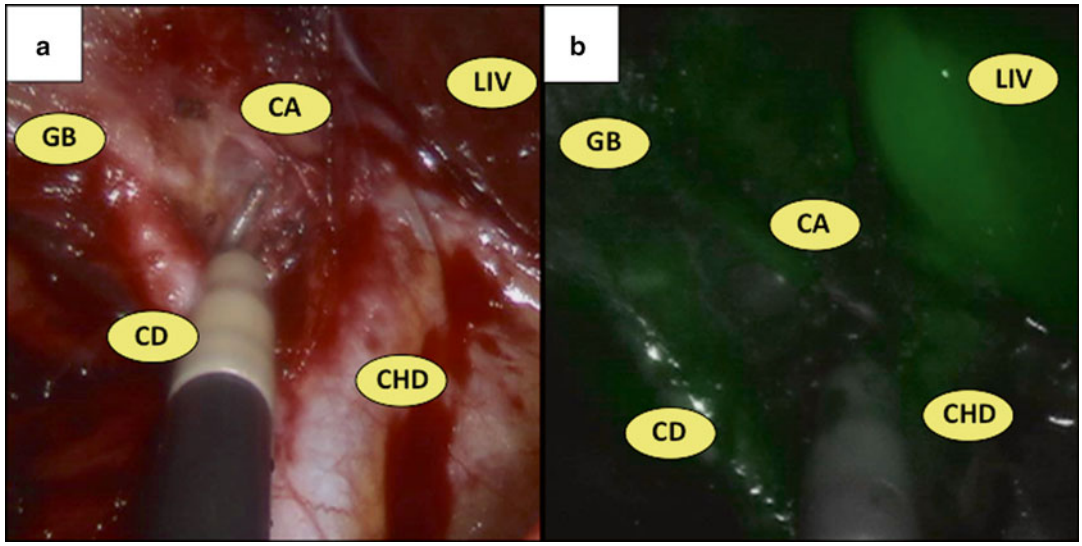

Fig. 8.4 Near-infrared fluorescent cholangiography. Identification of the gallbladder (*GB*), cystic duct (*CD*), cystic artery (*CA*), common hepatic duct (*CHD*), and liver (*LIV*) during cholecystectomy (**a**) using near-infrared fluorescent cholangiography (**b**)

safe option during SILC to obtain a 360° view around the cystic duct before transection [87, 88]; only two case series have reported this approach in SSRC [89, 90]. This method begins with caudal retraction of the gallbladder away from the liver. A fundal dissection plane is started while leaving a small rind of the edematous gallbladder wall on the liver bed. This rind can be grasped and provide retraction of the liver bed away from the gallbladder. The dissection is continued until the cystic duct and artery are identified, while confirming a 360° view around the cystic duct prior to transection. This method is reserved as an attempt to avoid conversion to open; however, if safe dissection is difficult, we recommend converting directly to the open approach. We typically do not convert to a multi-port laparoscopic approach as an intermediate step because it has not been shown to reduce conversion rates after a failed anterograde and retrograde laparoscopic approach, and it will only prolong the operative time. However, during the learning phase, conversion to MPLC may be employed to aid in difficult dissections, or when there is bleeding that cannot be controlled via the single-site platform.

Intraoperative Cholangiography and Choledocholithiasis

Intraoperative cholangiography (IOC) is generally employed to investigate suspected choledocholithiasis or to identify aberrant or obscured anatomy. Specific indications include a clinical history of jaundice, transaminitis, direct hyperbilirubinemia, pancreatitis, increased amylase or lipase levels, ultrasound findings of dilated common duct or intra-ductal stones, or failed preoperative endoscopic retrograde cholangiopancreatography (ERCP) [91–93]. Some groups have concluded hyperbilirubinemia and dilated common duct on preoperative ultrasound should be the sole indications for IOC [94].

If preoperative choledocholithiasis is suspected, there are several management options including preoperative ERCP followed by cholecystectomy (two-stage) or cholecystectomy with common bile duct exploration (single-stage). One study performed a decision tree analysis summarizing the literature and found that single-stage laparoscopic common bile duct exploration during cholecystectomy has lower morbidity and mortality rates compared to preoperative ERCP

followed by cholecystectomy [95]. While common bile duct exploration has been well described in MPLC, there has been only one small retrospective review describing 13 patients who underwent successful SILC with common duct exploration [96]. The single-incision CBD exploration technique has not been reproduced by another group yet, and only multi-port robotic CBD explorations have been reported [97, 98].

There are substantial data advocating for routine IOC to be performed during cholecystectomy, suggesting that it decreases the risk of common bile duct injury [99–102]. However, there is conflicting evidence reporting no improvement in bile duct injury, overall morbidity, or mortality with routine IOC [103–105]. One systematic review of eight randomized trials evaluating the ability of IOC to detect choledocholithiasis and biliary injury concluded there is no evidence to support or abandon use of IOC, and the decision to perform IOC should be left to the discretion of the surgeon [106]. Routine IOC during SILC without making a separate incision for the cholangiogram catheter has been demonstrated as safe and feasible [107]. However, while IOC during SSRC has also been reported in the literature [20, 108], it extends operative times, involves a multidisciplinary team, and requires C-arm placement which typically necessitates re-docking at least one robotic arm. Thus, most robotic surgeons do not routinely perform IOC during SSRC, and will selectively pursue it only if there is a clinical suspicion for choledocholithiasis or if the biliary anatomy needs to be clarified before further dissection.

When traditional IOC is indicated in SSRC, a 14-gauge angiocath is placed through 2 mm stab incision in the right upper quadrant under direct visualization. The needle is removed, leaving the angiocath sheath in place to provide access for the cholangiogram catheter. As in MPLC, a small transverse incision is made in the cystic duct with robotic shears. The cholangiogram catheter is then inserted into the cystic duct and secured with a laparoscopic clip applier. Saline is flushed to ensure adequate flow and the IOC is performed using intraoperative fluoroscopy. Typically, the robot will have to be undocked to accommodate the C-arm. Upon completion of the cholangiogram, the clip, cholangiogram catheter, and angiocath are removed and discarded.

If stones are identified in the common hepatic or common bile duct, we recommend completing the cholecystectomy and performing intraoperative or postoperative ERCP for stone retrieval. If this is not possible, a common duct exploration needs to be performed. As mentioned above, CBD exploration has been described via single-incision laparoscopic, multi-port robotic, and open approaches depending on the expertise of the surgeon. However, at this point, further studies analyzing the feasibility, safety, and outcomes of single-incision CBD exploration are warranted before we recommend it for routine usage.

Organ Extraction and Closure

Upon successful completion of gallbladder dissection, and IOC if necessary, the gallbladder is placed in an Endo Catch specimen retrieval bag (Covidien, Mansfield, MA, USA). The liver bed is inspected for hemostasis and the operative field is irrigated with saline. The instruments are then removed from the ports and the abdomen is desufflated. The robotic arms are detached from the instrument ports, the multichannel *da Vinci*® *Single-Site*® port is removed, and the specimen is extracted through the umbilical incision. Finally, the transverse fascia is closed with at least four 0-vicryl sutures on a GU needle and the skin is closed with a continuous subcuticular 4-0 monofilament absorbable suture.

Aberrant Anatomy

The most common cause of iatrogenic liver and common duct injury is secondary to misperception of anatomy, not a failure in technical skill, knowledge, or judgment [109]. There are several common anatomic variants that the surgeon must be aware of to avoid a catastrophic complication, especially when learning the single-incision and robotic techniques.

Alterations in normal gallbladder geometry can obscure the anatomy. Enlargement of the cystic duct and infundibulum secondary to an obstructing cystic duct stone, also known as the Hartman's pouch, can obscure the cystic and common bile duct anatomy. The most severe form of this scenario is Mirizzi's syndrome, where a large stone in Hartman's pouch causes obstruction, adhesion, or erosion into the common duct [110]. Although the incidence of Mirizzi's syndrome is only estimated at 0.5–1.0 % of all laparoscopic cholecystectomies, it has a conversion-to-open rate of 40–75 % [22–24].

There are several distinct features of the cystic duct that promote accurate identification. A normal cystic duct is 2–4 cm in length and approximately 5 mm in diameter. The absence of a true cystic duct is extremely rare, thus an inability to identify the duct is likely secondary to obscured anatomy, not an anatomical variant. Additionally, any tubular structure larger than 5 mm should be fully delineated before identifying it as a dilated cystic duct. The incidence of multiple cystic ducts is also quite rare, thus identification of multiple tubular structures near the gallbladder should raise suspicion of a tortuous CBD or accessory ducts. Furthermore, the cystic duct can take a variable course originating from the CBD: it may course perpendicular, parallel, or spiral around the CBD before entering the gallbladder [110]. Regardless of configuration, the best way to identify the cystic duct is by clearly dissecting Calot's triangle and visualizing the duct fully entering the gallbladder.

Accessory extrahepatic bile ducts draining directly from the liver bed exist in up to 20 % of patients and can be misidentified as the cystic duct during cholecystectomy. An accessory right anterior or right posterior hepatic duct can originate from the right lobe of the liver, cross Calot's triangle, and insert into the cystic, common hepatic, or common bile ducts [110, 111]. These ducts may be of significant diameter and biliary drainage, thus injury to them may require Roux-en-Y hepaticojejunostomy reconstruction [112]. Real-time near-infrared cholangiography during SSRC could potentially help the surgeon differentiate between these variants.

The cystic artery must be fully isolated before ligation. It originates from the right hepatic artery (RHA) and is commonly found in the center of Calot's triangle in approximately 85 % of cases. It divides into an anterior and posterior branch near the gallbladder wall, also supplying the cystic duct with a small accessory branch. There are several variants of which the laparoscopic surgeon must be aware. A double cystic artery occurs in 15–25 % of patients, where two vessels originate from the RHA and travel through Calot's triangle into the gallbladder. Approximately 13 % of patients may have a cystic artery that does not travel through Calot's triangle secondary to variations in arterial origin. These variant vessels can arise from the gastroduodenal artery, superior mesenteric artery, a replaced right hepatic artery, the left hepatic artery, or directly from the liver parenchyma [113]. Lastly, the cystic artery can be misidentified as the right hepatic artery, which normally courses posterior to the common duct then enters the liver at the superior edge of Calot's triangle. In up to 5 % of cases, the right hepatic artery may tortuously travel through Calot's triangle, known as Moynihan's hump, resulting in a short cystic artery and high risk of vascular injury [114]. These anatomic variants must be properly identified to avoid inadvertent ligation or injury. Since ICG remains intravascular before being excreted by the liver, intravenous injection 45 s prior to clipping could help identify the cystic artery.

Indications for Conversion

Although one of the major benefits of performing SILC or SSRC is to attain a nearly "scarless" cosmetic result, the surgeon must be cognizant to abandon the goal of improved cosmesis and convert to an open procedure for patient safety. The conversion-to-open rate for acute cholecystitis in MPLC is estimated to be 9.0–9.5 %, and

is associated with a 1.3-fold increase in morbidity [115, 116]. Similarly, the rate of conversion in SSRC to multi-port or open cholecystectomy (in a patient population including acute cholecystitis) is approximately 6 % [17]. Thus, it is important to understand that this patient population can be very ill, and certain scenarios should be recognized to convince the surgeon to convert to open and minimize operative length and risk for biliary injury.

We typically do not recommend conversion to four-port conventional cholecystectomy since it likely does not confer a higher success rate and may just prolong the operation unnecessarily. Several studies have supported this as a method of avoiding laparotomy during SSRC [17]; however, if dissection is too difficult for a single-incision approach, it is generally safer to convert directly to an open approach. The only scenarios warranting conversion to MPLC is bleeding or assistance during the learning curve.

Severe cholecystitis may be an indication for conversion to avoid biliary or vascular injury, depending on the surgeon's laparoscopic skill level. However, some centers advocate laparoscopic subtotal cholecystectomy with IOC as a safe, viable method to avoid laparotomy or biliary injury [117–120]. This procedure has been associated with a longer operative time and higher operative blood loss; however, these risks do not necessarily outweigh those of conversion to open [121]. These patients usually require intraoperative drain placement to monitor for biliary leak and potential ERCP with stent placement if one is detected. Nevertheless, there are risks of recurrent cholecystitis in patients with a gallbladder remnant, thus it may be preferable to completely remove the gallbladder even if via laparotomy.

A less common relative indication for conversion to open includes Mirizzi syndrome, which has a 75 % conversion rate, with some patients ultimately requiring a common duct repair intraoperatively or even a Roux-en-Y hepaticojejunostomy reconstruction depending on the degree of CBD involvement [23]. Additionally, there is up to 28 % incidence of gallbladder carcinoma associated with Mirizzi syndrome, thus an open operation with an experienced surgical oncologist should be considered [122].

Morbidity

Two studies have summarized the growing body of literature regarding the safety and morbidity of single-incision cholecystectomy, each evaluating nearly 1200 SILC patients with comparable results [69, 123]. The overall technical success rate without conversion to multi-port or open was over 90 %, but only 60 % for acute cholecystitis. While there were no mortalities reported, major complications requiring intervention or readmission occurred in 2.7 % of patients including retained stones (0.9 %), biliary leak (0.6 %), CBD stricture (0.1 %), and bile duct injury (<0.1 %). The minor complication rate was approximately 3 %, including wound infection (2 %), seroma (1.5 %), and ileus (0.2 %). Notably, the presence of acute cholecystitis did not appear to significantly affect complication rates. Thus, these two large studies have elucidated an acceptably low rate of overall complications, bile duct injury, readmission, and minor complications similar to MPLC provided adequate laparoscopic skills of the operating surgeon.

Nevertheless, there have been reports in the literature documenting higher rates of postoperative incisional hernia after single-incision cholecystectomy. Marks et al. performed a large, prospective, randomized, multicenter study analyzing SILC vs. MPLC [124]. While there was no difference in adverse events between groups, they found a significantly higher incisional hernia rate in the SILC group at 12-month follow-up (8.4 % vs. 1.2 %, $p = 0.03$). One-half of these hernias required operative repair by the time of publication. However, fascial closure during cholecystectomy was left to surgeon preference and there were not enough patients enrolled to determine if different techniques predisposed to hernia formation. Furthermore, the study noted it included surgeons with prior experience of at least ten SILC operations—since the learning curve may take approximately 20 cases, the study's outcomes may have varied if it required surgeons with more SILC experience. Indeed, one single-surgeon, prospective study analyzed the incisional hernia rate after SILC with mean follow-up of 17 months and observed a 2 % incisional hernia rate [125], which is comparable to

the known MPLC hernia rate of 1.7 % [126]. This lower rate may be a result of using the same closure technique on each patient, which were several interrupted Vicryl-1 (or PDS-1) sutures. Other studies including meta-analyses have also observed no difference in rates of postoperative hernia after single-incision cholecystectomy [12, 13, 70, 127, 128]. However, further prospective long-term studies are warranted to evaluate the optimal orientation of fascial incision and method of closure in order to ensure a low rate postoperative incisional hernia.

The rate of bile duct injury for MPLC has been estimated at 0.5 % and is associated with a more than twofold increased risk for mortality [129]. These patients usually require at minimum an ERCP and biliary stent placement if there is a minor injury, but more commonly these patients require a hepaticojejunostomy reconstruction by an experienced hepatobiliary surgeon. Although there have been over 350 SSRC cases reported in the literature without biliary injury [15–20] and the two SILC reviews discussed above reported <0.1 % rate of bile duct injury, one recent study suggested otherwise [130]. These authors performed a comprehensive literature search of SILC, including 45 studies and 2626 patients. The calculated overall complication rate was 4.2 % with a bile duct injury rate of 0.72 %. This is higher than the expected 0.4–0.5 % bile duct injury rate known for MPLC. There were no comparison groups to assess for statistical significance in this study; however, it is important to conclude that there may be a higher rate of biliary injury with the introduction of a single-incision procedure, and the technique should be reserved to surgeons with capable skills on minimally invasive platforms. It is also important to determine if these complications occur during the learning curve phase or afterwards with experienced surgeons.

Convalescence Data

As the main benefit of the single-incision technique is to be minimally invasive and "scarless," there are convalescence data now reporting recovery events such as patient satisfaction, postoperative pain, mean hospital stay, and time to resume normal functional capabilities. These findings have been well studied in the SILC population, and will be reviewed here.

Convalescence data has been well documented for MPLC [131, 132]. Pain is most intense for the first 72 h postoperatively, which can be minimized with local anesthesia, oral opioids, or nonsteroidal anti-inflammatory drugs (NSAIDs). Most patients require 1 week until return to work and 2 days until return to recreational activity. Additionally, some studies advocate satisfactory cosmetic outcome based on postoperative patient questionnaire [133].

Now that single-incision cholecystectomy has been a surgical option for over a decade, there are reports in the literature documenting improved patient satisfaction with SILC when compared to MPLC [12]. One prospective trial demonstrated that there was no difference in scar assessment at early postoperative follow-up; however, patients do perceive a statistically significant superior scar assessment at longer-term postoperative follow-up [134]. Another similar randomized prospective trial supported this finding by observing increased patient satisfaction with wound appearance as early as two weeks postoperatively [135]. Other meta-analyses had consistent findings of improved cosmetic outcomes with SILC [11, 13, 70, 136].

The consensus of postoperative pain control has been controversial. Some randomized trials as well as meta-analyses have not found any statistical difference in postoperative pain control between SILC and MPLC [12–14, 70, 135, 137]. On the other hand, several studies and meta-analyses have documented improved pain control postoperatively, especially within 24-h [11, 127, 136, 138, 139]. This discrepancy is likely due to the widely different methods of pain control available, including oral opioids, NSAIDs, subcutaneous injection of local anesthetic, and even epidural anesthesia. We recommend local anesthetic for all patients combined with an oral modality best fit for the individual patient.

As the SILC procedure is a laparoscopic approach, one would expect the length of hospital stay and mean days until return to work to be similar to MPLC. Indeed, several studies

have confirmed this hypothesis, finding the mean length-of-stay to be between 0 and 3 days without significant difference when compared to MPLC [11, 12, 14, 70, 128, 140]. Initial SSRC cohorts have reported an average number of days until return to normal activity and work of 4.5 and 7.5, respectively [16].

These comprehensive results are reiterated in one of the largest meta-analyses to date, which analyzed 25 randomized controlled trials including 944 SILC and 897 MPLC patients [136]. They observed that SILC was statistically superior to MPLC in cosmetic score, shorter length of incision, and postoperative pain within 12 h. In conclusion, these data support the use for patients interested in improved cosmesis and possibly improved pain control postoperatively; however, further convalescence data regarding SSRC remains to be elucidated.

Comparison to Standard Laparoscopy

Since no studies have compared SSRC to either SILC or MPLC, this chapter has compared the SILC technique vs. MPLC in several important aspects. With regard to operative times, SILC typically takes about 40–80 min depending on degree of dissection difficulty. This has been shown to be significantly longer compared to MPLC by approximately 15–20 min [13, 136]. Initial SSRC cohorts have reported a mean overall operative time of approximately 70–100, with console time ranging from 30 to 65 min [15–20]. These times will likely decrease as surgeons and dedicated operative room staffs become familiar with the robotic platform.

The overall main benefit of SILC compared to MPLC is improved patient satisfaction, cosmesis, and potentially pain control. Many studies confirm that SILC is as safe and efficacious as MPLC, showing comparable complication rates including minor (e.g., wound infection, seromas) and major complications (e.g., bile duct injury). While some studies report increased rates of bile duct injury and hernia formation, more studies are warranted to confirm these findings. Additionally, it is difficult to control for individual surgeon skill in these analyses. Thus, the literature should only be used as a guideline based on one's own expertise and comfort level with single-incision surgery.

Integration into Practice

Perhaps the most important aspect of implementing a novel technique is incorporating it into surgical practice safely. Several studies have addressed the observed learning curve of experienced laparoscopic surgeons in developing an efficient operative time for SILC while maintaining patient safety and operative success. The data suggest there is an initial 20-patient SILC training phase, which have the longest operative times. The operative time improves gradually over the subsequent 20 patients. After the 40th case, surgeons' operative times reach a nadir, stabilize, and become reproducible [141]. These results are analogous to another single surgeon's initial experience [142]. This study observed that the initial mean operative time for the first 20 patients was 91 min. However, this improved to 81 min for the second 20 patients, followed by 64 min in the final series of patients. Furthermore, other studies describe learning curves that showed an improvement and plateau in operative times after only ten patients [143, 144]. Most importantly, regardless of the learning curve, these studies did not observe any increase in complication rate compared to MPLC.

Several initial SSRC cohorts have described the initial learning curve using the robotic platform. Surgeons in these studies were experienced in minimally invasive operations, and generally agreed that dissection during SSRC was more complex than conventional MPLC but easier than SILC [19]. Operative times were consistent with SILC and MPLC operative times and did not decrease significantly during initial robotic cases—this suggests that surgeons with expertise in minimally invasive and robotic procedures may not necessarily have a significant learning curve for cholecystectomy [19]. However, other studies noted a significant decrease in docking

time [17, 20] and port insertion [17] as case number progressed, most notably in obese patients. Thus, these preliminary analyses suggest that the learning curve for SSRC is primarily a function of familiarization with the setup of the system and not necessarily the dissection itself, provided that the surgeon has expertise in minimally invasive platforms and SILC. Nevertheless, larger studies are required to confirm these findings and further define the caseload that a surgeon and operating room staff should expect to reach proficiency when implementing this new technology.

Several studies have analyzed resident training during SILC operations and have demonstrated a short learning curve without disruption of standard operating room procedure [145]. There also were not any complications as a result of resident training. These studies conclude that patient safety and outcomes are preserved without a dramatic increase in operative length, provided the resident has proficiency in basic laparoscopy and is guided with strict supervision by an experienced laparoscopist [146]. These findings need to be explored regarding SSRC.

In summary, single-incision cholecystectomy has become more commonplace for minimally invasive surgeons. The robotic platform has the advantage of overcoming the limitations of SILC, namely improving space constraints and reducing instrument collisions. While most studies analyzing the safety, efficacy, and outcomes of single-incision cholecystectomy are based on the SILC literature, both SSRC and SILC appear to be safe and efficient methods for cholecystectomy that are correlated with improved patient satisfaction, cosmesis, and pain control. This technique is reserved for experienced minimally invasive surgeons whose practice includes patients interested in these specific outcomes. Incorporating this technique into practice requires prior experience in laparoscopy and proficiency in robotics, and one should expect an initial learning curve of approximately 20 operations. Caution must be taken during the surgeon's initial experience, and scrubbing with another surgeon with SSRC and SILC experience may prove very useful. Furthermore, the surgeon must take away from this chapter the indications for conversion to open surgery to reduce the risk of complications.

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Infectious Considerations in Complicated Acute Cholecystitis

9

Robert G. Sawyer and Stephen W. Davies

Introduction

An appreciation for complicated cholecystitis begins with an awareness of gallbladder embryology, anatomy and physiology, and pathology. Briefly, the gallbladder primordial bud, derived from the foregut, arises off the extrahepatic biliary tree during the fourth and fifth weeks of gestation as the cells between the newly developing liver parenchyma and foregut begin to proliferate [1]. This process is aided by the presence of transcription factors: hepatic nuclear factor 1β, HNF6, Sox17, and Hes1. When these are absent, malformations occur giving rise to various congenital disorders (Table 9.1) [1–6].

The most common extrahepatic biliary anatomy involves a right and left hepatic duct, which exit the liver and merge to form a common hepatic duct [1]. The gallbladder, commonly located inferior to and between hepatic lobes IV and V, connects to the common hepatic duct via the cystic duct, which then forms the common bile duct, distally. The common bile duct, a structure that lies anterior to the portal vein and lateral to the proper hepatic artery, courses inferiorly to either join the pancreatic duct before connecting with the second portion of the duodenum or join the second portion of the duodenum directly via the sphincter of Oddi.

The gallbladder serves as a reservoir for bile produced daily by the liver [7]. Bile, produced by hepatocytes and composed primarily of water, bile acids, proteins, phospholipids, cholesterol, and inorganic electrolytes, drains from the liver and empties into the second portion of the duodenum via the common bile duct [8]. In times of fasting, the sphincter of Oddi remains constricted, forcing buildup of bile within the common bile duct and gallbladder [7]. While stored in the gallbladder, bile is concentrated through absorption of water. This process continues until the next meal, whereupon cholecystokinin is released from the duodenum. This hormone serves to stimulate gallbladder contraction and sphincter of Oddi relaxation, thus releasing bile into the second portion of the duodenum to aid in digestion and fat absorption.

Cholecystitis was first described in 1888 by Hutchinson et al. [9], and has since been defined as, "an inflammation of the gallbladder, generally caused by obstruction of the cystic duct [10]." Once obstructed, egress of bile and the mucous continuously produced by the gallbladder is impeded, placing direct outward pressure upon the gallbladder wall. As tension increases, venous and lymphatic outflow become compromised

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(i.e., edematous cholecystitis; 2–4 days) [11]. Eventually, the wall tension reaches a threshold whereupon arterial inflow becomes compromised, leading to ischemic injury, necrosis (i.e., necrotizing cholecystitis; 3–5 days), intramural abscesses (i.e., suppurative cholecystitis; 7–10 days), and possible perforation. If this process is repeated multiple times, fibrous proliferation replaces much of the wall tissue and the gallbladder mucosa atrophies and contracts (i.e., chronic cholecystitis). Obstruction is most commonly attributable to gallstones [10, 12] (Table 9.2) [13]; however, it may also be due to biliary stasis (e.g., acalculous cholecystitis) [14], cancer [15, 16], volvulus or torsion [17, 18], gallbladder polyps [19], common bile duct cysts [20], scarring (e.g., prior cholecystitis, cholangitis, or pancreatitis, or primary sclerosing cholangitis) [10], or parasites [21]. This process typically remains sterile; however, secondary infection with bacteria, fungi, viruses, and parasites may further complicate the cascade of events.

Table 9.1 Congenital malformations of the gallbladder

Type	Incidence
Biliary atresia [1, 2]	Europe and North America = 0.43–0.85/10,000 live births
	East Asia and French Polynesia = 0.86–2.0/10,000 live births
Choledochal cysts [1, 3]	Western Countries = 1/100,000–150,000 live births
	Asian Populations = 1/1000 live births
Gallbladder agenesis [1, 4]	10–65/100,000 live births
Gallbladder duplication and septation [5]	1/3800 live births
Left-sided gallbladder [6]	4/10,000 live births

Bacterial Infections

Bacteria have previously been thought to colonize the hepatobiliary tract and contribute to gallstone formation [12, 22]. Prior murine models evaluating this theory, have observed a greater rate of gallstone formation in mice infected with *Helicobacter* spp. compared to uninfected, genetically identical mice [12, 23]. Hazrah et al., prospectively evaluated the gallstones of 100 consecutive patients [24]. They observed that bacterial colonization was present in 81 % of patients with cholelithiasis and 77 % of patients with gallbladder carcinoma. Bacterial isolates included: *Klebsiella* spp., *Escherichia coli*, *Pseudomonas* spp., *Enterococcus* spp., *Enterobacter* spp., *Acinetobacter* spp., *Proteus* spp., *Staphylococcus aureus*, *Citrobacter* spp., and *Salmonella* spp. Additionally, *Helicobacter* spp. have been recovered from gallstones and bile [12, 22, 25]. It is thought that these bacteria either migrate in a retrograde fashion or translocate from the gastrointestinal epithelium. Once present, bacteria firmly attach to the hepatobiliary epithelium and protect themselves from the antibacterial properties of biliary secretions (i.e., bile salts and IgA) via fimbriae and biofilm (i.e., glycocalyx) [26].

During an obstructive process of the hepatobiliary system (e.g., acute cholecystitis), upregulation of inflammatory markers result in leaky capillaries and a permeable epithelium, which resultantly allow colonized bacteria to gain access to the systemic circulation [22, 26].

Table 9.2 Types of gallstones [13]

Types	Prevalence	Formation location	Etiology
Cholesterol	85 % within DC	Gallbladder primarily, CBD secondarily	Obesity, female gender, older age, and genetic disorders
Black pigment	15 % within DC	Gallbladder primarily, CBD secondarily	Hemolytic disorders and cirrhosis
Brown pigment	Predominate within East Asia	CBD primarily, intrahepatic bile ducts secondarily	Infection and biliary strictures

CBD common bile duct, *DC* developed countries

Of patients who develop acute cholecystitis complicated by bacterial infection, the most common etiology is gallstones (85 %) and the most common isolates include *Escherichia coli*, *Klebsiella* spp., and *Enterococcus faecalis* [12, 14] (Table 9.3) [12, 14]. Patients usually present with complaints of epigastric pain (diffuse, visceral) that migrate toward the right upper quadrant (focal, somatic) as time progresses [10]. This is typically associated with nausea, vomiting, anorexia, and fever. Additionally, a prior history of biliary colic (i.e., intermittent, postprandial abdominal pain with meals high in fat) may be reported. This clinical picture may be complicated in areas of poor sanitation and/or immunosuppressed patients, such as that seen with critical illness (medical or surgical), transplant, immunosuppressant medication, AIDS, hepatitis, liver

Table 9.3 Bacterial infections complicating acute cholecystitis and antimicrobial therapy

Bacteria	Antimicrobial treatment
Non-immunosuppressed	
Escherichia coli [12, 14]	β-Lactam/β-lactamase inhibitor or
	Carbapenem
	or
	Second- or third-generation cephalosporin
	or
	Quinolones
Klebsiella spp. [12, 14]	β-Lactam/β-lactamase inhibitor or
	Carbapenem
	or
	Second- or third-generation cephalosporin
	or
	Quinolones
Enterococcus faecalis [12, 14]	β-Lactam/β-lactamase inhibitor or
	carbapenem
	or
	Second- or third-generation cephalosporin
	or
	Fluoroquinolone
Immunosuppressed	
Pseudomonas putida [27]	β-Lactam/β-lactamase inhibitor
	or
	Third- or fourth-generation cephalosporin
	or
	Monobactam
	or
	Fluoroquinolone
	or
	Carbapenem
	or
	Aminoglycoside and β-lactam

(continued)

Table 9.3 (continued)

Bacteria	Antimicrobial treatment
Moellerella wisconsensis [28]	Tetracycline
	or
	Aminoglycoside
	or
	β-Lactam
	or
	Fluoroquinolone
	or
	Folate-pathway inhibitor
	or
	Chloramphenicol
	or
	Nitrofurantoin
Actinomyces spp. [29, 33]	Penicillin G
Salmonella spp. [14, 30, 31]	Fluoroquinolone
–Typhi	or
–Enterica	Third-generation cephalosporin
Brucella spp. [32]	Doxycycline
	and
	Streptomycin
	or
	Rifampin
Mycobacterium [34, 35]	Isoniazid
–Tuberculosis	and
–Bovis	Rifampin
	and
	Pyrazinamide
	and
	Ethambutol
Haemophilus parainfluenzae [36]	Ampicillin
	or
	Clarithromycin
	or
	Doxycycline
	or
	Cotrimoxazole
Coxiella burnetii [37]	Doxycycline
Staphylococcus aureus [38]	Nafcillin
	or
	Vancomycin
Leptospira interogans [39]	Penicillin G
	or
	Ampicillin

(continued)

Table 9.3 (continued)

Bacteria	Antimicrobial treatment
Vibrio cholerae [40]	Cephalothin
	or
	Tetracycline
	or
	Aminoglycoside
	or
	Trimethoprim/sulfamethoxazole
Campylobacter jejuni [41]	Ofloxacin
Edwardsiella tarda [42]	β-Lactam
	or
	Cephalosporins
	or
	Aminoglycosides
	or
	Oxyquinolones

cirrhosis, malignancy, or diabetes, all conditions that may predispose patients to additional, opportunistic pathogens [12, 14] (Table 9.3) [12, 14, 27–42]. While patients may present with complaints similar to the ones described above (i.e., right upper quadrant pain, nausea, vomiting, anorexia, and fever), the clinical picture may often be varied and nondescript owing to patient acuity and critical illness [10]. In these scenarios, a high suspicion for acalculous cholecystitis must be maintained given the increased frequency of gallbladder gangrene (50 %), emphysema (45 %), perforation (10 %), and patient mortality (30 %) [10, 14].

Fungal Infections

Fungal infections of the hepatobiliary system are rare and usually indicative of disseminated illness [43]. Of patients who develop acute cholecystitis complicated by fungal infection, the most common etiology is acalculous cholecystitis [14]. The prevalence of acalculous cholecystitis is greatest within critically ill (medical or surgical) patients exposed to cardiac/vascular surgery, trauma, burns, prolonged parenteral nutrition, and multisystem failure [14, 44]. Additionally, diabetics, cancer patients, and patients with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) may develop acalculous cholecystitis without critical illness. Similar to above, patients may present with right upper quadrant pain, nausea, vomiting, anorexia, and fever. However, symptoms may be skewed or absent altogether. Thus, the clinical picture along with exam findings become paramount. For example, one should not disregard culture results yielding *Coccidioides immitis* in the southwestern region of the United States or *Histoplasma capsulatum* in the Ohio and Mississippi river valleys of the United States or Central and South America as contaminants [43, 45]. Fungal pathogens previously linked to acute cholecystitis are provided in Table 9.4 [43, 45].

Viral Infections

Similarly, viral infections of the extrahepatic biliary system are rare and indicative of disseminated illness. While acalculous cholecystitis is thought to be the most common cause of cholecystitis in this population, additional factors may play a role. For example, in a case report detailing acute acalculous cholecystitis associated with acute hepatitis B virus infection, Unal et al., theorized that

Table 9.4 Fungal infections complicating acute cholecystitis, characteristic features, and antifungal treatment

Fungi	Characteristic features	Antifungal treatment
Pneumocyctis carinii [45]	– 39 % hepatobiliary involvement in AIDS patients	Pentamidine
	– Diagnosed using silver stain	
Cryptococcus neoformans [43, 45]	– 19 % hepatobiliary involvement in AIDS patients	Amphotericin B
	– Identified by cryptococcal antigen latex agglutination test	or
	– Cerebral spinal fluid should be tested in all cases	Fluconazole
	– Diagnosed using India ink or Gomori's silver stain	or
		Fluconazole
		and
		Flucytosine
Coccidioides immitis [43]	– Endemic to Southwestern United States	amphotericin B
	– Serum IgM antibodies may be detected	or
		Fluconazole
		or
		Itraconazole
Histoplasma capsulatum [43, 45]	– 16 % hepatobiliary involvement in AIDS patients	Amphotericin B
	– Endemic to Ohio and Mississippi River Valleys of the United States	or
	– Endemic to Central and South America	Itraconazole
	– Diagnosed using periodic acid-Schiff, Wright's, or Giemsa stains	
Candida albicans [43]	– Rare	Amphotericin B
	– Bull's-eye appearance on abdominal imaging	
	– Invasive mycelia demonstrated on silver stains	

AIDS acquired immunodeficiency syndrome

extrahepatic complications of the virus (i.e., polyarteritis nodosa) may also be responsible [46]. They suggest that increased viral replication gives rise to immune complex accumulation in the walls of small-to-medium diameter arteries. Likewise, in a case report examining hepatitis B-related polyarteritis nodosa, Takeshita et al., discovered necrotizing vasculitis in the biopsy specimen of a gallbladder wall removed for alithiasic cholecystitis [47]. Thus, in addition to the common signs and symptoms of acute cholecystitis, hepatitis B patients may also present with bilateral wrist and ankle erythema, edema, and pain. A cell-mediated immunologic response has also been proposed as a mechanism contributing to cholecystitis in patients with hepatitis A [48]. Dengue fever increases vascular permeability, plasma and protein leakage, and serous effusion resulting in gallbladder wall thickening [49]. It is thought that the extent of gallbladder wall thickening is associated with disease severity and progression of dengue fever. In addition to the common signs and symptoms of acute cholecystitis, dengue fever patients may also present with biphasic fever, skin rash, headache, retro-orbital pain, photophobia, cough, vomiting, myalgia, arthralgia, leukopenia, thrombocytopenia, and lymphadenopathy. Viral pathogens previously linked to acute cholecystitis are provided in Table 9.5 [43, 46–54].

Parasitic Infections

Parasitic infections are commonly endemic to underdeveloped or developing countries lacking adequate sanitation, potable water, and vector control [21, 55–62]. Their association with acute cholecystitis may involve a combination of HIV/AIDS, direct hepatobiliary obstruction secondary to heavy parasitic load, and/or biliary stasis

Table 9.5 Viral infections complicating acute cholecystitis, characteristic features, and antiviral treatment

Virus	Characteristic features	Antiviral treatment
Cytomegalovirus [54]	– Found throughout the world	Valganciclovir
	– Transmitted via organ transplant or exchange of bodily fluids	
	– Patients may present with mononucleosis-like syndrome, pneumonitis, retinitis, gastroenteritis, hepatitis, or central nervous system infection, or may be asymptomatic	
Hepatitis B [43, 46, 47]	– Found throughout the world	Lamivudine
	– History of parenteral exposure or unprotected sexual contact	
	– Polyarteritis nodosa most common extrahepatic manifestation (bilateral wrist and ankle erythema, edema, and pain)	
Hepatitis A [48, 50]	– Found throughout the world	Supportive care
	– Transmitted by fecal-oral route	or
	– Potential association with cell-mediated immunologic response	Vaccine in patients with concomitant chronic liver disease
	– Self-limiting	
Flavivirus [49, 51]	– Worldwide condition spread through tropical and subtropical zones (i.e., South-East Asia, the Pacific, East and West Africa, the Caribbean, and the Americas)	Supportive care
	– Primarily near regions of explosive population growth and inadequate public health systems	(No vaccine available)
	– Transmitted by infected female Aedes mosquitoes	
	– Extent of gallbladder wall thickening associated with disease severity and progression of dengue fever	
	– Symptoms may include biphasic fever, skin rash, headache, retro-orbital pain, photophobia, cough, vomiting, myalgia, arthralgia, leukopenia, thrombocytopenia, and lymphadenopathy	
	– Self-limiting	
Epstein–Barr [52, 53]	– May present as infectious mononucleosis (i.e., fever, pharyngitis, cervical lymphadenopathy, and hepatosplenomegaly)	Supportive care
	– Self-limiting	

secondary to malabsorptive diarrhea and dehydration. Parasitic pathogens previously linked to acute cholecystitis are provided in Table 9.6 [21, 55–63].

Diagnosis

As previously mentioned, patients presenting with acute cholecystitis generally complain of epigastric or right upper quadrant abdominal pain, nausea, vomiting, anorexia, and fever. Physical exam findings may include tachycardia, fever (32–53 %), jaundice, a Murphy's sign (i.e., cessation of inhalation with increased palpatory pressure directed towards the right upper abdominal quadrant), generalized abdominal tenderness with palpation, or peritonitis [10, 14]. Laboratory findings may reveal leukocytosis (51–53 %).

Ultrasonography is the most commonly performed imaging modality utilized for the diagnosis of acute cholecystitis due to rapidity of evaluation (10–15 min), low cost, availability, and low radiation exposure to the patient [10, 12, 14, 64]. It has a sensitivity and specificity greater than 95 % at detecting gallstones, a positive predictive value between 92 and 95 % for detecting acute cholecystitis, and a negative predictive value of 95 % for ruling out acute cholecystitis [12, 64]. Imaging findings suggestive of acute cholecystitis include: presence of gallstones or

Table 9.6 Parasitic infections complicating acute cholecystitis, characteristic features, and antiparasitic treatment

Parasites	Characteristic features	Antiparasitic treatment
Microsporidiosis [55]	– Prevalent worldwide	Albendazole
Enterocytozoon bieneusi	– Frequent enteric infection among patients with AIDS	
Enterocytozoon intestinalis	– Symptoms include diarrhea and weight loss	
	– Diagnosed using special stains, light microscopy, and immunohistochemical/molecular techniques	
Ascaris lumbricoides [21, 56]	– Worldwide distribution; however, most prevalent in the developing countries of India, China, Asia, South Africa, and Latin America	Pyrantel
	– Infection via ingestion of embryonated eggs	or
	– Symptoms include stunting of linear growth, reduced cognitive function, and malnutrition	Mebendazole
		or
		Albendazole
		or
		Levamisole
Malaria [58, 63]	– Most prevalent in sub-Saharan Africa and South Asia	Chloroquine
Plasmodium vivax	– Mosquito-borne illness	or
Plasmodium ovale	– Nonspecific symptoms similar to acute cholecystitis (i.e., fever, chills, flu-like symptoms, abdominal pain/tenderness)	Artemisinin derivatives
Plasmodium falciparum	– Diagnosis based upon parasite load within erythrocytes	or
		Quinine
		or
		Quinidine
		or
		Quinine and doxycycline
		or
		Quinine and clindamycin
Cryptosporidium [60]	– Worldwide distribution; however, more prevalent among developing countries	Supportive therapy; disease is self-limited in immunocompetent hosts
	– Occurs mainly among immunocompromised individuals (e.g., immunosuppression and AIDS); however, also occurs sporadically among animal handlers, travelers to and/or residents of endemic regions, and children	
	– Primarily infects gastrointestinal tract; however, has been identified in bronchial tissue	
	– Symptoms include frequent, voluminous, and watery diarrhea, abdominal pain, malabsorption, and weight loss	
	– Diagnosed using ELISA to detect immunoglobulins G and M, as well as identification of oocysts in feces using acid-fast stains, fluorescent auramine–rhodamine stain, and the PAS and carbolfuchsin-negative stains	
Cyclospora cayetanensis [62]	– Most prevalent in South and Central America, the Caribbean, Europe and Eastern Europe, Africa, the Indian subcontinent, and parts of Asia	Trimethoprim–sulfamethoxazole
	– Fecal-oral transmission	
	– Primarily infects cells of the jejunum	
	– Symptoms include anorexia, malaise, nausea, and abdominal pain	
	– Creates membranous-like sheath overlying the intestinal epithelium	

(continued)

Table 9.6 (continued)

Parasites	Characteristic features	Antiparasitic treatment
Fascioliasis hepatica [61]	– Most prevalent in Africa and Asia (F. hepatica and F. gigantica)	Triclabendazole
Fascioliasis gigantica	– Most prevalent in Americas (especially Peru and Bolivia), Europe, and Oceania (F. hepatica)	
	– Females suffer greater prevalence rates, infection severity, and liver/biliary complications compared to males	
	– Children affected more than adults	
	– Contracted through the consumption of raw vegetables contaminated with metacercariae	
	– (2) phases: acute and chronic	
	– Acute phase	
	– Lasts 3–5 months	
	– Immature larvae migrate from duodenum to liver/bile ducts	
	– Symptoms include hypereosinophilia, fever, hepatomegaly, hypodense lesions seen on CT scan, nausea, vomiting, diarrhea, anorexia, and weight loss	
	– Chronic phase	
	– begins after 6 months and may last for 10 years or more	
	– parasites mature within bile ducts	
	– biliary obstruction, cirrhosis	
	– Diagnosed using Fas2-ELISA, rapid sedimentation technique (RST), or the Kato-Katz technique	
Opisthorchis viverrini [61]	– Most prevalent in Laos, Thailand, Vietnam, and Cambodia (O. viverrini)	Praziquantel
Opisthorchis felineus	– Most prevalent in Soviet Union, Kazakhstan, and Ukraine (O. felineus)	
	– Contracted by eating raw or uncooked cyprinoid fish products in rural areas	
	– Migrate to liver through the duodenum via the ampulla of Vater	
	– Reside in bile ducts	
	– 2 phases: acute and chronic	
	– Acute phase	
	– Right upper quadrant pain, flatulence, fatigue, fever, nausea, vomiting, malaise, arthralgia, lymphadenopathy, skin rash, peripheral eosinophilia	
	– Chronic phase	
	– hepatomegaly, intrahepatic duct stones, suppurative cholangitis, cholangiocarcinoma, liver abscess	
	– Diagnosed using ELISA, Kato-Katz, ether-formalin concentration technique	

(continued)

Table 9.6 (continued)

Parasites	Characteristic features	Antiparasitic treatment
Clonorchis sinensis [61]	– Most prevalent in northeast China, southern Korea, Japan, Taiwan, northern Vietnam, eastern Russia	Praziquantel
	– Contracted by eating raw or uncooked cyprinoid fish products in rural areas	
	– Migrate to liver through the duodenum via the ampulla of Vater	
	– Reside in bile ducts	
	– 2 phases: acute and chronic	
	– Acute phase	
	– Symptoms include fever, rash, malaise, and right upper quadrant pain	
	– Chronic phase	
	– Symptoms include cholangitis, cholecystitis, obstructive jaundice, hepatomegaly, cholecystitis, hepatic tumors, and cholelithiasis	
	– Diagnosed using Kato-Katz, ether-formalin concentration technique	
Leishmaniasis [57]	– Most prevalent in Asia, Africa, South and Central America and Southern Europe	Meglumine antimoniate
Giardia [59]	– Symptoms include diarrhea, vomiting, and abdominal cramping	Metronidazole
	– Patients may have HIV/AIDS with low CD4 counts	
	– Stool examination for ova and parasites	

sludge, pericholecystic fluid, thickened gallbladder wall (i.e., >3.5–4 mm), sonographic Murphy's sign (i.e., right upper abdominal quadrant tenderness with increased ultrasound probe pressure), and/or gallbladder distention (i.e., >5 cm in the transverse diameter) [12, 14, 64] (Fig. 9.1).

Negative ultrasonography in the presence of positive clinical findings warrants alternative imaging modalities potentially including hepatobiliary iminodiacetic acid (HIDA) scanning (Figs. 9.2 and 9.3), computed tomography (CT) scanning, or magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP) [10, 12, 14, 64]. HIDA scans utilize technetium to illuminate the hepatobiliary tree. It has a 95 % accuracy at diagnosing acute cholecystitis, which may be enhanced by the use of intravenous morphine; however, it is more expensive and time intensive, exposes patients to ionizing radiation, and requires specialized staff members to perform the necessary imaging [10, 14]. Technetium is administered intravenously whereupon it is absorbed by the liver and excreted into the biliary system. Under normal circumstances, absorption and excretion take approximately 1 h (Fig. 9.2) [10]. Morphine may be used to constrict the sphincter of Oddi, thereby facilitating retrograde flow into the gallbladder. If obstruction within the cystic duct is present, illumination of the liver, extrahepatic biliary system excluding the gallbladder, and duodenum will occur via a gamma camera (Fig. 9.3). CT (similar sensitivity at diagnosing acute cholecystitis compared to ultrasonography, although 60 % of gallstones are not radiopaque) and MRI/MRCP (50–91 % sensitivity at diagnosing acute cholecystitis) imaging are less frequently used, but may be more beneficial for evaluating the etiology of generalized abdominal pain, emphysema of the gallbladder (Fig. 9.4),

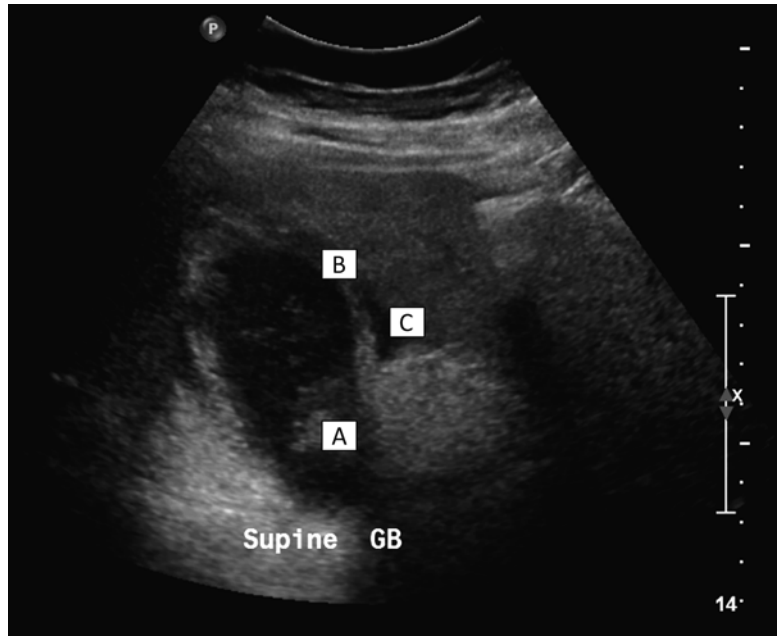

Fig. 9.1 Ultrasound image of acute cholecystitis. The gallbladder is significantly distended. Heterogeneous echotexture within the gallbladder lumen, which contains numerous stones and sludge (**a**). The gallbladder wall is thickened (**b**), measuring approximately 10 mm and there is a small amount of pericholecystic fluid (**c**). Positive sonographic Murphy's sign

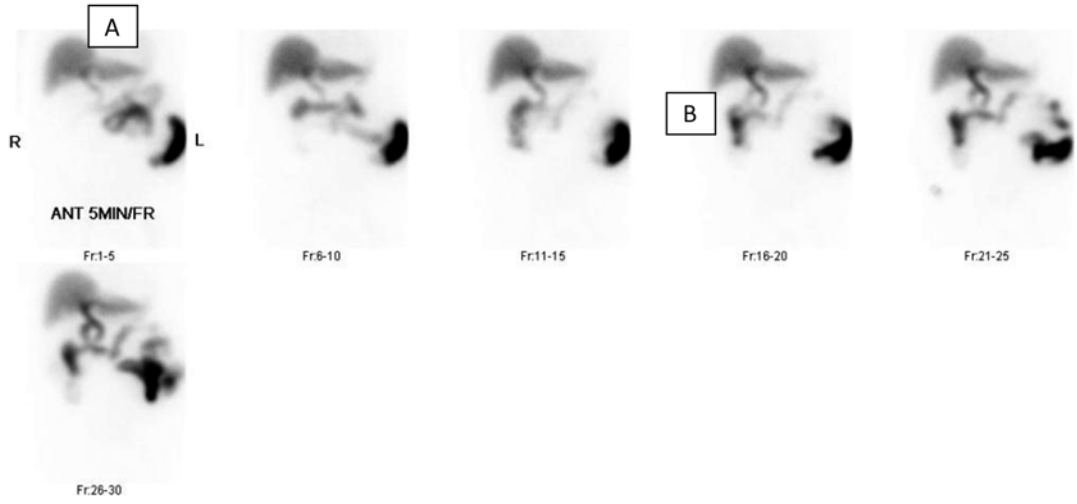

Fig. 9.2 Hepatobiliary Iminodiacetic Acid imaging of an unobstructed hepatobiliary tree. There is prompt uptake of the radiotracer by the liver (**a**). Normal excretion of the radiotracer into the intra- and extra-hepatic biliary tree (**b**). There is no filling of the gallbladder by 60 min. There is no evidence of common bile duct obstruction. After morphine administration, there is no filling of the gallbladder by 30 min

gangrenous cholecystitis, or gallbladder hemorrhage [10, 12, 64]. Imaging findings are similar to ultrasonography. Clinical and radiographic findings suggestive of infectious etiology should be further evaluated using cultures, special stains, or ELISA (Tables 9.3, 9.4, 9.5 and 9.6).

Treatment

When possible, early cholecystectomy is considered to be the gold standard for the treatment of cholecystitis [10, 12, 64]. Previous studies have

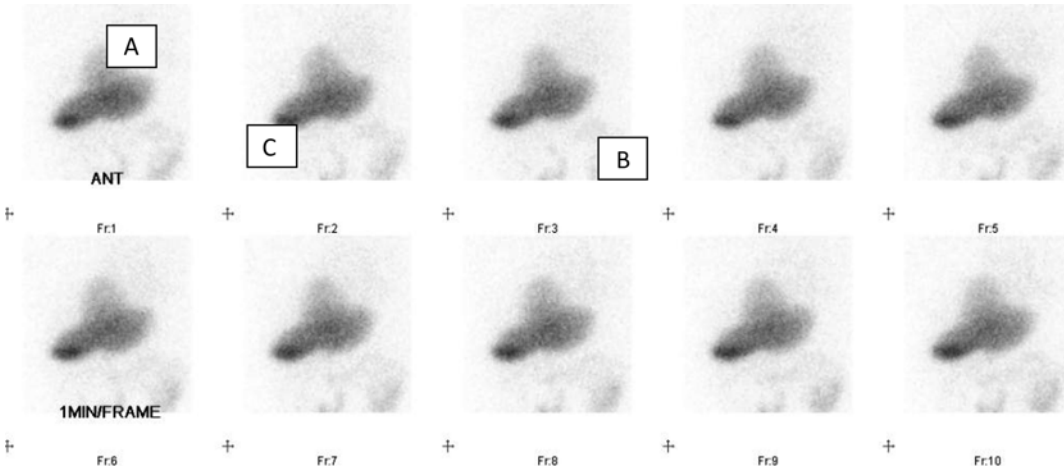

Fig. 9.3 Hepatobiliary Iminodiacetic Acid imaging of an obstructed hepatobiliary tree. There is prompt uptake of the radiotracer by the liver (**a**). There was no excretion into the common bile duct (**b**). There is delayed uptake within the gallbladder at 4 h (**c**)

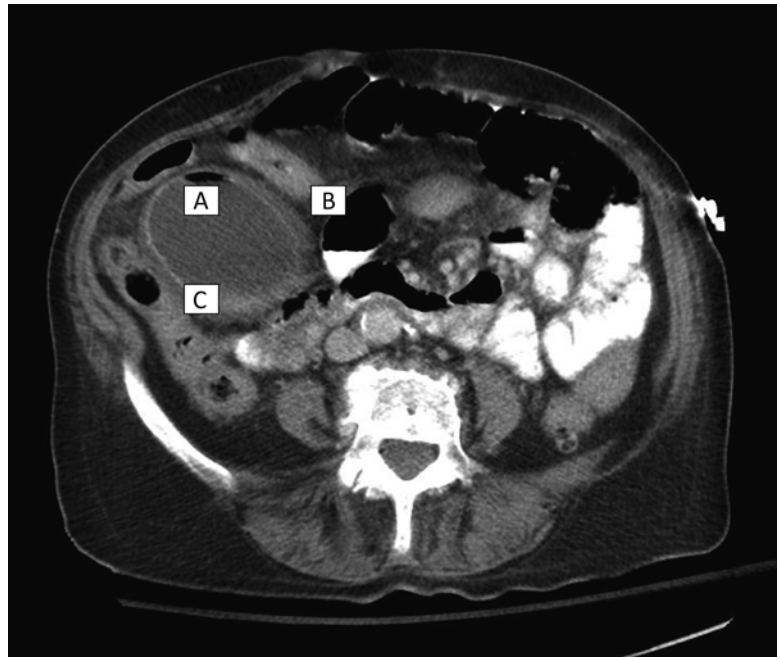

Fig. 9.4 Computed Tomography Imaging of Emphysematous Cholecystitis. (**a**) Gas trapping within the gallbladder lumen. (**b**) Pericholecystic fluid. (**c**) Thickened gallbladder wall. Evidence of acute cholecystitis with air within the gallbladder lumen (**a**) suggestive of early acute emphysematous cholecystitis

observed decreased in-hospital mortality, long-term mortality, and gallstone-related readmission rates for early (index hospitalization) versus late (sometime after index hospitalization) cholecystectomy. De Mestral et al., retrospectively evaluated 25,397 adults with uncomplicated acute cholecystitis [65]. Of these, 41 % did not receive cholecystectomy during the index admission and were observed to have a 14 %, 19 %, and 29 % probability of a gallstone-related event at 6, 12, and 52 weeks following discharge, respectively. Additionally, Brooks et al., retrospectively evaluated 5268 patients undergoing same-admission emergency cholecystectomy for acute cholecystitis

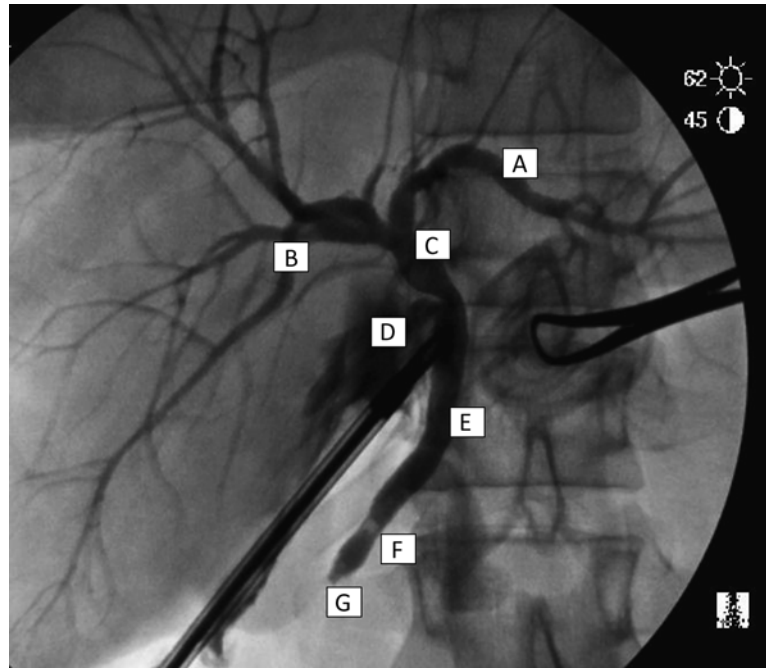

Fig. 9.5 Intraoperative Cholangiography with Retained Stone. (**a**). Left hepatic duct. (**b**) Right hepatic duct. (**c**) Common hepatic duct. (**d**) Cystic duct stump. (**e**) Common bile duct. (**f**) Retained stone. (**g**) Distal obstruction of the common bile duct. Intraoperative cholangiogram demonstrating emulation of the cystic duct with filling of the intrahepatic bile ducts. Initial images demonstrate a filling defect in the distal common bile duct (**f**) and truncation of the duct at the ampulla suggesting stone obstruction (**g**)

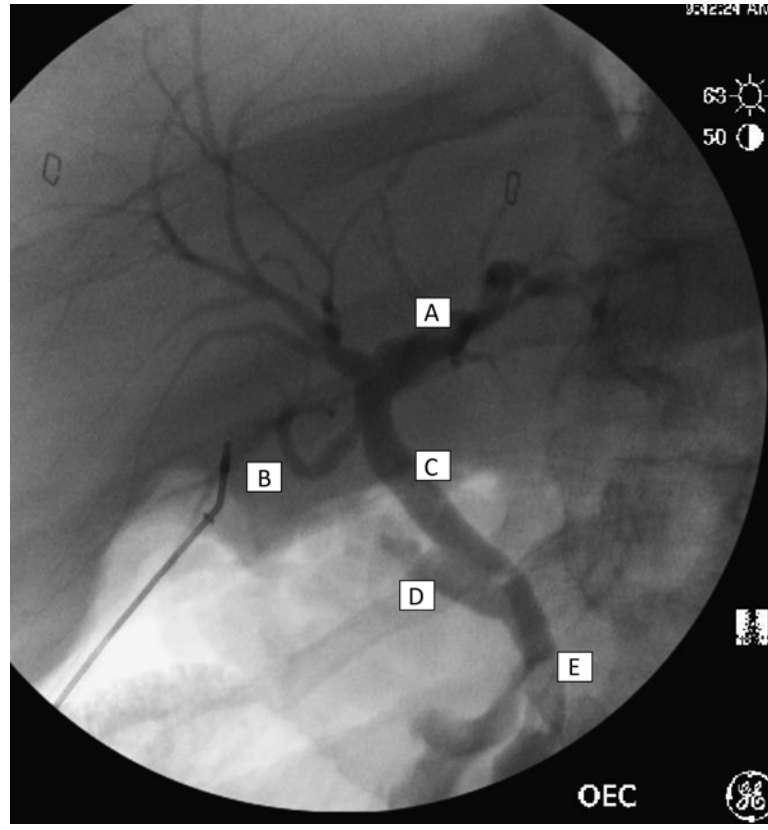

Fig. 9.6 Intraoperative Cholangiography of Right Hepatic Duct Injury. (**a**) Left hepatic duct. (**b**) Injured right hepatic duct. (**c**) Common hepatic duct. (**d**) Cystic duct stump. (**e**) Common bile duct. A transected right hepatic duct is opacified (**b**) showing anomalous insertion of the duct into the common ectatic duct below the confluence. The common hepatic (**c**) and common bile duct (**e**) are patent. The cystic duct and the small gallbladder infundibulum remnant (**d**) are visible. Right and left bile duct bifurcations are visible

and observed an increased operative time, rate of laparoscopic converted to open procedure, and length of postoperative and overall hospitalization with increased length of preoperative hospitalization [66].

When necessary, common bile duct imaging may be performed preoperatively [i.e., endoscopic retrograde cholangiopancreatography (ERCP) or magnetic resonance cholangiopancreatography (MRCP)], intraoperatively (i.e., cholangiography), or postoperatively (i.e., ERCP or MRCP) [10]. However, this should be reserved for patients suspected of having concomitant choledocolithiasis, gallstone pancreatitis, jaundice, increased hepatic enzyme levels, or a dilated common bile duct. A meta-analysis performed by Sajid et al., evaluated four randomized control trials encompassing 860 patients undergoing cholecystectomy. Of these, 427 underwent routine on-table cholangiography, and 433 did not. Routine on-table cholangiography was observed to be helpful for perioperative common bile duct stone detection (Fig. 9.5); however, it resulted in increased operative time and perioperative complications compared to no cholangiography [67]. Additionally, a difference in common bile duct injury was not appreciated between the two groups, intraoperatively. That being said, previous studies have shown that if a common bile duct injury is detected intraoperatively, hospital mortality rates, postoperative biliary complications, and reinterventions may be reduced (Fig. 9.6) [68].

Cholecystectomy is not always possible during the index hospitalization, however. Patient acuity may dictate that cholecystectomy be delayed until further stabilization is achieved. In these circumstances, percutaneous cholecystostomy for gallbladder decompression and medical management are performed [12]. Medical management includes intravenous fluid resuscitation, bowel rest (nil per os [NPO]), and antibiotics if clinical and radiological evidence suggest infectious etiology (Tables 9.3, 9.4, 9.5, and 9.6). It is important to note, however, that percutaneous cholecystostomy is only a temporizing measure and completion cholecystectomy should be performed once patient stability has been achieved, as gallstone-related readmission rates may be as high as 50 %, 1-year following discharge [69]. In the setting of acalculous cholecystitis; however, interval cholecystectomy may be avoided if an unobstructed duct and absence of gallstones are demonstrated. Alternatively, the acuity of the disease process and associated inflammation may increase the risk of intraoperative injury (e.g., bile duct or hepatic artery). In this situation, performing a cholecystectomy may be unsafe and partial cholecystectomy is an alternative choice [70]. This procedure avoids dissection of Calot's triangle, and possibly the need for a second operation.

A few select cases do not require operative intervention. These are primarily limited to viral-induced acute cholecystitis, and include infections with hepatitis A, flavivirus, and Epstein–Barr virus [48–53]. Management of these patients primarily involves supportive care unless gallbladder gangrene, emphysema, or perforation is observed.

More recently, alternative surgical procedures have been developed for cholecystectomy. These include, but are not limited to single incision laparoscopic cholecystectomy, natural orifice transluminal endoscopic cholecystectomy, and robotic cholecystectomy. Due to cost issues, technical difficulty, increased operative time, and a lack of proven benefit over laparoscopic cholecystectomy, they have not gained popularity [10, 64, 71].

Complications

Following laparoscopic cholecystectomy, the majority of patients with acute cholecystitis will experience an uncomplicated surgical and postoperative recovery period. However, those who experience a complication may be at increased risk for prolonged recovery and increased cost, morbidity, and mortality. Complications may be defined as occurring intraoperatively or postoperatively and have a combined incidence of 9–19.6 % [68, 72–74]. Postoperative complications may be further broken down into local or systemic.

The incidence of intraoperative complications among patients with acute cholecystitis ranges

between 2.8 and 13.1 % [72, 74]. The most common intraoperative complications include needle and trocar insertion errors (0.18–1 %) and bleeding (1–8 %) [68]. The most serious intraoperative complication is a common bile duct injury that is unrecognized and results in increased mortality (0.4–0.7 %). Additional intraoperative complications include bowel or colon injury, injury to the hepatic artery, and unintentional injury/opening of the gallbladder [72–74]. Giger et al., retrospectively evaluated 22,953 patients (Swiss Association of Laparoscopic and Thoracoscopic Surgery Database) undergoing laparoscopic cholecystectomy for acute and chronic cholecystitis. Using multivariable analysis, the authors observed that male gender, age, increased body weight, increased operative time, and surgeon experience independently predicted intraoperative complication [72].

As a result of intraoperative complications (e.g., bile duct injury or bleeding), difficulty with surgical exposure, inability to identify anatomical structures (e.g., triangle of Calot or cystic duct), and/or intrahepatic gallbladder presence, surgeons may elect to convert from laparoscopic to open cholecystectomy (1.5–35 %) [72, 73]. A meta-analysis by Tang et al., reviewed 109 publications (68 retrospective, 16 prospective nonrandomized, eight prospective randomized control trials, five prospective case-controlled studies, five reviews, three observational studies, two population-based studies, one national survey, and one editorial) on laparoscopic to open cholecystectomy conversions [75]. Based upon their observations, specific patient characteristics (i.e., male gender, old age, morbid obesity, prior abdominal surgery, comorbid cardiopulmonary disease, and severe/emergent gallbladder disease), disease-related characteristics (i.e., gangrenous or empyema-related cholecystitis, cirrhosis, concomitant pancreatitis, retained stone, or concomitant cancer), and surgeon-related characteristics (i.e., caseload, proficiency, or intraoperative complication) appeared to be associated with increased risk for laparoscopic to open cholecystectomy conversion. While patients who require laparoscopic to open cholecystectomy conversion may be expected to experience longer operating time, greater morbidity (20 % greater than patients who underwent successful laparoscopy), longer hospital stay, and greater cost (30 % greater than patients who underwent successful laparoscopy), it should not be viewed as a complication or failure. Rather, surgeons should convert expeditiously as prolonged operating time has also been associated with increased complication, as previously mentioned [72].

Postoperative local complications have previously been observed to occur at an incidence of 5.9 % [72]. These include bleeding, bowel injury, biloma, cystic duct leak, common duct injury, chyle leak, and surgical site infection [72, 74, 76]. Risk factors determined to be independently predictive of postoperative local complications include conversion to open surgery, increased operative time, increased age, emergency surgery, male gender, presence of intraoperative complication, increased body weight, and an American Society of Anesthesiologists (ASA) risk score >2 [72]. Surgical site infection may be defined as superficial, deep, and/or organ space and is most commonly caused by gallbladder perforation secondary to tissue fragility; however, it may also be caused by hepatic bed injury or cystic clip migration [73, 77]. As a result, bile, stones, and/or other colonizing or infecting pathogen may leak into the intraperitoneal space (more commonly the infrahepatic space) or wound (more commonly the umbilical trocar site) [73]. If an intraperitoneal bile leak is suspected intraoperatively, options include saline irrigation and/or prophylactic drain placement. Alternatively, radiologic drain placement along with antibiotics may be used should an abscess develop postoperatively.

Postoperative systemic complications have previously been observed to occur with an incidence of 6.3 % [72]. These include pulmonary embolism, myocardial infarction, sepsis, and acute renal failure [72, 74]. Risk factors determined to be independently predictive of postoperative systemic complications include conversion to open surgery, emergency surgery, increased age, and increased operating time [72]. The mortality rate has previously been observed to range from 0 to 5 % [73].

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Gallstone Pancreatitis

10

Brandon A. Guenthart and Thomas J. Fahey III

Introduction

Gallstone disease is the most common cause of acute pancreatitis in the Western hemisphere, accounting for 35–75 % of cases [1]. Although it is a disease that often has a mild course, which typically subsides in 3–5 days, it can be severe and have an associated mortality as high as 5–10 % [2]. The recognition and diagnosis of acute pancreatitis is essential. Understanding the underlying etiology, severity of disease, and available therapeutic options are all equally important in the treatment of patients affected with this disease.

Epidemiology

Gallstone pancreatitis is most common in women in their sixth or seventh decade of life. It is less common in men and younger individuals. The annual incidence in the United States is 40 cases per 100,000 adults, and the incidence is increasing, both in the United States and in the United Kingdom [2–4]. Many have speculated that this observed increase is related to the ongoing obesity epidemic [5, 6]. As the incidence has risen, so too have the number of hospital admissions. The financial impact related to hospitalizations for acute pancreatitis now totals $2.2 billion annually [7, 8].

Risk factors for gallstone pancreatitis are the same risk factors we attribute to gallstone formation. These include: rapid weight loss, female gender, age >60, obesity, pregnancy, cholesterol-reducing drugs, cirrhosis, and diabetes. A large cystic duct >5 mm, greater than 20 stones, and small stones <0.5 mm have been proposed as additional risk factors [9].

Etiology and Pathogenesis

In the United States and the rest of the Western world, gallstone disease is the most common cause of acute pancreatitis. Gallstones, microlithiasis, and biliary sludge account for 35–75 % of cases [10]. Alcohol is the second leading cause, and should be considered in patients with chronic pancreatitis or a history of alcohol abuse even when concurrent cholelithiasis is found.

The association between gallstones and pancreatitis was first described in 1901 by Opie [11]. Subsequently, many have sought to better understand exactly how gallstones elicit the inflammatory response in acute pancreatitis. Gallstones are found in the feces of up to 85–90 % of patients with gallstone pancreatitis as compared to only 10 % of patients with symptomatic

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cholelithaisis with no pancreatitis [12]. This suggests that the pancreaticobiliary obstruction is transient and stones often pass spontaneously into the duodenum.

The obstruction of the bile or pancreatic duct by an impacted or passing stone is the most widely accepted mechanism behind gallstone pancreatitis. Reports of early autopsy specimens published in the 1890s described the morphologic appearance of the pancreas in cases of acute pancreatitis suggesting the disease is caused by autodigestion [13]. Even now, after years of investigation and an impressive body of research, the process of autodigestion and activation of intracellular enzymes within the pancreas is not fully understood. Under normal conditions cholecystokinin (CCK) stimulates the acinar cells of the pancreas, triggering its exocrine function. The biogenesis of pancreatic digestive enzymes includes several proteolytic steps, with the final step and activation occurring in the luminal space of the duodenum [14]. Enterokinase located on the duodenal mucosa converts trypsinogen to trypsin, and once in its active form trypsin is responsible for converting the inactive pancreatic enzymes (zymogens) into their active state.

There are several protective mechanisms in place to prevent the premature activation of these enzymes within the pancreas. These include the delayed luminal activation of trypsinogen in the duodenum, the pancreatic sphincter, and exocrine secretions and mucosal barriers aimed at inhibiting protease activity. However, in gallstone pancreatitis at least one of these mechanisms fails, leading to premature enzyme activation and acinar cell damage and inflammation. Recent animal studies suggest that a lysosomal cystein proteinase, cathespin B, plays an important role in intrapancreatic trypsinogen activation leading to acute pancreatitis [15]. This activation causes systemic effects and resultant multiple organ dysfunction, similar to the cascade of events observed in trauma, severe burns and sepsis. Key inflammatory mediators involved in acute pancreatitis include: TNF-alpha, IL-1beta, IL-6, IL-8, PAF, IL-10, C5a, ICAM-1, and substance P [16].

Presentation

Pain is the most common presenting complaint in patients with gallstone pancreatitis. Pain often begins abruptly, and is severe and unrelenting. It can be localized to the right upper quadrant or epigastric region, but can also be more diffuse. Approximately 50 % of patients will also complain of pain radiating to the back [17]. Like acute cholecystitis, pain is often exacerbated with eating, and patients generally present with anorexia. Patients with severe gallstone pancreatitis may present with symptoms of severe dehydration and SIRS, such as altered mental status. Nausea and vomiting are frequent associated symptoms. Few patients will provide a history of biliary colic, and a thorough history should be obtained to help rule out less common causes of pancreatitis, such as alcohol abuse, recent endoscopic retrograde cholangiopancreatography (ERCP), medication use, and recent viral/bacterial infections.

Physical examination findings vary based on the severity of disease. In mild cases, patients will have minimal to moderate abdominal tenderness. In severe cases of gallstone pancreatitis, patients may have impressive abdominal tenderness, with an abdominal examination mimicking a surgical abdomen. Severe peripancreatic inflammation may cause a generalized ileus and hypoactive bowel sounds on examination. Patients with severe dehydration due to fluid sequestration and vomiting may show signs of shock such as hypotension, tachycardia, tachypnea, and lethargy.

Diagnosis

Laboratory Evaluation

Although there is not a single biochemical "gold standard," laboratory testing is useful in both diagnosing gallstone pancreatitis and in assessing the severity of disease. Serum amylase and lipase are important markers of pancreatic inflammation. Advantages of measuring serum amylase include that it is easy to measure and consequently is widely available. Serum amylase increases 2–12 h after onset and normalizes in 3–5 days.

Though it has a high sensitivity for the diagnosis of pancreatitis, perhaps its greatest disadvantage is a relatively low specificity and thus, a high false positive rate. The pancreas is not the only source of amylase, and in fact, in normal circumstances, as much as 65 % of amylase arises from the salivary glands. In contrast, serum lipase has a higher sensitivity (85–100 %) and specificity (95–100 %) [18, 19]. Lipase is primarily produced by pancreatic acinar cells. However, it should be noted that nonspecific elevations in lipase have been reported in many conditions, slightly decreasing its specificity for acute pancreatitis. Serum lipase peaks at 24 h after onset and stays elevated longer than amylase, and thus is a better marker for pancreatitis in patients who present days after the onset of their pain [20]. The degree of elevation of amylase and lipase does not correlate with severity of disease, and once the diagnosis of acute pancreatitis is made, daily measurement should be discouraged. The trend of amylase and lipase does not correlate with clinical progress or overall prognosis [21].

A basic metabolic panel is valuable in detecting metabolic derangements, including acute kidney injury, hyperglycemia, and hypocalcemia. Obtaining a complete blood count will identify the degree of leukocytosis and hemoconcentration. These markers are essential in determining disease severity (see section "Severity of Disease"). A serum triglyceride level and calcium level should be examined to rule out hypertriglyceridemia and hypercalcemia as possible causes of pancreatitis. If autoimmune pancreatitis is suspected, IgG4 should be examined [22].

Liver function testing may reveal a transaminitis and elevation in serum bilirubin. While gallstone pancreatitis inevitably involves some degree of biliary obstruction, in most cases this is transient and thus there is variability in liver function test (LFT) abnormality. LFTs may be normal in up to 10 % of patients with gallstone pancreatitis [23]. A serum alanine aminotransferase (ALT) three times the normal value has a positive predictive value (PPV) of 95 % in distinguishing gallstone pancreatitis from other causes of acute pancreatitis [24].

Imaging Modalities

Imaging in patients with acute pancreatitis can help determine etiology (e.g., gallstones, neoplasms, and anatomic variants such as pancreas divisum). In patients with gallstone pancreatitis, imaging helps complement physical examination findings and laboratory testing to stratify patients and provide appropriate care. Imaging can also be used to assess the severity of disease and degree of peripancreatic inflammation or parenchymal necrosis and, in many cases, identify complications such as pseudocysts, fluid collections, or hemorrhage.

All patients presenting with pancreatitis without an obvious source should undergo dedicated right upper quadrant ultrasonography. Ultrasound can identify cholelithiasis with greater than 95 % sensitivity, and this widely available, noninvasive test offers the advantage of speed at little cost. Ultrasound may fail to detect stones smaller than 4 mm, and its sensitivity in detecting choledocholithiasis ranges from 40 to 60 % [25]. Although ultrasound can identify pancreatic edema, it is a poor study to gauge disease severity of pancreatitis. Despite its limitations, ultrasound remains the first test of choice to make a diagnosis of gallstone pancreatitis. When severe disease or common bile duct stones are suspected, further imaging is indicated.

Contrast-enhanced computed tomography (CT) has a high sensitivity in detecting pancreatic necrosis, and thus is useful in moderate and severe cases. A repeat CT at 3–4 days can also be helpful in determining progression of disease. Obtaining a pancreas protocol CT entails thin cuts (2–3 mm) through the pancreas during two phases. The first phase is referred to as the arterial or pancreas phase, during which the pancreas parenchyma, celiac plexus, and superior mesenteric artery are filled with contrast. Later, the venous phase allows for visualization of the superior mesenteric, portal, and splenic veins [26]. CT is less sensitive than ultrasound in detecting cholelithiasis; however, it is 75–95 % sensitive in detecting a dilated common bile duct or choledocholithiasis. Routine use of CT on admission is not recommended, as traditional

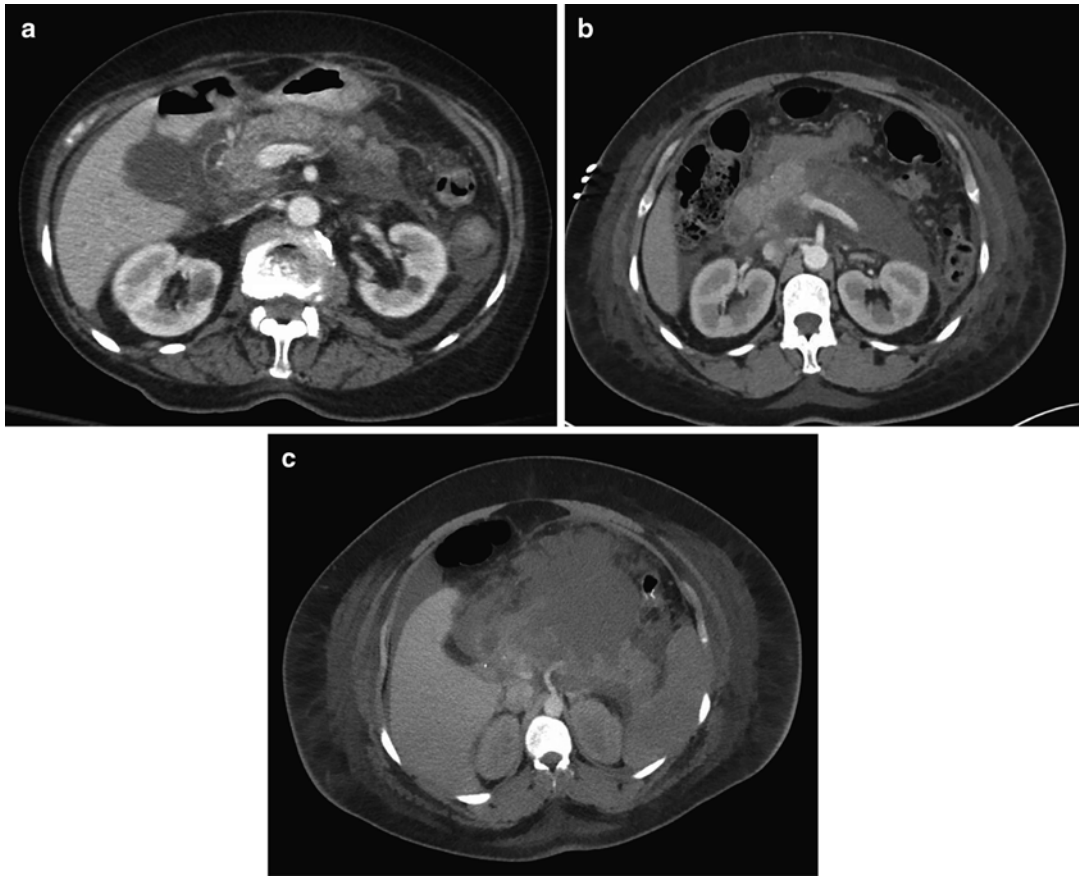

Fig. 10.1 (**a**) Peripancreatic inflammation and fluid. (**b**) Irregular heterogenous enhancement of the pancreatic gland with peripancreatic inflammation and fluid suggestive of pancreatic necrosis, along with mesentery infiltration. (**c**) Severe pancreatic necrosis with surrounding fluid and phlegmon

scoring systems to estimate severity have been shown to be equally effective [27, 28]. However, in patients with severe disease who present with an acute abdomen, CT can provide key information to establish a diagnosis, and determine the degree of inflammation, necrosis, presence of complications such as fluid collections, or evaluate for signs of superinfection (Fig. 10.1). Balthazar et al. developed a grading system based on CT features of acute pancreatitis to stratify patients [29] (see section "Severity of Disease").

Although more expensive and less available, magnetic resonance imaging (MRI) with gadolinium contrast is a reliable method in the evaluation of acute pancreatitis. MRI has fewer contraindications than CT, and is an ideal substitute in pregnant patients or those with renal insufficiency. It is especially useful in visualizing complications of gallstone pancreatitis such as hemorrhage and has the ability to differentiate fluid collections from liquefied necrosis [30]. Magnetic resonance cholangiopancreatography (MRCP) involves a specific MRI protocol designed to enhance the fluid signal within the biliary system allowing for more accurate delineation of biliary and pancreatic anatomy. Filling defects and anatomic disruptions in the pancreatic duct can be better appreciated, and many clinicians use MRCP as a screening tool to select patients for ERCP. The sensitivity of MRCP for detecting choledocholithiasis has been reported to be 85–90 %, making it an ideal study when CBD stones are suspected [31].

Severity of Disease

In gallstone pancreatitis there is a wide spectrum of disease. Although as many as 80 % of patients will have a benign course, the remaining 20 % can have severe disease with a mortality rate in this group as high as 30 % [32, 33]. Mortality associated with this disease is often due to multisystem organ failure (MOF) and later to septic complications of pancreatic necrosis. Many have sought to develop prognostic scoring systems or markers in order to identify patients most at risk. Multiple studies have evaluated the ability of clinicians alone to differentiate between mild and severe AP. Sensitivity of clinical assessment alone ranges from 34 to 64 %, suggesting that without additional disease severity stratification tools, many patients with severe pancreatitis might not be triaged to the appropriate level of care [34, 35].

Ranson Criteria

Ranson Criteria (Table 10.1) is the most frequently used multifactorial scoring system in the United States. It was first introduced by Ranson et al. in 1974 to score the severity of alcoholic-induced pancreatitis and later modified for gallstone pancreatitis in 1979 [36]. It is based on 11 clinical and laboratory data points in nonbiliary pancreatitis, and ten data points in gallstone pancreatitis (arterial oxygen saturation (PaO_2) is omitted from the original scoring system). Data points are collected at presentation and at 48 h into the hospital course. A score of three or more is the cutoff for severe pancreatitis, however, mortality predictions are not accurate until 48 h into the course of acute pancreatitis.

Table 10.1 Ranson criteria

	Gallstone pancreatitis	Nongallstone pancreatitis
At admission		
Age (years)	>70	>55
WBC (cells/μL)	>18 K	>16 K
Blood glucose (mg/dL)	>220	>200
Serum AST (U/L)	>250	>250
Serum LDH (U/L)	>400	>350
At 48 h		
Serum calcium (mmol/L)	<8	<8
Hematocrit fall (%)	>10	>10
PaO_2 (mmHg)	Omitted	<60
BUN increase (mg/dL)	>2	>5
Base deficit (mEq/L)	>6	>4
Sequestration of fluid (L)	>4	>6

APACHE-II

The Acute Physiology and Chronic Health Evaluation II (APACHE-II) scoring system was developed by Knaus et al. in 1985 [37]. It was initially developed to estimate mortality in all patients admitted to an intensive care unit (ICU) but has been widely applied to patients with acute pancreatitis. It offers a distinct advantage over Ranson Criteria because it can be calculated at any time during the hospital admission, and changes in the APACHE-II score have been shown to correlate with clinical improvement or deterioration. The score is a composite of 12 individual variable points, age points, and chronic health points (Table 10.2). Calculating an

Table 10.2 APACHE-II parameters and units of measurement

Age (years)
Temperature (°C)
Mean arterial pressure (mmHg)
pH
Heart rate (beats per min)
Respiratory rate (breaths per min)
Serum sodium (mEq/L)
Serum potassium (mEq/L)
Serum creatinine (mg/dL)
Hematocrit (%)
WBC (cells/μL)
Glasgow-coma-scale (points)
A—a gradient (if $FiO_2 \geq 0.5$) (mmHg)
PaO_2 (if $FiO_2 < 0.5$) (mmHg)
History of organ insufficiency
History of immunocompromise

Table 10.3 The APACHE-II severity of disease classification system

Physiologic variable	+4	+3	+2	+1	0	+1	+2	+3	+4
Temperature—rectal (°C)	≥41	39–40.9		38.5–38.9	36–38.4	34–35.9	32–33.9	30–31.9	≤29.9
Mean arterial pressure (mmHg)	≥160	130–159	110–129		70–109		50–69		≤49
Heart rate	≥180	140–179	110–139		70–109		55–69	40–54	≤39
Respiratory rate (nonventilated or ventilated)	≥50	35–49		25–34	12–24	10–11	6–9		≤5
Oxygenation (mmHg) a. $FiO_2 > 0{,}5$ use $A\text{-}aDO_2$	a ≥500	350–499	200–349		<200				
b. $FiO_2 < 0{,}5$ use PaO_2	b				>70	61–70		55–60	<55
Arterial pH	≥7.7	7.6–7.69		7.5–7.59	7.33–7.49		7.25–7.32	7.15–7.24	<7.15
Serum sodium (mmol/L)	≥180	160–179	155–159	150–154	130–149		120–129	111–119	<110
Serum potassium (mmol/L)	≥7	6–6.9		5.5–5.9	3.5–5.4	3–3.4	2.5–2.9		<2.5
Serum creatinine (mg/dL, Double point score for acute renal failure)	≥3.5	2–3.4	1.5–1.9		0.6–1.4		<0.6		
Hematocrit (%)	≥60		50–59.9	46–49.9	30–45.9		20–29.9		<20
White blood count (in 1000/mm^5)	≥40		20–39.9	15–19.9	3–14.9		1–2.9		<1
Glasgow-Coma-Scale (GCS)	Score = 15 minus actual GCS								
Serum HCO_3 (venous, mmol/L, use if no ABGs)	≥52	41–51.9		32–40.9	22–31.9		18–21.9	15–17.9	<15
A = Total Acute Physiology Score APS		Sum of the 12 individual variable points							
B = *Age points*		*C = Chronic Health Points*							
≤44 years	0 points	If the patient has a history of severe organ system insufficiency or is immunocompromised, assign points as follows:							
45–54 years	2 points								
55–64 years	3 points	a. For nonoperative or emergency postoperative patients—5 points							
65–74 years	5 points	b. For elective postoperative patients—2 points							
≥75 years	6 points								
APACHE-II Score = Sum of A (*APS points*) + B (*Age points*) + C (*Chronic Health points*)									

APACHE-II score can be cumbersome (Table 10.3), and this difficulty in clinical practice is often cited as its greatest shortcoming. An APACHE-II score of eight or above is indicative of severe disease [38].

(From: Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE-II: a severity of disease classification system. Crit Care Med 1985; 13(10):818-29)

Glasgow Score

The Glasgow Score, also known as the Glasgow-Imrie Score, is a modification of Ranson's criteria, that includes age and laboratory data points with alerted cut offs. Hematocrit, base deficit, and fluid sequestration are omitted from this system, while albumin is included. It was published by Imrie et al., in 1984, but its current use is lim-

Table 10.4 Glasgow score parameters

P	– PO_2 (mmHg)		<60
A	– Age (years)		>55
N	– Neutrophills/WBC (cells/μL)		>15 K
C	– Calcium (mmol/L)		<2
R	– Renal function/Urea (mmol/L)		>16
E	– Enzymes	ALT (U/L)	>100
		LDH (U/L)	>600
A	– Albumin (g/L)		<32
S	– Sugar/glucose (mg/dL)		>180

Table 10.5 CT severity index (CTSI)

Grading of pancreatitis		Score		Degree of necrosis	Score
A	Normal pancreas	0	+	0 %	0
B	Enlargement of the pancreas	1		≤30 %	2
C	Inflammatory changes in the pancreas and peripancreatic fat	2		30–50 %	4
D	Findings of grade C plus 1 fluid collection	3		>50 %	6
E	Findings of grade C plus 2 or more fluid collections, and/or the presence of gas in or adjacent to the pancreas	4			

ited to Europe. The Glasgow score has been shown to be equally effective in predicting mortality and is as accurate (though not better than) Ranson's criteria [35, 39]. Like the Ranson criteria the Glasgow score also requires 48 h to complete; and a score of three or greater is indicative of severe pancreatitis (Table 10.4).

CT Severity Index

Balthazar et al. introduced the CT Severity Index (CTSI). Its aim is to grade the severity of acute pancreatitis radiographically and does not take into account clinical parameters [29]. CTSI combines the morphologic features of the pancreas including the degree of pancreatic and peripancreatic inflammation with the degree of necrosis (Fig. 10.1 and Table 10.5). Subsequent modifications of the CTSI have been proposed, but when compared head-to-head with the CTSI of Balthazar, no significant differences were noted in their ability to evaluate the severity of acute pancreatitis. The CTSI score not only correlates with disease severity and mortality, it has also been shown to correlate with the duration of hospitalization, and need for necrosectomy [28]. The CT findings are scored from 0 to 10, and a score of two or greater is indicative of moderate disease. Scores greater than six are associated with higher rates of complications and death [40, 41].

Biochemical Markers of Severity

C-reactive protein (CRP) is the best laboratory marker of disease severity. In a multicenter prospective study, CRP levels of >150 mg/L at 48 h after symptom onset was significant in differentiating cases of mild and severe acute pancreatitis [42]. Although CRP is unable to identify necrotizing pancreatitis or predict mortality, serial measurements can help to identify the development of localized complications. CRP is widely used in Europe but has not been adopted as standard practice in the United States. Several initial studies showed promising results with regard to the predictive value of procalcitonin (PCT), however, newer evidence suggests that the measurement of PCT is of limited value [42]. Several new serologic and urinary markers of severity are being investigated but remain experimental. These include, urinary trypsinogen activation peptides, and cytokines IL-6 and IL-8.

Revised Atlanta Classification (2012)

In 1992, the Atlanta Symposium attempted to standardize and create a globally accepted classification of acute pancreatitis and its complications. Better understanding of the etiology and pathophysiology of this disease has led to the most recent 2012 revision [43] (Table 10.6).

Table 10.6 Atlanta criteria for severity of acute pancreatitis

Grades of severity		Supplemental definitions	
Mild	– No organ failure	Organ failure	– SBP <90 mmHg, not responsive to fluid
	– No local or systemic complications		– Serum Cr >2 (after resuscitation)
			– PaO_2/FiO_2 <200
Moderate	– Transient organ failure (<48 h) and/or	Local complications	– Peripancreatic fluid collections
	– Local or systemic complications without persistent organ failure		– Acute necrotic collections
Severe	– Persistent organ failure (>48 h), single or multiple organ failure	Systemic complications	– Exacerbations of underlying comorbidities

Treatment

Mild Disease

Initial management in patients with gallstone pancreatitis with mild disease (Ranson <3, APACHE-II <8, CTSI <2) is largely centered on supportive care. This involves correcting metabolic derangements, aggressive fluid resuscitation with intravenous fluids, and pain control. Patients can be triaged to a regular floor or monitored unit. These patients are generally kept NPO until pain control is optimized and enteral feeding can be tolerated. Early enteral feeding has been shown to be safe and effective in reducing hospital length of stay [44]. However, feeding should be avoided if it interferes with early cholecystectomy. In patients with mild disease, and without concomitant cholecystitis, use of prophylactic antibiotics does not reduce morbidity or mortality [45, 46].

The clinical practice and management of potential CBD stones in patients with mild disease varies greatly. Some surgeons image the CBD routinely preoperatively with MRCP, ERCP, or endoscopic ultrasound (EUS), while others routinely perform intraoperative cholangiogram (IOC) or laparoscopic ultrasound. The current trend is towards a more selective approach when clinical suspicion is high. As many as 95 % of stones in gallstone pancreatitis pass spontaneously and routine imaging is often unnecessary and costly. Previous data promoting ERCP in the first 24 h for all-comers of gallstone pancreatitis has been challenged [47]. There is now ample evidence to show that ERCP has no diagnostic or therapeutic role in patients with mild gallstone pancreatitis and no evidence of biliary obstruction [48, 49].

Historically, surgical intervention was delayed 6–8 weeks following an acute attack of pancreatitis to allow for inflammation to subside [50]. This approach led to high readmission rates and complications of recurrent attacks. If cholecystectomy is not performed, the risk of recurrence of biliary pancreatitis or other biliary events is as high as 75 %, with 50 % of the recurrent episodes occurring in the first 90 days [51–53]. These data have led to the widely accepted principal that cholecystectomy should be performed during the index hospitalization. Most surgeons choose to schedule surgery when the pancreatitis and peripancreatic inflammation is improving, using resolution of pain and normalization of liver chemistries and pancreatic enzymes as their guide. Aboulian et al., demonstrated that early laparoscopic cholecystectomy within 48 h of admission, regardless of pain or laboratory values, did not compromise patient safety and resulted in shorter hospitalizations [54]. Several subsequent studies have supported these conclusions [55]. Thus, in patients with mild disease, early cholecystectomy should be considered when laboratory values are trending toward normal.

Severe Disease

Patients with severe disease (Ranson >3, APACHE-II >8, CTSI >2) require admission to an intensive care unit (ICU). In addition to standard laboratory exams, an ABG should be obtained and repeated to ensure proper tissue oxygenation. A nasogastric tube (NGT) and Foley catheter should also be placed. The correction of metabolic derangements, aggressive fluid resuscitation with intravenous fluids, and pain control are again the guidelines of supportive care. Low serum bicarbonate and base deficit are signs of underresuscitation, while a continual decrease in hematocrit or SaO_2/PaO_2 during resuscitation can be signs of worsening inflammation. The use of prophylactic antibiotics in patients with severe gallstone pancreatitis without concomitant cholangitis is controversial. Previous data in the 1990s suggested that prophylactic antibiotic use in patients with pancreatic necrosis decreased the rates of infectious complications, but did not alter overall mortality. Subsequent trials, and a recent systemic review and meta-analysis, however, failed to demonstrate a reduction in mortality or infectious events [56]. Current use of prophylactic antibiotics is not recommended.

Repeat imaging with CT or MRI should be obtained in 48–72 h to monitor for disease progression and detect complications such as peripancreatic fluid collections, necrosis, or signs of infection (air bubbles in areas of necrosis). Pancreatic necrosis can occur in as many as 50 % of patients with severe gallstone pancreatitis. Close clinical observation and a high degree of suspicion for infected pancreatic necrosis should be pursued in patients with fever, persistent leukocytosis, or signs of sepsis. Infection of peripancreatic fluid or areas of necrosis can occur in 30–70 % of cases of necrotizing pancreatitis, and usually occurs 2–3 weeks after the onset of disease. The diagnosis can be made by CT-guided fine-needle-aspiration (FNA) or via specimens obtained at the time of surgery. Once the diagnosis is made, necrosectomy, surgical debridement, or immediate radiographically guided-drainage, should be strongly considered.

Acute cholangitis is seen in 10 % of patients with severe gallstone pancreatitis, and urgent ERCP is indicated [57]. The role and timing of ERCP in severe gallstone pancreatitis in patients without cholangitis remains controversial despite extensive investigation. Currently, the use of ERCP should be targeted to those patients with severe gallstone pancreatitis complicated by biliary sepsis and cholangitis [49, 58]. Unlike mild gallstone pancreatitis, early surgical intervention in severe gallstone pancreatitis is associated with increased mortality, and increased infectious complications and sepsis [59, 60]. Suggested time intervals for delayed cholecystectomy range from 3 weeks to 3 months. Imaging may be useful to help guide surgical timing and aid in diagnosing complications such as pseudocysts.

Special Patient Populations

Unfit surgical candidates due to age and comorbid conditions can be managed with ERCP with endoscopic sphincterotomy (ES) as an alternative to laparoscopic cholecystectomy. Although recurrent attacks of pancreatitis are low, two randomized controlled trials have shown a high incidence of recurrent biliary disease and both advocate for cholecystectomy when patients are able to undergo the procedure [61, 62].

Pregnancy increases the risk of gallbladder disease, and its incidence, including acute cholecystitis and gallstone pancreatitis, in pregnancy ranges from 0.05 to 0.8 % [63]. If there is need for CBD imaging MRI/MRCP or EUS is recommended over diagnostic ERCP and CT to limit fetal exposure to radiation. Previous recommendations regarding surgical management warned against operative intervention during the first and third trimesters. Recent guidelines produced by the Society of American Gastrointestinal and Endoscopic Surgeons promote the use of laparoscopic surgery in any trimester of pregnancy [64]. They cite considerable data pointing to the improved safety of surgical intervention, and the significant morbidity and mortality associated with untreated gallbladder

disease and recurrent attacks. They propose that the indications for laparoscopic cholecystectomy for the general population be applied to the pregnant patient as well.

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Management of Cholecystitis in High-Risk Patients

11

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Introduction

The most common major abdominal operation in the Western Hemisphere is cholecystectomy [1]. In the United States alone, gallstone disease affects over 20 million people and is associated with $6.3 billion in direct costs annually [2, 3]. One factor that may contribute to these costs is the high rate of recurrence after initial presentation such that certain patients undergo multiple admissions and treatment regimens for the same disease process which has a nearly curative but potentially complication-fraught solution. For patients with acute cholecystitis and mild gallstone pancreatitis, evidence exists to support cholecystectomy within 48 h of presentation [4, 5] but only 40–75 % of patients with acute cholecystitis, gallstone pancreatitis, and common bile duct stones undergo cholecystectomy on initial hospitalization [6–8]. This rate of recurrence varies depending on the type of biliary disease which has been reported to be 6–50 % for acute cholecystitis [6, 9, 10], 5.3–50 % for common bile duct stones [11–13], and 16–76 % for gallstone pancreatitis [14–19].

Presumably, the major reason for this discrepancy between the need for cholecystectomy and the actual practice of the procedure in individual patients may be due to the preoperative categorization of certain patients as "high risk." Categorizing a patient in this manner is highly arbitrary in many cases but can follow predefined factors frequently used to assess operative risk including American Society of Anesthesiologists (ASA) class, age, and the presence of certain comorbidities. In this chapter, the relative value of each method of operative risk stratification for patients with biliary disease is discussed as well as the strategies available to manage "high-risk" patient with acute cholecystitis.

Stratifying Risk for Patients with Acute Cholecystitis

ASA Class

The original ASA system was created in 1941 [20] but since then has undergone modifications [21]. The ASA classification is used worldwide in different types of institutions to assess perioperative risk. This system consists of six categories of physical status ranging from status 1—a "normal" healthy patient to status 6—a brain-dead patient undergoing organ donation (Table 11.1).

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Different studies have shown the ability of the ASA scheme in paralleling operative risk. One analysis retrospectively examined 108,878 surgeries and showed that ASA class 4 patients displayed mortality rates ranging from 10–30 % (Fig. 11.1) [22] while a separate analysis of 5878 surgical patients similarly revealed ASA to correlate with postoperative outcomes [23].

The ASA classification has enjoyed its widespread use by its simplicity. Being fairly nonspecific allows it to be memorized by anesthesia personnel and be frequently utilized. However, the limitations are plentiful. One limitation of the ASA class is that it does not take into account the nature of the surgery [24], the experience of the anesthesiologist or the surgeon, and the type of facility in which the surgery is being performed [25–27]. Another limitation of the ASA system is that it does specifically not account for certain patient factors such as age, sex, body mass index, or pregnancy [25–27]. In addition, there is significant variability in interpretation of the categories among anesthesiologists [28].

Table 11.1 American Society of Anesthesiology classification system

ASA physical status 1	A normal healthy patient
ASA physical status 2	A patient with mild systemic disease
ASA physical status 3	A patient with severe systemic disease
ASA physical status 4	A patient with severe systemic disease that is a constant threat to life
ASA physical status 5	A moribund patient who is not expected to survive without the operation
ASA physical status 6	A declared brain-dead patient whose organs are being removed for donor purposes

The ASA system has been studied for operations pertinent to biliary disease. In a study of the National Surgical Quality Improvement Program (NSQIP) database, the authors retrospectively analyzed data from 2005 to 2008 in 65,511 cholecystectomies performed. Of these patients, 58.2 % of surgeries were in patients classified as ASA 2, and 2.6 % were performed in patients classified as ASA 4 (Fig. 11.2) [29]. This finding may signify that patients with acute cholecystitis who are described as ASA 4 are often undergoing percutaneous cholecystectomy instead of receiving cholecystectomy.

The limitations of the ASA system are seen in another study of biliary patients. In A retrospective study from 2005 to 2010 showed that sixty-one "high-risk" patients were treated for acute cholecystitis. In this study, 80 % of those who were ASA 4 received percutaneous cholecystostomy, while only 4 % of those who were ASA 3 received this intervention [30]. This observation in not explained by the ASA system which does not examined the reasons for a given procedure. However, one must infer that clinicians in this study might have tended to perform less invasive

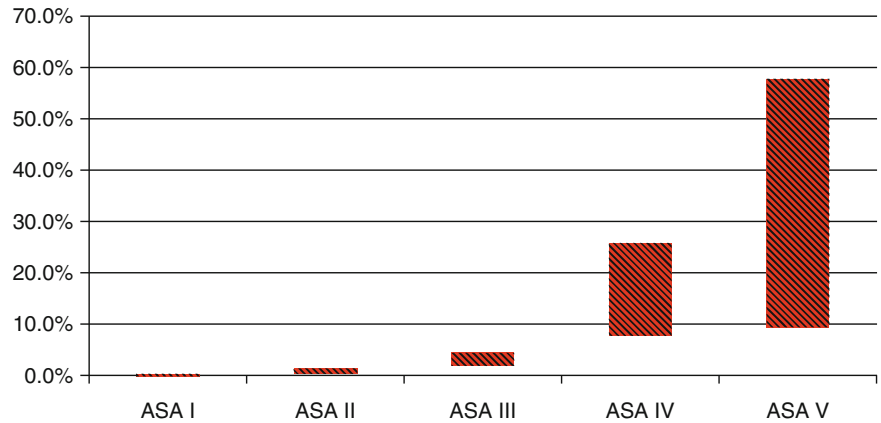

Fig. 11.1 ASA classes and associated mortality rates. Figure from Farrow et al. [22]

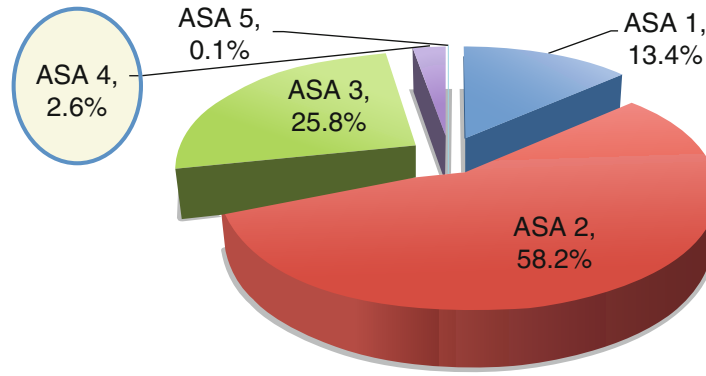

Fig. 11.2 ASA class of cholecystectomies in the National Surgical Quality Improvement Program from 2005 to 2008. Figure from Ingraham et al. [29]

procedures in patients they deemed to be sicker. The study also noted a 17.2 % mortality rate in the percutaneous group compared to a zero percent mortality in the cholecystectomy group ($p=0.02$). The study additionally revealed no differences in age, APACHE II score, Physiological and Operative Severity Score for the enumeration of Mortality and Morbidity (POSSUM), or severity of cholecystitis between the percutaneous group and the cholecystectomy group.

Consequently, ASA classification has been unsuccessful in stratifying patients for possible surgery with acute cholecystitis. There are no prospective randomized studies evaluating outcome after cholecystectomy in patients who are ASA class 4. Additionally, studies have been poor in gleaning whether the ASA class or another feature influenced the need for surgical vs. nonsurgical interventions. Given the limitations of the ASA class system, this alone should not be used to determine operative risk in patients with acute cholecystitis.

Age

A patient's age is also often used to determine operative risk for many operations, including acute cholecystitis. In a retrospective study evaluating patients with emergency operations, Matsuyama and colleagues found that age over 80 was associated with increased morbidity but not mortality [31]. In a separate retrospective study of 411 patients treated specifically for acute cholecystitis, 17 % were 80 years or older [32] and of these elderly patients, more were observed to present with gangrenous cholecystitis (44 % vs. 31 %; $p=0.033$), more complications (31 % vs. 13 %; $p<0.001$), and higher mortality (4 % vs. 1 %; $p=0.038$). After adjusting for comorbidities, age was still found to be independently associated with poor outcomes after cholecystectomy.

In contrast, in a larger NSQIP study of 15,248 patients aged 65 years or older who underwent elective cholecystectomy, the overall mortality rate was 0.9 % [33]. Elective ambulatory cholecystectomies were associated with decreased mortality (0.2 % vs. 1.5 %, $p<0.001$) and decreased complications.

Age may also influence the time to treatment and the type of treatment a patient undergoes in acute cholecystitis. In another retrospective database study of 29,818 Medicare patients admitted for acute cholecystitis, the authors observed that 25 % of patients did not undergo cholecystectomy at their first admission. In the study, the authors also noted a 38 % gallstone-related readmission rate compared to a 4 % readmission rate in those who received cholecystectomy ($p<0.0001$) [6]. In this study, failure to perform cholecystectomy was associated with an increased 2-year mortality (Fig. 11.3). These data would suggest that laparoscopic cholecystectomy should be performed in earlier in the elderly if the patient can tolerate the surgery. However, since the cause of the mortality is not determined from these data, one can not definitively conclude whether the delays in treatment contributed to mortality or whether the patient had serious other life-threatening illnesses that were more responsible for true attributable mortality than the biliary disease.

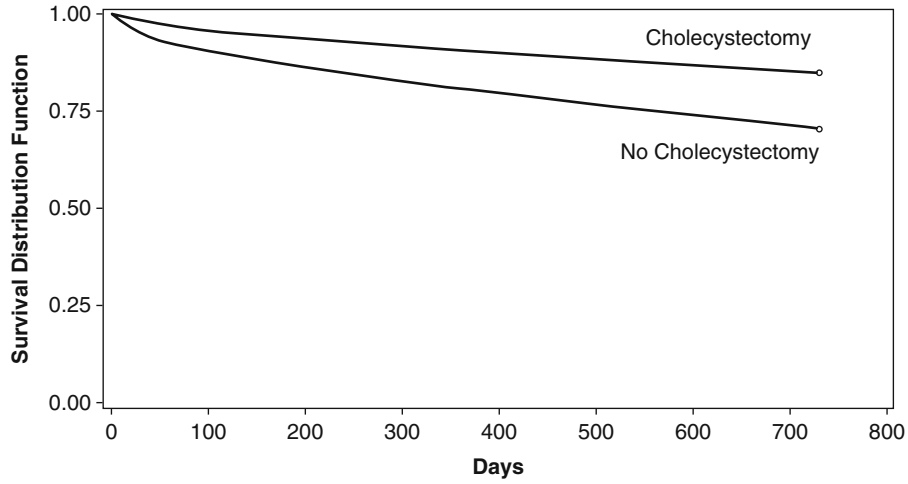

Fig. 11.3 Kaplan Meier curves for patients who received cholecystectomy at index admission and those who did not. Figure from Riall et al. [6]

Critical Illness Scores

Critically ill patients are at considerable risk for biliary disease for several reasons. These patients are predisposed to impaired tissue perfusion due to decreased cardiac output from hypovolemia or inadequate cardiac function due to coronary disease or suboptimal contractility. These factors render them susceptible gallbladder mucosal ischemia which can lead to secondary acalculous cholecystitis or biliary stasis and acute calculous cholecystitis [34, 35].

Illness severity scores can sometimes capture a patient's risk for mortality in the ICU setting but does not specify how much risk a particular operation can confer. A retrospective review of critically ill patients with a mean APACHE II score of 25 possessing acalculous cholecystitis underwent open cholecystectomies [36]. These patients displayed a mortality rate of 44 % as 64 % of these patients had multiorgan failure on the day of cholecystectomy (Fig. 11.4). While the APACHE II (Acute Physiology and Chronic Health Evaluation) and the SAPS II (Simplified Acute Physiology Score) scores were not significantly different between survivors and non-survivors, the SOFA (Sequential Organ Failure Assessment) score was (9.5 vs. 12.9, $p = 0.007$).

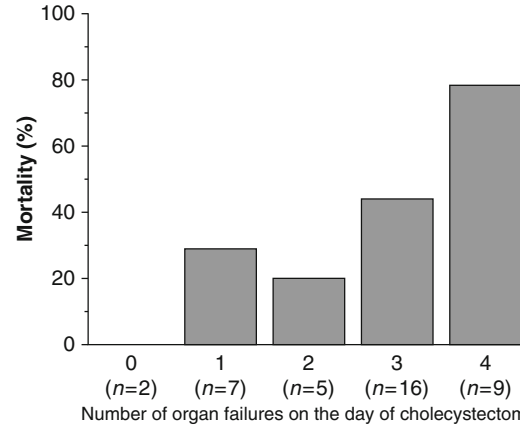

Fig. 11.4 Numbers of patients with organ failure on the day of cholecystectomy. Figure from Laurila et al. [36]

While the intervention in this study is not controlled, and all the cases were done open, the high mortality rate associated with cholecystectomy in this population of patients with acalculous cholecystitis suggests that an alternate strategy is preferred. This alternate strategy would appear to be percutaneous cholecystostomy (PC) with delayed cholecystectomy in patients with this degree of critical illness. While a cutoff of a particular APACHE score deeming a patient too high a risk for surgery is not available from these data, many clinicians now feel

that PC to be the preferred treatment for acalculous and perhaps even calculous cholecystitis in critically ill patients who secondarily develop the biliary condition. A review of 55 patients treated in this fashion demonstrated a mortality rate of 5.4 %, a number far more favorable than the mortality in the study by Laurila et al. [37]. Notably, in the study by Spira et al., 95.7 % of patients had resolution of their symptoms.

Another study of 42 patients by Melloul et al. with sepsis and either calculous or acalculous cholecystitis compared emergent cholecystectomy to PC [38]. The mortality rates were not significantly different between the PC and emergent cholecystectomy groups (13 % vs. 16 %, $p=1$). However, PC was associated with significantly less complications (8.7 % vs. 47 %, $p=0.011$). Two patients who did not respond to PC required emergent cholecystectomy secondary to gangrenous cholecystitis. Incidentally, the likelihood of gangrenous cholecystitis is reported to be higher (40–80 %) in patients with acalculous cholecystitis compared to calculous cholecystitis (2–31 %) [36, 39–43]. In aggregate, these data strongly suggest that PC in this critically ill patient population with delayed cholecystectomy may be the safest option.

Cardiovascular Disease

Specific for emergency procedures vary greatly based on the type of cardiovascular illness and type of procedure. In the study by Matsuyama et al. examining outcomes patients after emergency surgery, cardiovascular surgery, ischemic heart disease, shock state, deteriorated consciousness, Chronic Obstructive Pulmonary Disease (COPD), hemorrhage requiring transfusion, surgeries at night, and surgeries over 2 h contributed to postoperative mortality and morbidity [31]. In particular, the highest risk factors for mortality of these comorbidities were shock, deteriorated consciousness, COPD, and ischemic heart disease in that order. Notably, ischemic heart disease conferred a 3.8 times, as measured by odds ratio, increased risk for mortality.

Importantly, clinicians may approach patients differently if they possess certain comorbidities. In the NSQIP study by Ingraham et al. of 65,511 cholecystectomies performed between 2005 and 2008, the authors observed that 7.7 % of the patients had CAD and 0.71 % of patients had congestive heart failure. In both these groups, the authors observed that the groups with the comorbidity were more likely to undergo open cholecystectomy than laparoscopic cholecystectomy [29]. The reasons for this discrepancy are not clear from the data. Speculated reasons include whether the patients with the comorbidities presented later with the acute cholecystitis or the clinicians were biased away from laparoscopic surgery in this population. As data do not explain this effect, possible reasons, which are again speculative, could show this result may be due to a perception that the patients may not tolerate the laparoscopic surgery from insufflation effects or a potential prolongation of surgical duration time.

However, other studies have suggested that biliary surgery may be safe in patients with severe CAD. In a retrospective study of patients who received laparoscopic cholecystectomy, the authors compared those with severe cardiovascular disease (New York Heart Class III and IV) to those without severe heart disease and found that no significant difference existed in mortality rates between the two groups [44]. The patients with severe cardiovascular disease did experience increased hospital stay, but there was no significant difference in the morbidity rate (7.6 % vs. 4.3 %, $p=0.188$).

Even patients with extreme CAD have been shown to be potential candidates for biliary surgery. Different groups have reported successful laparoscopic cholecystectomies in patients with severe heart disease including left ventricular assist devices [45–48]. A separate review of 15 patients who underwent placement of an intra-aortic balloon pump in order to undergo cholecystectomy documented a mortality rate of only 13 % [49]. A study of cholecystectomy in patients who received heart transplants showed that 72.2 % were operated on for acute cholecystitis and the overall mortality rate was only 2.2 %. Notably, in this study the mortality rate was higher for open cholecystectomy compared to laparoscopic cholecystectomy (3.6 % vs. 0.9 %, $p=0.009$) [50]. The mortality rate was also significantly higher in

emergent cases compared to elective cases (3.6 % vs. 0 %, $p=0.04$).

Overall, the studies demonstrate that severe CAD is not an absolute contraindication to elective laparoscopic cholecystectomy but perioperative mortality rates are higher than in healthier populations. Given the high mortality rate associated with emergent operations in this group of patients, cholecystectomy in the elective setting should be considered in patients with even severe CAD if the management of their heart disease can be optimized.

Chronic Obstructive Pulmonary Disease

Severe lung disease can render a patient high-risk for elective surgery preoperatively, intraoperatively, and postoperatively. Preoperatively, severe pulmonary disease can lead to chronic deconditioning, infectious complications that necessitate antibiotic use and complicate further antibiotic regimens, and delays in presentation for non-pulmonary diseases including acute cholecystitis. Insufflation during laparoscopic surgery is associated with adverse effects on pulmonary function. These effects can be more pronounced in patients with COPD and lead to potentially aborted surgical procedures. Postoperatively, abdominal incisional pain can limit pulmonary excursion, especially if the incision is a subcostal incision as used in open cholecystectomies. Data would support that the physiologic shortcomings inherent with COPD adversely affects outcomes. In the retrospective review by Matsuyama et al., the authors observed that patients with COPD who underwent emergency surgery had an increased mortality rate of 12 % [31].

From the NSQIP database, 2.6 % of cholecystectomies done between 2005 and 2008 were done in patients with COPD [29]. A case–control study was performed to evaluate outcomes after laparoscopic cholecystectomy in patients with and without COPD [51]. The study found no differences in mortality, lengths of surgery, or lengths of hospital stay in either of the two groups. The only difference noted in the groups was that end-tidal CO2 was higher in the COPD group, despite using limited insufflation pressures of 12 mmHg. These data would suggest that in patients with COPD, laparoscopic cholecystectomy in an elective setting should be given consideration. However, this study had several limitations. Complete preoperatively pulmonary function tests were not reported for the two groups which were largely deemed to have only "mild" COPD. Activity level of the two groups was additionally not reported. Also, the groups were small and did not include any patients who needed conversion to open surgery. Nonetheless, the study does show that laparoscopic cholecystectomy can be safely performed in selected patients with COPD.

Cirrhosis

The prevalence of gallstones in cirrhotic patients is three times higher than in non-cirrhotics [52, 53]. This observation is multifactorial and has been attributed to multiple factors including hemolysis secondary to concurrent hypersplenism, decreased biliary acidity, impaired gallbladder emptying, related to high estrogen and progesterone levels, and metabolic liver failure [54].

However, the influence of cirrhosis on biliary anatomy is not always predictable. In early cirrhosis, the cirrhosis may pose no anatomical distinction for patients undergoing cholecystectomy. In more advanced cirrhosis, extreme right upper quadrant bleeding may occur during perihilar gallbladder dissection due to collateralization, scarring of the gallbladder to the liver parenchyma, coagulopathy, or ectopic vasculature. In other cases, the gallbladder may be contracted and relatively avascular. Importantly, the consistency of the liver may vary as well in terms of vascularity in these patients independent of the individual ability of the patient to create clotting factors.

Due to some of these inconsistencies, clinicians for some years have debated whether cholecystectomy should be performed laparoscopically or open in cirrhotic patients. A meta-analysis of 3 randomized controlled trials comparing laparoscopic and open cholecystectomy in patients

with cirrhosis revealed decreased complications and shorter length of stay in the laparoscopic group [54]. In this study, there was no significant difference in Child-Turcotte-Pugh class (CTP) between laparoscopic and open groups. The rate of postoperative hepatic insufficiency was higher in the open cholecystectomy group, but this was not statistically significant (18.1 % vs. 7.7 %). Unfortunately, this study evaluated patients mainly to the Child class A and B whereas the differences in technical feasibility may be most pronounced in patients with advanced cirrhosis.

Other investigators have tried to examine risks in cirrhotic patients undergoing biliary surgery. A retrospective single-center review by Quillin et al. of 94 cirrhotic patients who underwent laparoscopic cholecystectomy from 2000 to 2009 showed that laparoscopic cholecystectomy could be performed safely in selected cirrhotic patients with a conversion rate of 11 %. The reasons for conversion were not enumerated in the study but appeared to be related to increased blood loss in the patients receiving open surgery. The study identified factors associated with increased morbidity to be low serum albumin, elevated INR, CTP, and number of red blood cell transfusions [55]. In this study, the mortality rate was 4 % but notably both patients who were CTP class C perished. The Model for End Stage Liver Disease (MELD) score was not associated with mortality, but was associated with morbidity.

A retrospective review of 220 cirrhotic patients from 1995 to 2008 by Delis et al. in Greece also demonstrated the feasibility of experienced surgeons performing laparoscopic cholecystectomy in this population. These authors had no deaths in their study while maintaining a 19 % morbidity rate. Interestingly, this study showed that preoperative MELD score greater than 13 was a predictor of complications while CTP class was not [56]. Impressively, the authors had only a 5.45 % conversion rate. The authors did describe some of their specific operative strategies to enhance their ability to perform the operation laparoscopically. These strategies included stapling the gallbladder at the level of Hartman's pouch when lower dissection was rendered difficult as well as performing a retrograde cholecystectomy or subtotal cholecystectomy when necessary. The authors also used intraoperative ultrasound to define anatomy in some cases. They also remarked that port placement in this population was safer with routine transillumination of the abdominal wall to avoid abdominal wall collaterals.

End Stage Renal Disease

According to the NSQIP database, of the 65,511 cholecystectomies done from 2005 to 2008, 1 % had End Stage Renal Disease (ESRD) [29]. ESRD affects about 900,000 people in the United States [57] and these patients have a higher prevalence of gallstones than the general population possibly due to increased hemolysis from dialysis [58]. A retrospective study of patients on hemodialysis who received abdominal surgery showed a 70 % mortality rate for those who received emergency surgery compared to a 10 % mortality rate for those who received elective surgery [59].

Given the high mortality for emergency surgery, an alternative to surgery in ESRD patients with acute cholecystitis may be percutaneous cholecystostomy. A study of patients with ESRD and acute cholecystitis (all deemed ASA class 4) who received percutaneous cholecystostomy as first-line therapy revealed a 21 % mortality rate with one of the 11 survivors requiring cholecystectomy [60]. In contrast, another study compared outcomes after percutaneous cholecystostomy and cholecystectomy in patients on chronic hemodialysis who presented with acute cholecystitis and showed no significant difference in overall morbidity or mortality between the two groups [61]. The authors did note however, a higher mortality, though not statistically significant, in the percutaneous cholecystostomy group compared to the cholecystectomy group (19 % vs. 7.7 %, $p=0.475$). The length of stay was also higher in the percutaneous cholecystostomy group (19.7 days vs. 3.7 days, $p=0.0019$). These results combined with the conclusions of another study [62] that compared outcomes after laparoscopic cholecystectomy in patients with and without ESRD indicate that ESRD alone is not a contraindication to performance of cholecystectomy in selected patients.

Summary

In general, the optimal treatment for acute calculous cholecystitis is expedient laparoscopic removal of the gallbladder whenever possible. No absolute criteria exist for deeming a patient too "high-risk" for safe gallbladder surgery. However, we feel based on interpretation of existing data and experience, certain patients who are classified as ASA class IV or V, or APACHE II scores of 25 or higher, or have SOFA scores of 8 or higher should undergo percutaneous cholecystostomy instead of surgical gallbladder removal as first-line treatment. Other candidates for this less invasive intervention would include patients with severe critical illness, sepsis, cardiovascular disease complicated by active ischemia, cardiogenic shock, acute congestive heart failure exacerbation, or severe debilitating pulmonary disease. Importantly, an overriding commonality of the patients who should undergo percutaneous intervention includes those who suffer severe life-threatening illness whose primary disease process does not include gallbladder pathology. Patients with Child classification of C and many uncompensated patients with a Child B score should also undergo percutaneous treatment as first-line treatment. Definitive gallbladder removal for Child B or C patients (if it needed) should be performed at centers capable of hepatic transplantation with the consultation of hepatology services who can assist in optimizing the patient for surgery or monitoring the patient for decompensation postoperatively. While ESRD does not contradict gallbladder surgery, the development of acute renal failure may be considered a reason to delay gallbladder removal until the other organ dysfunction can be more stabilized.

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Damage Control Techniques in Acute Cholecystitis

12

Linda A. Dultz, S. Rob Todd, and Soumitra R. Eachempati

Introduction

Acute cholecystitis (AC) is one of the most common causes of emergency admissions to a general surgery service. Although early laparoscopic cholecystectomy (LC) is considered the appropriate treatment for patients with AC, the procedure can be associated with significant morbidity and mortality in high-risk patients [1–3]. High-risk surgical patients, such as the elderly and those with cardiopulmonary comorbidities have pathological changes in their organ systems resulting in increased morbidity and mortality such as myocardial infarction, congestive cardiac failure, stroke, pneumonia or atelectasis [4]. Additionally, the exposure of such high-risk patients to the pneumoperitoneum of a LC can further lead to cardiopulmonary and renal dysfunction [4]. Due to these observations, less invasive or "damage control" techniques have emerged for AC. These techniques attempt to foster temporary and sometimes permanent disease management of AC. The following discussion addresses some of these techniques.

Gallbladder Drainage

Percutaneous transhepatic gallbladder drainage (PTGBD) (also known as a percutaneous cholecystostomy tube placement) is considered a safe alternative to early cholecystectomy in high-risk patients with AC. While PTGBD has been performed since the 1970s [5] and remains the most widely established technique, there are several alternatives that have been explored in the past two decades. Percutaneous transhepatic gallbladder aspiration (PTGBA) is an alternative method where the gallbladder is puncture-aspirated without placing a drainage catheter. Next, endoscopic transpapillary gallbladder drainage (ENGBD) and endoscopic transpapillary gallbladder stenting (ENGBS) are endoscopic alternatives via the traditional transpapillary route. Finally, with recent improvements in endoscopic ultrasound (EUS), EUS-guided gallbladder drainage has been described via the antrum of the stomach or

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Table 12.1 Advantages and disadvantages of damage control techniques in acute cholecystitis

Technique	Advantages	Disadvantages
PTGBD	Relatively easy	External drain in place
	High technical success rate	Possible dislodgement of drain
	Reliably effective	Relative contraindication in liver disease, coagulopathy, ascites
	Access to the gallbladder maintained	
PTGBA	Relatively easy	Relative contraindication in liver disease, coagulopathy, ascites
	No external drain in place	
ENGBD	Not limited by liver disease, coagulopathy, ascites	Technical success rate is low
	Physiological bile flow	External drain in place
	Access to the gallbladder maintained	Possible dislodgement of drain
		Post-ERCP pancreatitis
		Some cases inaccessible
Endoscopic transpapillary gallbladder stenting	Not limited by liver disease, coagulopathy, or ascites	Technical success rate is low
		Possible stent clogging
	Physiological bile flow	Post-ERCP pancreatitis
	No external drain in place	Some cases inaccessible
EUS-guided transmural nasogallbladder drainage	Not limited by liver disease, coagulopathy, or ascites	External drain in place
		Possible dislodgement of drain
	Access to the gallbladder maintained	Possible bile peritonitis
	No post-ERCP pancreatitis	
EUS-guided transmural gallbladder stenting	Not limited by liver disease, Coagulopathy, or ascites	Possible stent clogging
	No post-ERCP pancreatitis	Possible bile peritonitis
	No external drain in place	

PTGBD percutaneous transhepatic gallbladder drainage, *PTGBA* percutaneous transhepatic gallbladder aspiration, *ENGBD* endoscopic nasogallbladder drainage, *ERCP* endoscopic retrograde cholangiopancreatography, *EUS* endoscopic ultrasound

the bulb of the duodenum [6]. Advantages and disadvantages of each technique are listed in Table 12.1. While PTGBD remains the standard of care, these alternatives continue to be explored and should be considered in select patient populations.

Percutaneous Transhepatic Gallbladder Drainage

PTGBD is the most common method for nonoperative gallbladder drainage. The procedure is an interventional radiologic procedure designed to decompress the acutely inflamed gallbladder. Its use has been described in both high-risk surgical patients unresponsive to medical therapy and as first line treatment to delay cholecystectomy [7–9].

Various methods have been described for PTGBD, but the most common is ultrasound-guided transhepatic gallbladder puncture. This procedure is accomplished with minimal anesthesia and generally an 18-gauge needle for drainage. Gallbladder puncture is performed under direct ultrasound guidance to avoid injury to adjacent structures. A 6- to 10-Fr pigtail catheter is then placed in the gallbladder, using a guidewire under fluoroscopy (Seldinger technique) (Fig. 12.1) [6]. Technical and clinical response rates to PTGBD have been reported between 56 and 94 % [9–11], with consistently higher success being documented in more recent studies. The primary advantage of PTGBD in high-risk surgical patients is the avoidance of general anesthesia and those associated cardiovascular risks. That being said, up to 16 % of

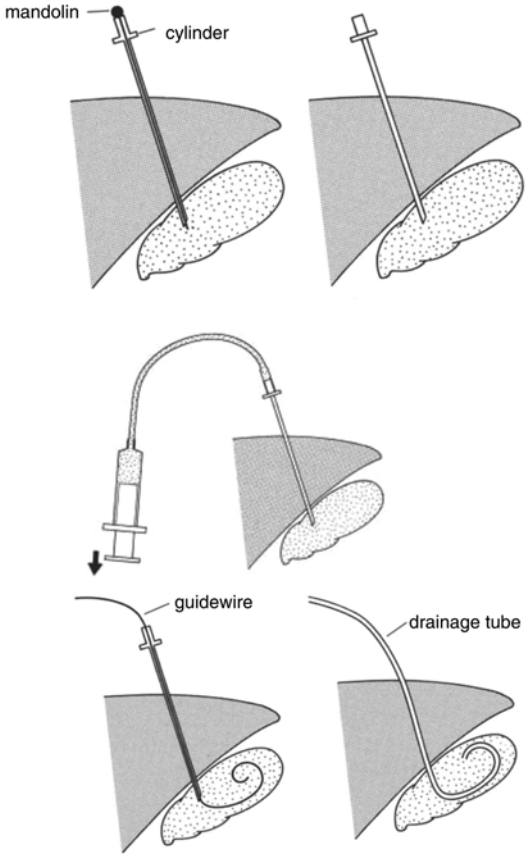

Fig. 12.1 Percutaneous transhepatic gallbladder drainage (PTGBD) technique. Figures from Tsuyuguchi et al. [27]

patients experience complications, including bile peritonitis, bleeding, catheter dislodgement and pneumothorax. In addition, PTGBD may be inappropriate for patients with massive ascites or coagulopathy, and patient discomfort from the catheter has been postulated to decrease quality of life [7, 8, 12, 13].

There are no randomized controlled trials that directly compare the outcomes of PTGBD to LC [10] although the morbidity [1, 2, 10, 14], mortality [2, 10, 14] among high-risk surgical patients undergoing LC is well documented. Success rates for PTGBD are fairly high, and the mortality related to the procedure (0.36 %) is fairly low, but the overall mortality rate following PTGBD (15.4 %) appears equal to or higher than that for emergency LC (4.5 %) [10]. However, the limitations of the literature preclude absolute conclusions to be made regarding the comparative advantages of this procedure.

There are two randomized controlled trials comparing PTGBD with conservative management. In 2002, Hatzidakis et al. found no difference in resolution of symptoms or overall mortality when comparing PTGBD to nonoperative management in high-risk surgical patients. These authors concluded that the nonoperative treatment should be attempted first, and PTGBD should be reserved for those unresponsive to initial medical management [8]. In a later study, Akyürek et al. compared PTGBD with early LC to medical management with delayed LC in high-risk surgical patients [7]. While the conversion to open cholecystectomy and complication rates were similar in both groups, the study did show a shorter hospital stay and lower overall cost in the group treated with PTGBD and early LC. Thus the authors advocate for percutaneous drainage in high-risk surgical patients over medical management [7].

As previously stated, there is no randomized controlled trial comparing PTGBD to emergency LC in high-risk patients. With the advances in surgical laparoscopic training, intensive care management and perioperative anesthesia, the outcomes of PTGBD and LC may be more similar than one thinks. To this end, the CHOCOLATE trial is an ongoing randomized controlled trial comparing morbidity and mortality between LC and PTGBD in high-risk surgical patients [15].

Percutaneous Transhepatic Gallbladder Aspiration

Percutaneous transhepatic gallbladder aspiration is a method to aspirate the gallbladder with a small-gauge needle under ultrasonographic guidance (Fig. 12.2) [6]. It is an easy, low-cost, bedside-applicable procedure, without the patient discomfort seen with an indwelling catheter (PTGBD).

Fundamentally, PTGBA should not work in the setting of infection by the principle of all infections needing continuous drainage. However,

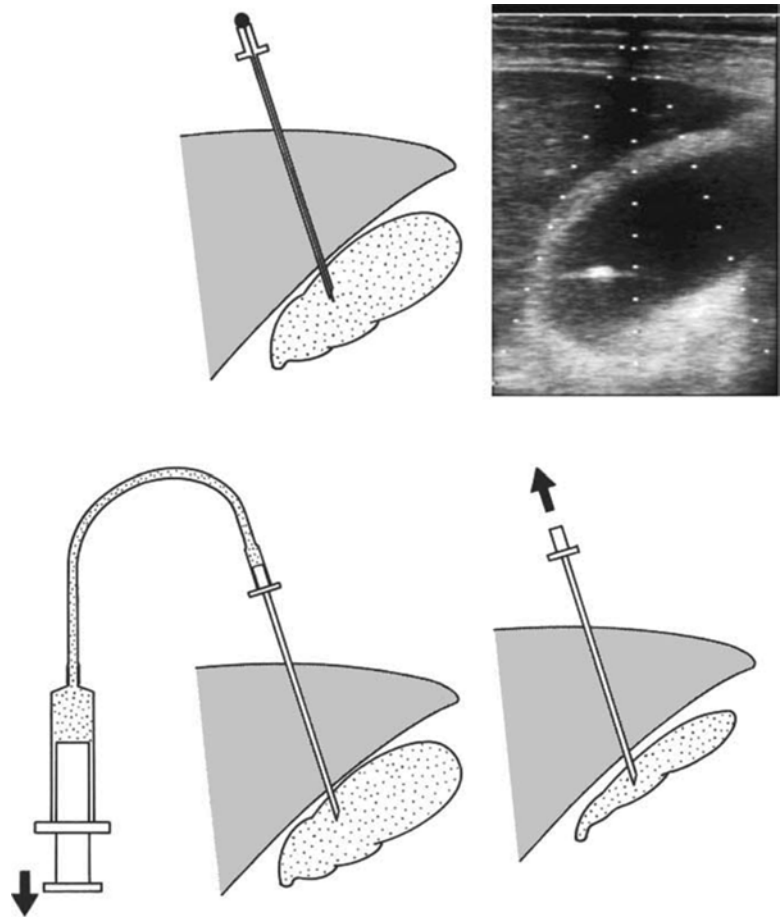

Fig. 12.2 Percutaneous transhepatic gallbladder aspiration (PTGBA) technique. Figures from Tsuyuguchi et al. [27]

infection is not the inciting factor in AC, with obstruction of the cystic duct causing increased intraluminal pressure, leading to venous congestion, compromised blood supply and impaired lymphatic drainage. The mucosa becomes ischemic and releases inflammatory mediators causing trauma, edema, ulcers and possible wall necrosis. Secondary bacterial infection can then occur from the initial obstruction and activation of the inflammatory cascade. Secondary infections complicate up to 50 % of clinical courses, as 40–50 % of cases have been shown to have positive bile cultures [16].

This idea corresponds to Chopra et al., who documented a lower clinical response rate to PTGBA in patients with positive bile cultures [17]. Since infection may not always be present, continuous drainage could be considered excessive treatment in some patients. One time aspiration of bile from the obstructed gallbladder removes the irritant luminal contents and reduces the intraluminal pressure, thereby providing relief prior to the onset of infection. Further studies have concomitantly used antibiotic irrigation during aspiration to counteract any infection that may be present; however, the effectiveness of this technique is unclear due to limited data [18]. In comparing PTGBA to PTGBD, Chopra et al. argues that PTGBA should be the procedure of initial choice as the technical (97–100 % [17, 18]) and clinical (71–77 % [17, 18]) response rates are remarkably high, thus PTGBD should be saved as a salvage procedure for those failing to respond to a single PTGBA. Using this method, 77 % of patients in this study avoided PTGBD [17]. Tsutsui et al. advocate for repetitive PTGBA

in patients that fail to initially improve, arguing that the vast majority of patients will respond within two PTGBAs, avoiding placement of an indwelling catheter [18].

The incidence of adverse events for PTGBA is lower (0–4 %) than in PTGBD, and no serious adverse events have been reported [19]. Instances may exist when PTFBD is favorable to gallbladder aspiration. These situations include patients with thick bile or pus that is difficult to aspirate or patients with a large amount of bile that requires continuous drainage for infection source control. In such patients, PTGBD has a greater chance of success because of the larger caliber of the catheter and the potential for repeated irrigation. Also, because it does not provide continuous drainage, PTGBA is inappropriate in patients in whom the indication for gallbladder drainage is to provide relief from a distal biliary obstruction, such as in biliary malignancies [17].

Despite its potential advantages, PTGBA has not been widely adopted as a standard treatment modality because AC is commonly thought to require continuous drainage and the data supportive of PTGBA is limited to case series and retrospective reviews.

Endoscopic Transpapillary Gallbladder Drainage and Stenting (ENGBD and ENGBS)

ENGBD involves placement of a nasobiliary drainage tube and generally does not require biliary sphincterotomy. After successful bile duct cannulation, a guidewire is advanced into the cystic duct and subsequently into the gallbladder. A 5–8.5Fr pigtail nasobiliary drainage tube catheter is then placed into the gallbladder (Fig. 12.3) [6]. It has been reported in patients with specific comorbidities, including end-stage liver disease or coagulopathy where transhepatic techniques are contraindicated.

In ENGBS, the procedure is identical to ENGBD, but a 6–10-Fr diameter double-pigtail stent is placed instead of a nasobiliary drainage tube (Fig. 12.4) [6]. When larger diameter stents are placed (i.e., 10F), a sphincterotomy is performed to prevent post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis [19]. Also, unlike ENGBD, stents cannot be irrigated to prevent occlusion by blood or debris, which is a potential cause for concern over time [19].

While supportive data are limited, a meta-analysis of ENGBD and ENGBS by Itoi et al. demonstrated a technical success rate of 81 % and 96 % and a clinical response rate of 75 % and 88 % respectively [19]. These early results are comparable to the success rates of the more established approaches of PTGBD and PTGBA [19]. This meta-analysis also found the incidence of adverse events to be similar to that of PTGBD (0–16 %). It is important to note that LC can be performed following resolution of the acute inflammation and sepsis. The tube or stent can then be removed preoperatively or intraoperatively when the time comes [19].

Both ENGBD and ENGBS require difficult endoscopic techniques and only case series have been conducted at a limited number of institutions [6]. Both methods have not yet been established as a standard of care. Therefore, while results are promising, these are newer options for a specific patient population, and should currently only be performed in high-volume institutes by skilled endoscopists [6].

Endoscopic Ultrasound-Guided Transmural Gallbladder Drainage (EUS-GBD)

Although endoscopic ultrasound (EUS)-guided drainage procedures have been safely used with peripancreatic fluids, including those from pancreatic pseudocysts and pancreatic, subphrenic and splenic abscess, little is known regarding EUS-guided transmural gallbladder drainage (GBD) for high-risk patients with AC [20].

The endoscopic approach describes the initial puncture being made at the prepyloric antrum of the stomach or the bulb of the duodenum with a 19-gauge needle to access the gallbladder body or neck and avoid visible vessels. From there,

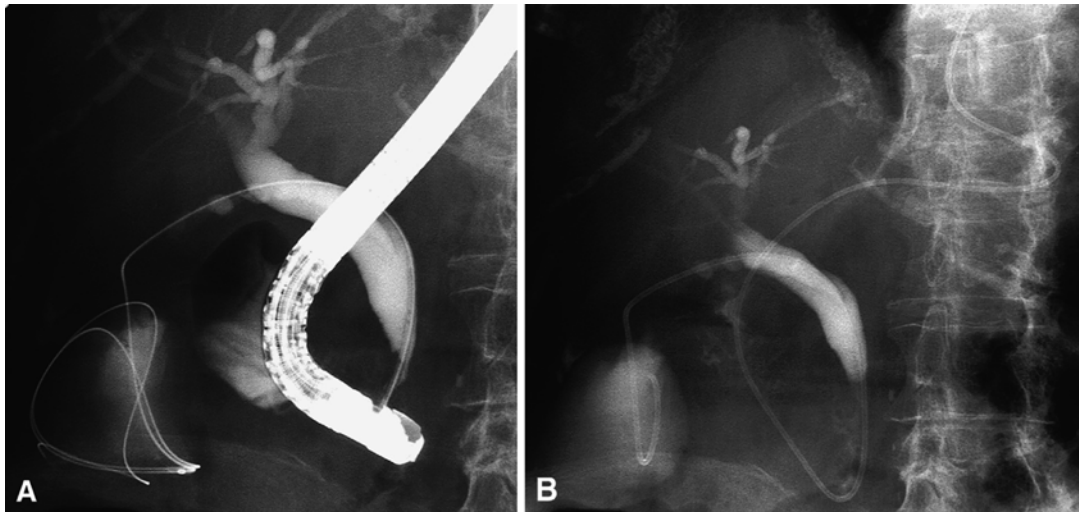

Fig. 12.3 Endoscopic transpapillary gallbladder drainage (ENGBD) technique. Figures from Itoi et al. [28]

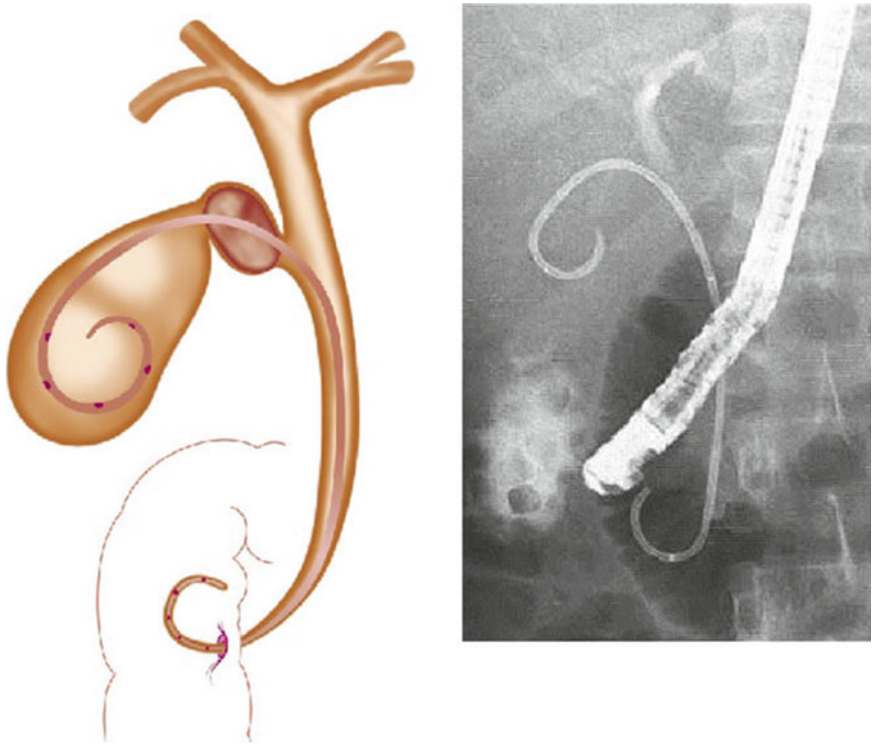

Fig. 12.4 Endoscopic transpapillary gallbladder stenting (ENGBS) technique. Figures from Tsuyuguchi et al. [6]

bile is aspirated and sent for culture. A guidewire is passed through the needle and coiled into the gallbladder. After removal of the needle, the tract is dilated using a 6–7Fr bougie. A 5Fr nasobiliary drainage tube or stent is subsequently placed [3] (Fig. 12.5) [6].

Endoscopic ultrasound-guided transmural gallbladder drainage is particularly useful in

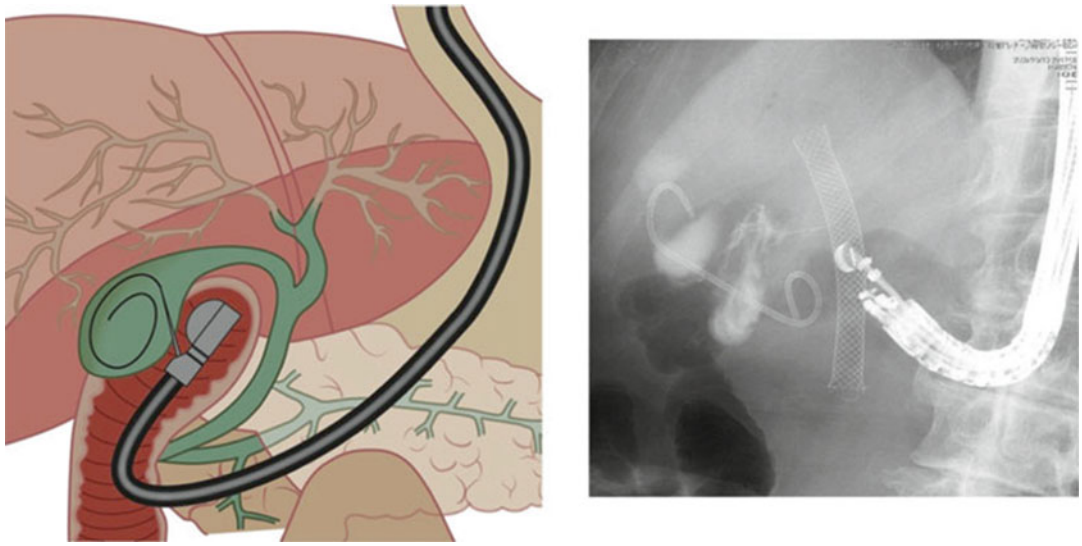

Fig. 12.5 Endoscopic ultrasound-guided gallbladder drainage (EUS-GBD) technique. Figures from Tsuyuguchi et al. [6]

patients with large amounts of perihepatic ascites who, therefore, cannot undergo PTGBD. In addition, it is useful and safe for patients with coagulopathy and for those taking antiplatelet or antithrombotic medication. As previously mentioned, the EUS-GBD puncture site is at the prepyloric antrum or duodenal bulb, both of which are less vascularized than the direct puncture through the liver compared to PTGBD. Furthermore, there is less discomfort with EUS-GBD than with PTGBD, primarily because the PTGBD puncture site is in the subcostal area of the right flank, an area very sensitive to pain [3].

The development of the linear echoendoscope has led to transmural entry and drainage of pancreatic fluid, and this is now regarded as the method of choice. More recently, the transmural approach has been reported to be successful in internal bile drainage of the gallbladder [3, 20]. The EUS-guided transmural approach to the gallbladder for bile aspiration raises concerns regarding the development of bile peritonitis. Theoretically, the gallbladder does not have adhesions to the gastrointestinal tract, raising the possibility of bile leakage during the procedure causing bile peritonitis. However, this has rarely been reported [21], suggesting that the inflamed gallbladder wall may have adhered to adjacent structures, preventing leakage through the puncture site.

The transmural approach has several potential advantages in comparison to the transpapillary approach, including the avoidance of cannulation-related pancreatitis and it is not limited by the configuration of the cystic duct. It also has several potential advantages compared with the percutaneous approach, including the avoidance of complications such as hematoma and pneumothorax and the ability to perform the transmural approach in patients with perihepatic ascites [20]. All this being said, there are disadvantages to EUS-GBD including bile peritonitis [21], pneumoperitoneum [22], stent migration into the gallbladder or intraabdominal space, puncture-induced hemorrhage, stent occlusion and inadvertent tube removal [6].

With regards to bile peritonitis, Jang et al. [22] address the issue by discussing the higher likelihood of bile peritonitis with a plastic stent than a metal stent. The authors argue that the insertion of a plastic stent requires a fistula tract of diameter larger than, or at least equal to, the diameter of the inserted stent. Because of expandability, a metal stent can seal the gap between the stent and fistula of the gallbladder wall better than a plastic stent, thus preventing bile leakage. While one

report of bile peritonitis has occurred with a plastic stent [21], few studies [20–23] with small sample sizes have examined this issue making it difficult to say definitively if metal stents are overall safer in preventing bile leakage during this procedure.

Additionally, it is important to note that the pneumoperitoneum reported in these studies is self-limiting, resolving almost immediately following the procedure [3]. The pneumoperitoneum typically occurs during dilation; the use of carbon dioxide for insufflation during the procedure may lead to the rapid resolution of the pneumoperitoneum and relief of pain [3].

All this being said, EUS-GBD is not a well-established technique. Therefore, it should be performed in high-volume institutes by skilled endoscopists and further prospective evaluations are needed [6].

Intraoperative Damage Control

Acute cholecystitis can make LC difficult with the increased potential for morbidity. If the surgeon deems intraoperatively that a LC cannot be performed safely, several intraoperative damage control techniques should be considered. Some authors have advocated conversion to an open cholecystectomy if the "critical view" cannot be obtained during the dissection of Calot's triangle [24]. This approach has multiple drawbacks. The increased operative time for the open procedure and the more painful incision can harbor its own degree of morbidity. Also, sometimes an open approach does not always provide a better view of the anatomy [24] and an open damage control procedure may be needed. Finally, due to the rarity of the open procedure nowadays, some surgeons may have difficulty with this technique due to a lack of experience.

If dissection is deemed impossible during laparoscopic cholecystectomy, raising concerns of doing more harm than good with further dissection, a laparoscopic cholecystostomy tube should be considered. This procedure involves placing a purse string suture on the dome of the gallbladder. This is utilized to secure a 14–16 French Malekot tube in the gallbladder for drainage following the suctioning of as much bile and stones as possible.

In less complicated cases, there are various maneuvers to consider to facilitate the dissection of the gallbladder. The actual maneuver often depends on the situation creating the difficulty in the operation. In some cases, the difficulty is due to a thick rind around the gallbladder. Incising the rind and dissecting it away from the gallbladder will occasionally leave a soft gallbladder whose cholecystectomy can proceed in a standard fashion.

Sometimes the gallbladder can be too thick-walled to grasp and simple aspiration does little to improve the retraction. In this instance, creating a hole, at least 1–2 cm high on the gallbladder away from the primary structures can allow decompression. This hole may also be used to milk a large stone out of the gallbladder and enhance retraction. In situations where the gallbladder is unable to be grasped because the entire gallbladder lumen has been replaced with stones, a similar hole in the gallbladder can be made and the stones retrieved with a large stone grasper through the subxiphoid 10 mm port. In the authors' experience, sometimes up to 200 stones of varying sizes can be present in the gallbladder that requires many passes with the large stone grasper for full stone removal (Fig. 12.6). Remarkably in some cases, after removal of a large stone or multiple smaller stones, the dissection in Calot's triangle can become fairly routine as the capability for retraction improves. After creating a hole in the gallbladder for stone retrieval, the retracting surgeon can close the hole by grasping both sides of the hole with a endoscopic grasper to close the defect. If the gallbladder wall is extremely thick, the assistant can actually grasp the wall of the cholecystostomy to intensify the pull of the retraction.

In instances where the dissection in Calot's triangle is fraught with too much bleeding and suboptimal visualization, dissection in other areas of the gallbladder can create more mobility to facilitate the dissection. In this case, full division

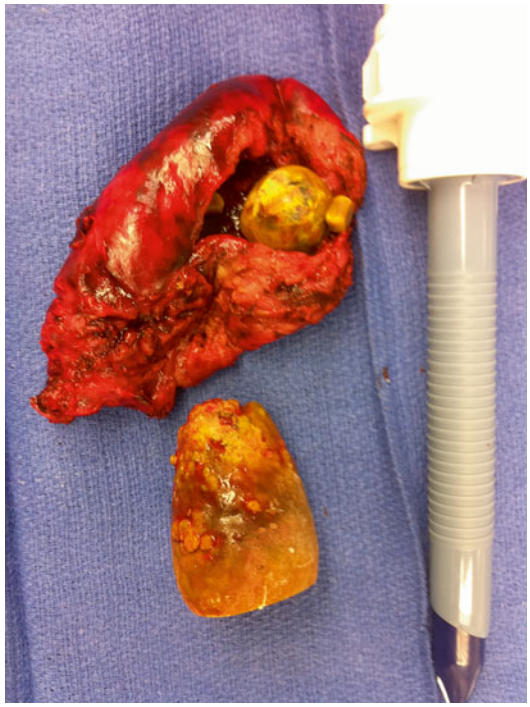

Fig. 12.6 Gallbladder specimen with large stones

of the medial and lateral peritoneal surfaces the entire length of the gallbladder may be invaluable. This maneuver allows full mobilization of the gallbladder and with effective traction may allow careful dissection inferiorly towards Calot's triangle.

A commonly taught *dictum* is that the gallbladder should be dissected "from the top down" when the inflammation is too intense in Calot's triangle. However, the better strategy is to dissect "from the middle down." This strategy allows the top of the gallbladder to stay fixed on the liver bed to give counter traction and prevent the situation where a floppy gallbladder is difficult to grasp. Dissecting from the middle down is performed by slowly dissecting each side of the gallbladder safely above the critical structures with increased depth behind the gallbladder until a window exists behind the gallbladder anterior to the liver bed. For this maneuver to be done properly, the gallbladder is not to be entered on the side of the liver bed and the dissection must not be performed too deeply to create a liver injury. After this window is created, the surgeon can then cautiously dissect toward the neck of the gallbladder and the cystic duct. This maneuver can allow the gallbladder to be stretched and allow lengthening of the fundus and cystic duct to ensure proper visualization of the critical structures. After the cystic duct is visualized, the operation can proceed in the conventional manner.

In other cases, the gallbladder can only be isolated at the level of the infundibulum or cystic duct-gallbladder junction. The skilled laparoscopic surgeon can suture the structure closed. However, this maneuver may not always be possible as sometimes the tissues are too friable. The surgeon can then attempt to divide the gallbladder at the level of the infundibulum. Since this area is generally too large for the standard 5 or 10 mm surgical endoclips, the surgeon needs to use an Endo GIA Universal Stapler (Covidien, Dublin, Ireland) or an Endoloop (Ethicon Endo-Surgery, Blue Ash, Ohio). In these cases, we would recommend placement of a Jackson Pratt drain (10Fr) to capture and identify any potential biliary leak. When bile is noted in the drain effluent, a low threshold should be given to investigate for a biliary leak by a hepatobiliary iminodiacetic acid (HIDA) scan or imaging study. Early detection of a biliary leak generally decreases the patient morbidity as the gastroenterology service can then perform an endoscopic retrograde cholangiopancreatography (ERCP) with biliary ductal decompression and stenting. In some cases the cystic duct stump breakdown is due to a retained stone. In this scenario, the ERCP can also be accompanied by stone retrieval.

A final laparoscopic option is a laparoscopic partial (or "subtotal") cholecystectomy (LPC) and employs the principles of damage control surgery [24, 25]. The indication for a LPC is that safe standard surgery is not possible laparoscopically and the patient will *not* receive better treatment for the disease process with open surgery. In some cases, the patient is a poor candidate for open surgery or the anticipated extra time or blood loss needed for the successful laparoscopic surgery is detrimental (Fig. 12.7). Factors warranting LPC can include severe congestion, edema and adhesions at Calot's triangle, tenacious fibrosis at Calot's triangle or severe bleed-

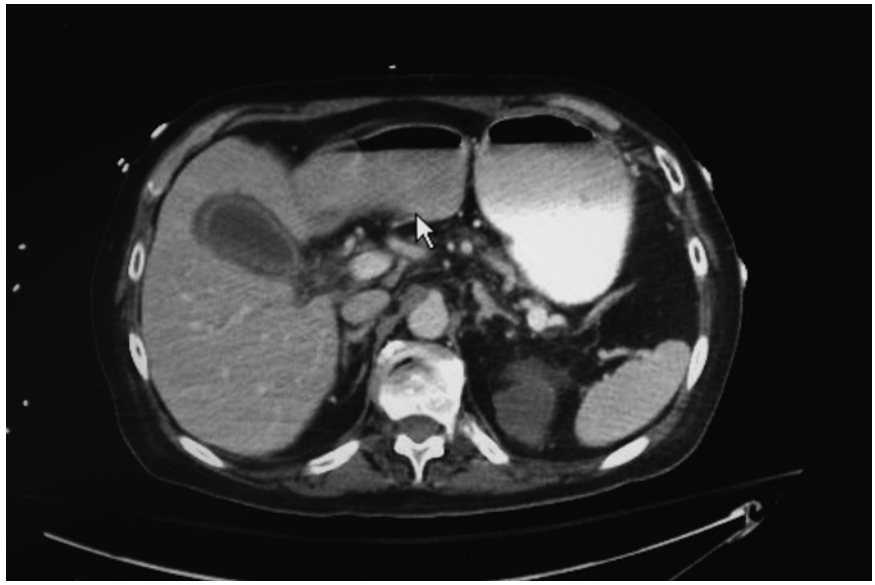

Fig. 12.7 A patient with severe acute cholecystitis. This patient had an extremely thick rind around the gallbladder, especially in the anterior infundibulum as shown in the CT scan image below. The patient required a laparoscopic subtotal cholecystectomy

ing upon performing any aspect of the operative dissection. Situations where bleeding during LC can become prominent include intense inflammation in Calot's triangle, dense adherence of the gallbladder or posterior rind to the liver bed, and an operative field complicated by portal hypertension. A LPC is sometimes chosen preemptively to avoid a major injury such as right hepatic artery or bile duct injury while trying to dissect in a bleeding field with poor visualization of the important structures in a LC.

The LPC technique is relatively straightforward. Optimally, as much gallbladder as possible is removed and closure of the stump or cystic duct is performed. However, in many cases where LPC is needed, adequate dissection to visualize enough cystic duct length to facilitate a secure closure is not possible [24, 25]. In LPC, a common strategy includes stapling of the gallbladder neck near the cystic duct, as previously described. Another common strategy entails leaving a portion of the gallbladder wall behind in situ on the liver bed to minimize the severe bleeding that may be encountered when trying to separate the gallbladder from the liver bed. When a portion of the gallbladder is left on the liver bed, attempts should be made to cauterize as much residual gall bladder mucosa as possible. Regardless of the individual characteristics of the technique, current reviews document that LPC is feasible in approximately 90 % of patients undergoing a difficult resection [24].

Importantly, a LPC does not eliminate all of the potential complications that could occur with a LC. In a recent meta-analysis [24], the most common complication of a LPC was postoperative bile leak, which occurred in 10.6 % of patients. Additional complications included recurrent symptoms of gallstones (2.2 %), immediate reoperation (2.7 %), and the need for postoperative ERCP (7.5 %) or postoperative percutaneous interventions (1.4 %). Further analysis revealed that fewer bile leaks, less need for ERCP, and less recurrent symptoms of gallstones seemed to occur when the cystic duct and gallbladder remnant were closed. These data support a low threshold for postoperative ERCP with biliary decompression in cases of LPC and cautious inspection of a patient's physical examination, clinical status, and laboratory parameters prior to a potentially premature discharge.

Summary

Early cholecystectomy is the treatment of choice for acute calculous or acalculous cholecystitis. For acutely sick patients or chronically ill patients who could benefit from medical optimization, initial nonoperative treatment should be attempted. For those in whom the risk of surgery remains high despite optimization, PTGBD with or without stenting remains the standard of care for nonoperative gallbladder drainage. Patients with moderate ascites, coagulopathy or aberrant anatomy may be better served using an endoscopic approach by skilled endoscopists. Laparoscopic partial cholecystectomy should be reserved as an intraoperative damage control option along with open cholecystectomy and drainage. Overall, the treatment of AC in high-risk patients remains controversial with many therapeutic options [26]. Better studies are needed to aid the physician in management decisions.

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Indications for and Considerations Surrounding Interval Cholecystectomy

13

Christine S. Cocanour and Ian E. Brown

Introduction

The management strategies involving acute cholecystitis have evolved over time. Prior to 1970, management of acute cholecystitis included initial treatment of the inflammation with antibiotics if clinically feasible and time followed by elective open removal of the gallbladder 4–6 weeks after the acute episode. In the 1970s and 1980s, this paradigm began to change and early cholecystectomy became the treatment of choice. This approach allowed early cessation of the patient's pain, a decreased length of stay, and a minimization of the complications associated with failed nonoperative management. Supporting this approach, studies demonstrated no difference in the amount of hemorrhage or the duration of surgery when compared to delayed open cholecystectomy [1–7].

In the early 1990s, laparoscopic cholecystectomy became the preferred method for removal of the gallbladder. Initially, acute cholecystitis was considered a contraindication to laparoscopic cholecystectomy because of higher conversion rates and an increased risk of complications [8]. However, as laparoscopic expertise accrued, equipment improved, conversion rates and complications decreased. A major advance was popularization of visualizing a "critical view of safety" as advocated by Strasberg et al. [9] as adhering to this concept decreased the occurrence of biliary ductal injuries and allowed more widespread utilization of the technique. Currently, laparoscopic cholecystectomy is now considered the treatment of choice for acute cholecystitis [2, 10] as it allows a shorter hospital stay, quicker recovery and a reduction in overall medical costs [11–14].

Delaying Gallbladder Removal

In the current standard of treatment for acute cholecystitis, clinicians have the option to perform either early or delayed gallbladder removal or follow a completely nonoperative treatment strategy. "Early cholecystectomy" is most commonly regarded as removal of the gallbladder within 72 h from the onset of symptoms but the term has been applied by other authors for any cholecystectomy removed within 7 days from the onset of symptoms [15]. The term "delayed cholecystectomy" was defined as greater than 96 h to 6 or more weeks after symptom onset in an attack of acute cholecystitis. Here, delayed cholecystectomy refers to the longer time period of 6 or more weeks after the onset of symptoms.

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Postponing cholecystectomy after development of gallbladder symptoms may foster certain risks to the patient. This strategy can lead to persistent pain but also feared complications as acute cholecystitis and gallstone pancreatitis. One study found that 22.5 % of patients presenting with biliary colic developed gallstone-related complications within an average monitoring period of 4.2 months prior to their cholecystectomy [16]. Other described complications have included gallbladder empyema, gallbladder perforation, cholangitis, and obstructive jaundice. Other studies of patients presenting with acute cholecystitis have detailed 18–50 % of patients will develop gallstone-related complications during the delay before the scheduled cholecystectomy [15–21].

Investigators have also studied the natural history of acute cholecystitis from a different perspective. Riall et al. studied a large Medicare database and found that 25 % of patients did not undergo cholecystectomy in their initial admission [21]. Twenty-seven percent of these patients went on subsequently to have a cholecystectomy. Of the remaining patients that did not undergo cholecystectomy within 2 years, 38 % had a gallstone-related readmission and patients that did not undergo cholecystectomy had an overall worse 2-year survival [21]. However, in gathering its data from a database, the authors were not able to ascertain why the patients did not undergo early cholecystectomy or whether the acute cholecystitis was even the patients' primary health problem at the time of initial diagnosis. The authors were also not able to determine whether the patients that did not undergo surgery had more comorbidities and risks for mortality than the other patients who underwent earlier cholecystectomy.

Currently, international guidelines generally recommend that patients presenting with biliary pancreatitis undergo early cholecystectomy after resolution of pancreatitis during the same hospitalization [22–25] as a similar incidence of recurrent biliary symptoms may be seen in patients presenting with mild biliary pancreatitis. However, practice varies as some clinicians may preferentially delay cholecystectomy after acute pancreatitis. In a meta-analysis of 998 patients, 48 % underwent cholecystectomy during the index admission and 52 % underwent a delayed cholecystectomy that ranged from 19 to 58 days after the initial onset of symptoms. During that time, 18 % of the patients were readmitted, 3 % with acute cholecystitis, 8 % with biliary pancreatitis, and 7 % with biliary colic [26].

Some centers advocate that endoscopic sphincterotomy in lieu of early cholecystectomy after biliary pancreatitis can prevent recurrent biliary symptoms prior to delayed cholecystectomy. A retrospective study observed that patients who underwent ERCP with sphincterotomy showed a decreased risk of readmission from 24 to 10 % and a decreased recurrent biliary pancreatitis (9 % versus 1 %). The authors also observed the risk of developing acute cholecystitis or biliary colic was unchanged after the sphincterotomy with ERCP. Unfortunately, this series did not have a control group of early cholecystectomy patients with whom to compare outcomes in this series [26].

To determine the optimal time for gallbladder removal occurrence, the Dutch pancreatitis study group is currently studying patients with gallstone pancreatitis in the "PONCHO trial" (pancreatitis of biliary origin, optimal timing of cholecystectomy). This randomized study compares early laparoscopic cholecystectomy (within 72 h of symptom onset) with late laparoscopic cholecystectomy (25–30 days). The primary endpoints of the PONCHO trial are mortality and acute readmission for biliary events [27]. Results of this trial will certainly alter practice patterns in the future.

Early Cholecystectomy in the Elderly

Elderly patients undergoing either a semi-elective cholecystectomy or an outpatient elective cholecystectomy can maintain similar outcomes to younger patients also undergoing this procedure under similar circumstances [28]. For acute cholecystitis, some studies reinforce that early cholecystectomy can be performed safely in the

elderly population as long as there is sound patient selection [21, 28–32]. Nonetheless, this practice still harbors more risk in elderly patients due to their comorbidities and decreased physiologic reserve [33, 34]. Part of the risk lies in the finite possibility that a minority of cholecystectomies will require conversion to an open approach and dramatically increases the chances of cardiopulmonary complications [33, 34]. A recent review noted that elderly patients with acute cholecystitis may have morbidity rates over 51 % and mortality rates as high as 34 %. Based on these observations, these authors concluded that early cholecystectomy be performed in medically stable elderly patients as soon as they are found to have symptomatic gallstones [28].

Delayed Cholecystectomy After Percutaneous Drainage

Certain populations definitely benefit from a delayed cholecystectomy after the onset of acute cholecystitis. Several groups have reported that critically ill patients treated with percutaneous drainage instead of emergency cholecystectomy for acute cholecystitis had an overall complication rate significantly lower than those treated with the more invasive procedure performed immediately after the detection of the acute cholecystitis [35, 36]. One study showed a high open cholecystectomy rate in severely critically ill patients who had attempted laparoscopic cholecystectomy [35]. The same study found other major complications were noted following emergency cholecystectomy such as bleeding or biliary leak requiring reoperation. Mortality in this study did not differ between the two groups, but this finding most likely results from the overall severe critical illness of the patients.

Although the invasive nature of cholecystectomy can be detailed, the practice of cholecystostomy poses potential risks of its own. Multiple authors have found that patients who underwent cholecystostomy in lieu of cholecystectomy possessed higher mortality rates, increased total charges and longer lengths of stay for acute cholecystitis [36, 37]. In one study by Windbladh et al. 30-day mortality rates were 15.4 % in patients treated with PC and 4.5 % in those treated with acute cholecystectomy ($P<0.001$). In a separate population-based cohort of 27,718 patients with acute cholecystitis managed by percutaneous drainage, at 1 year, 40 % had undergone cholecystectomy, 18 % had died and 49 % had another gallstone-related emergency department visit or admission [17]. When comparing the patients who underwent initial percutaneous drainage to those who underwent initial cholecystectomy, both patients who died and who survived without cholecystectomy were older and had greater comorbidities. These and other observational series of patients treated with cholecystostomy may just demonstrate that patients necessitating cholecystostomy were more likely to be older and have more comorbidities than those treated with cholecystectomy [17, 36]. The studies lack the methodology to capture whether the cholecystostomy led to more complications because the procedure was insufficient treatment for the biliary pathology or whether the patients were truly too sick to undergo the more invasive procedure. The results could also suggest that clinician bias propagated the performance of cholecystostomy on the sicker patients.

The notion that the risk of recurrent acute cholecystitis mandates the need for future cholecystectomy after percutaneous drainage for acute cholecystitis, remains controversial [33, 35, 38]. In a study by Melloul et al., the authors found a 17 % recurrence rate of acute cholecystitis in patients with gallstones that underwent percutaneous drainage [35]. These authors and others have therefore recommended that cholecystectomy is necessary for patients with calculous cholecystitis, whether performed early or in a delayed fashion [35, 38]. Other clinicians have observed that since postoperative morbidity can lead to major complications in certain populations, cholecystectomy should only be considered in patients with recurrent acute cholecystitis [33, 39]. Since the time interval for follow-up in all these studies has been variable, standard recommendations based on the likelihood of recurrence have been elusive to generalize.

Due to the ongoing debate, the currently enrolling CHOCOLATE (Percutaneous cholecystostomy versus laparoscopic cholecystectomy for

acute calculous cholecystitis) trial is designed to provide an evidence-based guideline for the treatment of acute calculous cholecystitis in high-risk patients. The eligible patients, defined as those with APACHE-II scores ranging from 7 to 14 with acute calculous cholecystitis are being randomized to either percutaneous drainage or laparoscopic cholecystectomy [40]. The ultimate aim of the study is to prove superiority for the laparoscopic cholecystectomy group.

Other outstanding issues surround the practice of percutaneous drainage for both acute acalculous and calculous cholecystitis. One question surrounds the duration of the percutaneous drain for both these diseases. Practice patterns have historically maintained that the drain should generally be left in place until interval cholecystectomy or an arbitrary time period of several weeks to several months. Most clinicians feel that for acalculous cholecystitis, an interval cholecystectomy is not necessarily required if the cystic duct regains patency. The issue is vital as the patients requiring delayed cholecystectomy have higher risks for complications with delayed surgery including increased length of stay, cardiopulmonary complications, and a higher conversion rate to open cholecystectomy [38]. The CHOCOLATE trial is designed to address the benefit of the practice of delayed cholecystectomy for this population.

Cholecystectomy in the Patient with Active Myocardial disease

In assessing the patient with active myocardial disease for cholecystectomy, the risks and benefits of the patient's myocardial disease as well the indications for the procedure must be individualized. Since large studies are not available studying exclusively cholecystectomy with regard to active myocardial disease, one must study more population-based series examining all types of surgery in terms of outcomes. Even so, the starting point in understanding the risks of myocardial disease on outcomes of surgery for acute cholecystitis is to examine the influences of the comorbidity on surgical patients as a whole.

In general terms, several large surveys have demonstrated that perioperative cardiac morbidity is particularly concentrated among patients 70 years of age or older who undergo major thoracic, abdominal or vascular surgery. Using the American College of Surgeons' National Surgical Quality Improvement Program database for derivation, a risk index was recently developed that found that ASA class, dependent functional status, age, abnormal creatinine (>1.5 mg/dL), and type of surgery were associated with cardiac risk after surgery [41]. The risk calculator can be found online at http://riskcalculator.facs.org/. Other risk calculators have also been developed to estimate the risk of perioperative myocardial infarction or cardiac arrest [42–45].

Different authorities have opined on the proper strategy regarding elective surgery after a myocardial infarction. The American College of Cardiology and the American Heart Association 2007 Guidelines advocated waiting at least 4–6 weeks for elective surgery after a major cardiovascular event [46]. In another study, Livhits et al. analyzed the California Patient Discharge Database for patients undergoing common elective procedures and found that for patients undergoing cholecystectomy, the rate and relative risk of another postoperative myocardial infarction did not significantly decrease until 60 days after the first ischemic event. (Tables 13.1 and 13.2) Thirty-day mortality risk was greatest when cholecystectomy was performed within 30 days of MI, and this risk did not wane until after 60 days [47]. Consequently, these authors recommended delay to any elective surgery for at least 8 weeks after myocardial infarction and evaluate options for medical optimization during this interval. In the absence of stronger levels of evidence, this seems to be a reasonable recommendation for the majority of patients.

Cholecystectomy Following Stroke

The time to perform elective surgery after a major cerebrovascular event has been controversial. After a stroke, the brain must recover sufficiently from the insult before further ischemia can be

Table 13.1 Postoperative myocardial infarction and mortality rate for patients undergoing surgery by time elapsed from recent myocardial infarction

Post-operative outcomes	Time elapsed from recent MI	Cholecystectomy (%)
30-day MI	0–30 days	28.8[b]
	31–60 days	17.8[b]
	61–90 days	6.5[b]
	91–180 days	5.7[b]
	181–365 days	3.9[b]
	No Recent MI	0.9
30-day mortality	0–30 days	10.5[b]
	31–60 day	6.9[b]
	61–90 days	5.9[b]
	91–180 days	4.8[b]
	181–365 days	5.9[b]
	No recent MI	2.3
1-year mortality	0–30 days	28.0[b]
	31–60 days	26.4[b]
	61–90 days	19.9[b]
	91–180 days	18.7[b]
	181–365 days	19.2[b]
	No recent MI	8.0

Adapted from Livhits, et al Ann Surg 2011;253:857–864
MI myocardial infarction
[b]$P < 0.001$ (compared to patients with no recent MI for same time frame and procedure)

Table 13.2 Odds ratio of repeat myocardial infarction (MI) or mortality after cholecystectomy

30-day MI [RR (95 % confidence interval)]	
0–30 days	26.59 (15.37-34.73)
31–60 days	21.95 (13.13–32.54)
61–90 days	7.15 (2.46–14.14)
91–180 days	4.74 (1.97–7.97)
181–365 days	4.71 (2.43–7.60)
30-day mortality [RR (95 % confidence interval)]	
0–30 days	3.84 (2.06–6.38)
31–60 days	2.08 (0.86–3.93)
61–90 days	1.56 (0.41–4.34)
91–180 days	1.58 (0.68–3.05)
181–365 days	2.23 (1.25–3.38)

tolerated. From a cellular standpoint, the past ischemia and inflammation need to be resolved fully before the brain can withstand any new hemodynamic stressors from surgery and anesthesia. Cerebral autoregulation is also impaired following a stroke [48, 49]. This alteration in normal cerebral physiology allows the brain to be more vulnerable to subsequent ischemic events for an indeterminate time course. Aries et al. studied this phenomenon by examining transcranial Doppler studies after an ischemic stroke and found a progressive deterioration of cerebral autoregulation in the first 5 days after stroke. The authors also concluded that a full recovery back to baseline of cerebral autoregulation required at least 3 months and possibly more [49].

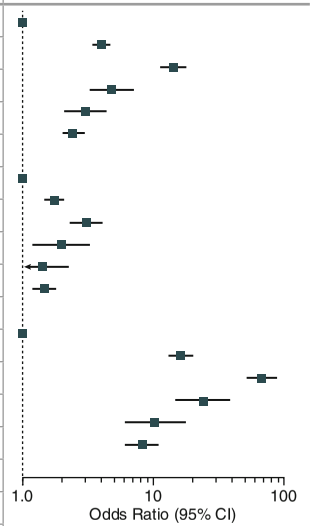
Unfortunately, concrete recommendations regarding the safety of elective surgery following stroke are largely nonspecific and based largely on opinion. A recent investigation of the association between prior stroke and further risk of adverse cardiovascular events found that prior ischemic stroke was associated with an adjusted 1.8 and 4.8-fold increased relative risk of 30-day mortality and 30-day major adverse cardiovascular events, respectively, compared to those without prior stroke [50]. An interpretation of these findings can be that the risk for stroke parallels the recovery of the brain's cerebral autoregulation as patients in this study with strokes were particularly at morbidity for the first 3 months after the stroke and the risks did not fully decrease until about 9 months after the stroke (Table 13.3). The increased risk did not differentiate between low- and high-risk surgeries. Based on these data, a logical recommendation is that elective surgery should be delayed for at least 3 months and preferably 9 months following a major cerebrovascular event.

Acute Acalculous Cholecystitis

The utility and necessity of cholecystectomy after acute acalculous cholecystitis (AAC) has been debated for some time. The disease most often occurs in patients with more overall illnesses and comorbidities who cannot tolerate surgery at the time of diagnosis. The main populations for AAC include hospitalized patients, those with long-term illnesses, and those with chronic dis-

Table 13.3 Adjusted Odds Ratios of 30-Day Major Adverse Cardiac Events Stratified by Stroke Prior to Surgery and Time Elapsed Between Stroke and Surgery

	Crude events, No.	Sample size, No.	Odds ratio (95 % CI)
30-day MACE			
No prior stroke	1923	474,046	1 [Reference]
Prior stroke anytime	389	7137	4.03 (3.55–4.57)
Stroke <3 months prior	153	862	14.23 (11.61–17.45)
Stroke 3 to <6 months prior	34	469	4.85 (3.32–7.08)
Stroke 6 to <12 months prior	37	898	3.04 (2.13–4.34)
Stroke ≥12 months prior	165	4908	2.47 (2.07–2.95)
30-day all-cause mortality			
No prior stroke	2914	474,046	1 [Reference]
Prior stroke anytime	254	7137	1.75 (1.51–2.03)
Stroke <3 months prior	66	862	3.07 (2.30–4.09)
Stroke 3 to <6 months prior	21	469	1.97 (1.22–3.19)
Stroke 6 to <12 months prior	29	898	1.45 (0.95–2.20)
Stroke ≥12 months prior	138	4908	1.46 (1.21–1.77)
30-day ischemic stroke			
No prior stroke	368	474,046	1 [Reference]
Prior stroke anytime	210	7137	16.24 (13.23–19.94)
Stroke <3 months prior	103	862	67.60 (52.27–87.42)
Stroke 3 to <6 months prior	21	469	24.02 (15.03–38.39)
Stroke 6 to <12 months prior	16	898	10.39 (6.18–17.44)
Stroke ≥12 months prior	70	4908	8.17 (6.19–10.80)



MACE indicates major adverse cardiac events (acute myocardial infarction, ischemic stroke, or cardiovascular death). Adjusted for sex, age, body mass index, all comorbidities, all pharmacotherapy, surgery group, and surgery risk

Jørgensen ME, et al. JAMA. 2014;312(3):269–277. doi:10.1001/jama.2014.8165

eases. Other frequently cited groups with AAC include patients with trauma, burns, recent surgery, abdominal infection [38], diabetes mellitus [38], abdominal vasculitis [51], end stage renal disease [52], congestive heart failure, and recent resuscitation from cardiogenic or hemorrhagic shock [53]. Other groups for this disease include cancer patients with severe metastatic disease [54], acute myelogenous leukemia [55], and bone marrow transplant patients [56].

The risk factors and causes of AAC are generally present in the most severely ill hospitalized patients. Overall, AAC appears to be a result of failure of the gallbladder microcirculation with cellular hypoxia. Bile stasis and gallbladder ischemia have been generally implicated in the initial pathogenesis of AAC. Volume depletion, use of opioid analgesics, total parenteral nutrition, and even mechanical ventilation with positive end-expiratory pressure may facilitate the progression to AAC [38]. Gallbladder mucosal perfusion can be further decreased by hypotension, or the administration of vasoactive drugs. Reperfusion injury which can result in a variety of hospitalized settings has also been shown to contribute to AAC [38].

These observations may explain the high rates of gallbladder necrosis and perforation in patients with AAC compared to calculous cholecystitis [51, 57–59]. The differences in arterial perfusion patterns between acute calculous cholecystitis and AAC further supports the finding that AAC results from ischemia [60]. Gallbladders with gallstone disease were noted to have arterial dilatation and extensive venous filling consistent with acute inflammation, while AAC gallbladders have multiple arterial occlusions and minimal to absent venous filling.

As mentioned, many clinicians feel the obstruction of the cystic duct must be resolved before considering removal of the percutaneous drain in patients with AAC. Either tube cholangiography or clamp trials of the percutaneous tube are recommended after resolution of symptoms to determine whether the cystic duct is indeed patent and to confirm the absence of gallstones. If these criteria are met, the percutaneous drain may be safely removed and a cholecystectomy may not be required.

If the patient has persistent obstruction of the cystic duct, consideration for delayed cholecystectomy is required. Patients with AAC in whom death from underlying disease is expected in the near term should be considered for continued nonoperative management for their gallbladder disease. The timing of death in patients with terminal cancer, Gold stage IV COPD, NYHA class IV heart failure, or end stage hepatic failure is impossible to predict. The risk and benefits of surgery must be weighed against the risk of recurrent biliary tract disease. Although laparoscopic cholecystectomy appears to be better tolerated, laparoscopic gallbladder removal may require conversion into an open procedure. Risks of surgery in patients with multiple comorbidities are difficult to quantify and require frank conversations between physicians and patients. Although age does not pose an absolute indication for nonoperative management, patients older than 70 who require emergent abdominal surgery with ASA scores of 3 or 4 have reported mortalities of 31 % and 57 % respectively. Morbidity rates for ASA 3 or 4 have been reported as 63 % and 100 % [61]. Again, the aforementioned risk calculators may be beneficial in assistance to patient and family counseling.

Summary

Early cholecystectomy is the treatment of choice for acute cholecystitis. When patients are considered to have unacceptable risk for anesthesia and surgery, other nonoperative approaches may be considered including antibiotics with or without percutaneous drainage as shown in Fig. 13.1. If the patient's comorbidities can be successfully treated and the patient medically optimized, then surgery may become an option. For those in whom the risk of surgery remains high for acute calculous or acalculous cholecystitis, continued percutaneous drainage may be necessary. In some cases, removal of the drain can be performed when the cystic duct becomes patent in asymptomatic, stable patients.

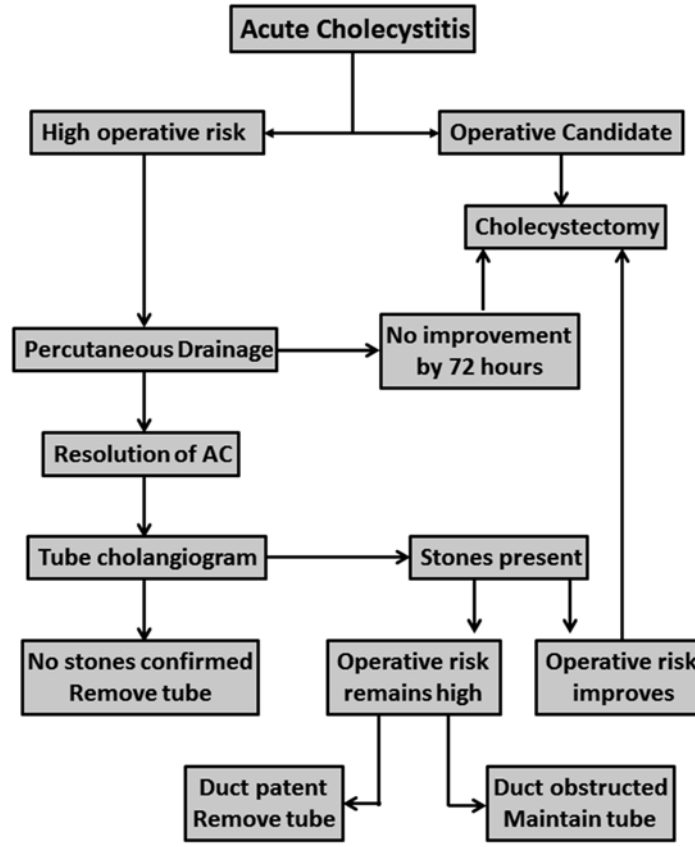


Fig. 13.1 Adjusted odds ratios of 30-day major adverse cardiac events stratified by stroke prior to surgery and time elapsed between stroke and surgery

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Management of Choledocholithiasis

14

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Introduction

Choledocholithiasis is defined as the presence of gallstones in the biliary tree, independent of the gallbladder and cystic duct (the presence of gallstones in the gallbladder is termed cholelithiasis). Approximately 75,000 annual US hospitalizations involve a diagnosis of choledocholithiasis [1]. The incidence of choledocholithiasis among patients undergoing cholecystectomy is between 3 and 40 % [2–7] and is dependent upon the preoperative index of suspicion. For example, incidental common bile duct (CBD) stones are found in approximately 3 % of cases of cholecystectomy in which routine intraoperative cholangiography (IOC) is employed [8]. By contrast, when IOC is performed in the setting of suspected choledocholithiasis (e.g., dilated CBD diameter on preoperative transabdominal ultrasonography or direct hyperbilirubinemia), this incidence can approach 40 %—although it is important to recognize that it is far from 100 % [9].

Advancements in technology for both diagnosing and treating choledocholithiasis have led to a number of controversies regarding the management of this condition. Issues that will be covered in this chapter include: (1) the utility of routine IOC during cholecystectomy; (2) management of incidentally discovered choledocholithiasis; (3) management of suspected or symptomatic choledocholithiasis, and (4) the optimal timing and method of clearance of the biliary tree.

Classification and Pathogenesis

Choledocholithiasis is divided into primary and secondary: whereas in primary choledocholithiasis stones form de novo within the biliary tree, in secondary choledocholithiasis stones form in the gallbladder and migrate into the biliary tree (Fig. 14.1). The distinction between primary and secondary CBD stones has therapeutic implications: cholecystectomy will prevent the recurrence of secondary stones but will not be curative of primary stone disease [10].

Primary stones represent only 5 % of cases of choledocholithiasis in the United States. However, they are an important cause of choledocholithiasis in Southeast Asian nations and in patients with biliary tree pathology [10–12].

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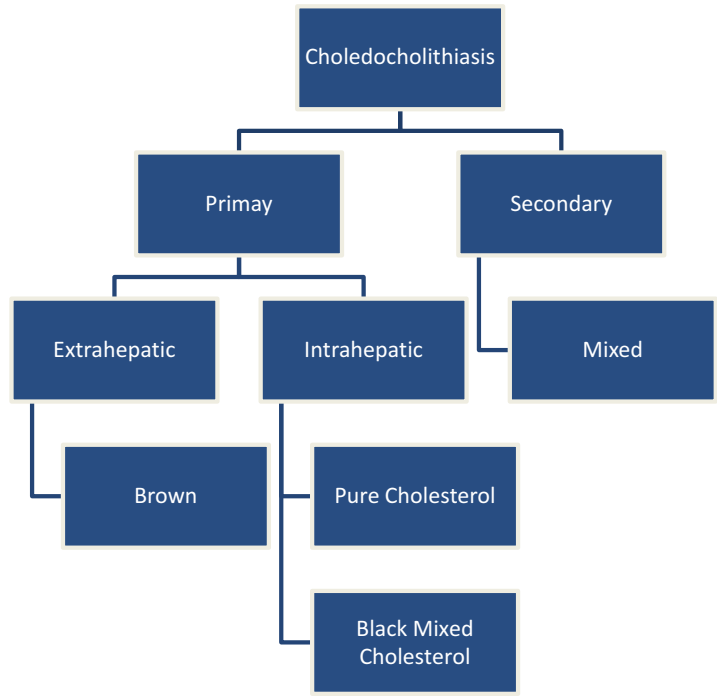

Fig. 14.1 Classification scheme for choledocholithiasis. Primary gallbladder stones form de novo within the biliary tree. In secondary choledocholithiasis stones form in the gallbladder and migrate through the cystic duct into the biliary tree

These stones typically form from bilirubin, and can be either intrahepatic or extrahepatic.

Extrahepatic primary bile duct stones are known as brown stones and are the most common type of primary bile duct stones. They are composed of a combination of fatty acids, calcium bile salts, and cholesterol [13]. Brown stones are found most commonly in Asian populations and their pathogenesis is thought to be due to a combination of bile stasis and bacterial infection. Bile duct stasis is usually due to obstruction from strictures, foreign bodies, or papillary stenosis. Obstruction in turn leads to bacterial overgrowth and production of bacterial β-glucuronidase, deconjugating bilirubin and forming insoluble calcium bilirubinate [11, 14–16]. *Escherichia coli*, *Bacteroides* spp. and *Clostridium* spp. are commonly isolated organisms. The fact that brown stones are more common in rural Asian populations and that this prevalence recedes upon emigration to Western countries suggests that their formation involves a dietary or environmental component [11, 15]. Protein-deficient animals have reduced levels of β-glucuronidase inhibitors in their bile, which has led to the hypothesis that the low protein diets of rural Asians contribute to their higher prevalence of brown stones [15]. Furthermore, the presence of periampullary diverticula has been shown to significantly increase the risk of developing brown bile duct stones [17]. Finally, CBD dilation has frequently been associated with the development of primary biliary stones after cholecystectomy [18]. As such, cholecystectomy at a young age is a risk factor for the development of primary stones [19].

Intrahepatic primary stones can be black mixed cholesterol or pure cholesterol [18]; the black mixed cholesterol type is more common. These CT hyperdense stones have a black outer layer of calcium bilirubinate over a core composed of up to 50 % cholesterol [11, 12]. The pathogenesis of these stones is not well understood but bacterial infection is thought to contribute.

Pure cholesterol intrahepatic stones are similar in composition to those found in the gallbladder, however their pathogenesis is thought to be different, as many of these patients do not have cholelithiasis [11, 20]. Deficiencies in antinucleating

factors have been hypothesized as one of the causes for intrahepatic stones. These factors, which normally counteract cholesterol nucleating factors, slow crystal precipitation and stone formation [21].

Secondary stones are formed in the gallbladder and subsequently migrate into the biliary tree. In the Western World, they are a far more common cause of choledocholithiasis as compared to primary stones. Secondary stones are typically mixed stones, composed primarily of cholesterol with a pigmented shell and about 80 percent of all stones found in the gallbladder fall into this category [11]. Recent research has shown that the pathogenesis of these stones involves multiple concurrent factors including cholesterol supersaturation in bile, crystal nucleation, gallbladder dysmotility, and gallbladder absorption and secretion abnormalities [22]. Most secondary stones remain in the gallbladder. However, approximately 10 % of stones will migrate from the gallbladder into the biliary tree to become symptomatic [23]. The fate of these stones determines both symptomatology and outcomes of secondary choledocholithiasis.

Presentation and Diagnosis

Regardless of origin (primary vs. secondary), gallstones in the biliary system become symptomatic when they obstruct the outflow of bile and/or pancreatic secretions. Consensus thinking holds that most gallstones that exit the cystic duct pass asymptomatically into the duodenum. Furthermore, most stones that remain in the CBD obstruct the flow of biliopancreatic fluid only transiently if at all. In fact, both primary and secondary stones can be present in the CBD for years without causing symptoms or elevating liver function enzymes [12]: This entity is described as "uncomplicated choledocholithiasis" (uCDL).

However, in approximately 40 % of cases of choledocholithiasis, persistent obstruction of either the biliary or pancreatic ducts (or both) ensues, leading to abdominal pain and tenderness, as well as both laboratory and imaging derangements. The pathognomonic manifestations of this obstruction are cholangitis and pancreatitis, respectively, and, when caused by obstructing gallstones, are termed "complicated choledocholithiasis" (cCDL). In fact, over 50 % of patients presenting with ascending cholangitis have CBD stones [24]. The relatively high incidence of symptomatology seen in choledocholithiasis, as well as the morbidity of both cholangitis and pancreatitis [25–28], have been used as arguments for routine interrogation of the CBD in cases of cholelithiasis and clearance of it when choledocholithiasis is found.

Risk factors for cCDL include older age, nonelective admission, history of alcohol abuse, male gender, obesity, and Asian/Pacific Islander race [29]. Patients with cCDL have also been shown to have a 1.5× increased odds of mortality compared to those with uCDL [29].

In general, choledocholithiasis is diagnosed by a combination of history, physical exam, and imaging modalities. Importantly, 2–3 % of patients who have had a cholecystectomy will have retained stones implying the lack of gallbladder in a patient cannot rule out the possibility of choledocholithiasis [7]. Patients with uCDL present with symptoms related to cholelithiasis in the form of either biliary colic or cholecystitis. Physical exam findings will also be driven primarily by the underlying gallbladder pathology, and may range from normal (mild biliary colic) to severe tenderness with Murphy's sign (acute cholecystitis).

Transient obstruction of the CBD may lead to accumulation of conjugated bilirubin in the serum, with resultant jaundice and scleral icterus. Although painless jaundice and weight loss may occasionally be seen as a result of choledocholithiasis, this constellation of symptoms is much more commonly associated with pancreatobiliary malignancy [25]. A palpable gallbladder on physical exam, known as "Courvoisier's sign", can also rarely be seen in the setting of a stone obstructing the CBD but is more commonly associated with other obstructive processes that cause more chronically elevated intraductal pressures such as biliary malignancy [30].

Patients with suspected biliary pathology should have liver function tests (LFTs) obtained

routinely, including total bilirubin (TB), direct (conjugated) bilirubin, aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP) and Gamma-glutamyl transpeptidase (GGT). Choledocholithiasis is most strongly suspected in the setting of an elevation of ALP, as well as a direct hyperbilirubinemia. In a study of 1002 patients who underwent laparoscopic cholecystectomy (LC) after having preoperative LFTs and a variety of diagnostic imaging modalities, Yang and others found that the value of liver assays is primarily in ruling out CBD stones, as they have a 95 % or greater negative predictive values individually and a combined negative predictive value of nearly 98 % [31]. A normal GGT alone was also shown to have a nearly 98 % negative predictive value but none of the individual or combined assays had greater than 28 % positive predictive value with TB being the highest at 27.4 % [31].

Other studies have found positive predictive values in the 30 % to nearly 60 % range if minimum thresholds are set for lab values above those traditionally considered abnormal [32–34]. This finding is likely due to increased elevation of liver enzymes as the time and severity of obstruction increases [24]. In the most current American Society for Gastrointestinal Endoscopy (ASGE) treatment guidelines, Maple and others note that the true negative rate (specificity) of total bilirubin has been shown to be 60 % at 1.7 mg/dL but it rises to 75 % if the cutoff is raised to 4 mg/dL [32]. However, the applicability of this threshold is limited because the mean total bilirubin level in patients with choledocholithiasis has been reported to be between 1.5 and 1.9 mg/dL, and less than one-third of patients will have a TB of 4 mg/dL or more [32–34]. Fractionating bilirubin can be helpful when a background of indirect hyperbilirubinemia is suspected (e.g., hemolytic disorders or Gilbert's Disease) [24].

Certain subgroups of patients may not benefit from LFT determination. Specifically, one study evaluating patients undergoing elective LC found that preoperative LFTs do not alter management beyond the course that would be determined by history, physical exam, and transabdominal ultrasound (US) exam alone. This study concluded that routine LFT determination in this patient population was not cost effective [35].

Imaging is mandatory in the work up of suspected biliary disease, and affords valuable information about both the gallbladder and CBD. Because direct visualization of a CBD stone by imaging is rare, CBD dilation has been used as the primary surrogate radiographic marker for choledocholithiasis. However, both the definition and grading of pathologic CBD dilation remain debated. Many factors other than obstruction influence the CBD diameter, including age, prior cholecystectomy, and prior sphincterotomy. The ASGE guidelines suggest that a diameter of 6 mm or greater (gallbladder in situ) is a strong predictor of CBD stone obstruction. In the three studies cited by the ASGE [36–38], the weighted mean of normal CBD diameters was 3.7 mm [39]. In a younger population of 830 consecutive blood donors between 18 and 65 years old, with gallbladder in situ, the mean CBD diameter was 2.7 ± 1.2 mm (SD) and none of the study subjects had a CBD greater than 7 mm [40]. Another study found that in 30 patients over age 80, the average CBD diameter was 5 ± 1.1 mm (SD) with a range of 3.9–7.1 mm [37]. In the same study, the authors found that the CBD dilates by 0.04 mm/year [37].

Other studies have also investigated the clinical importance of the CBD diameter. In a 2011 paper, Urquhart et al. emphasize that the 6 mm diameter guideline should not be understood as an "inflection point" above which risk of choledocholithiasis absolutely increases. On the contrary, studies have shown that risk of CBD stone increases linearly with increased CBD diameter [41, 42]. In Hunt's study of CBD diameter in 870 patients, 85 were shown to have CBD stones and almost half (42) had CBD diameter less than 6 mm. For CBD size 0–4, 4.1–6, 6.1–8, 8.1–10, and >10 mm the respective percentages of positive CBD stone finding were 3.9, 9.4, 28, 32, and 50 [41]. In another study, Boys et al. found that the rate of stones among patients presenting with acute cholecystitis and CBD diameter less than 6 mm and 6–9.9 mm was the same (14 %). At a CBD diameter above 10 mm, still only 39 % of patients had confirmed stones. They also found

that US-based selection of patients for additional imaging via Magnetic resonance cholangiopancreatography (MRCP) resulted in a near 90 % negative rate; however, there was a delay in care of almost 3-days [43]. Therefore, instead of thinking of the CBD as either dilated or not dilated, it is perhaps best for clinicians to view the diameter of the CBD and risk of CBD stone on a continuous spectrum and to retain a high index of suspicion even if CBD diameter is less than 6 mm, especially in a younger patient.

The various imaging modalities employed in the diagnosis of choledocholithiasis possess unique combinations of information, invasiveness, and cost. Transabdominal US is useful for diagnosing both cholelithiasis and choledocholithiasis, and should be considered as a first imaging modality due to favorable accuracy, least invasiveness, and low cost. Although US has poor sensitivity for visualization of stones in the CBD [24, 44–48], the modality is very sensitive for detecting CBD dilation, [24, 49–52]. Furthermore, when a stone is detected in the CBD by ultrasound, the study boasts of a specificity of 100 % for the diagnosis of choledocholithiasis, [48].

Endoscopic retrograde cholangiopancreatography (ERCP) involves a more invasive and costly means by which to diagnose choledocholithiasis, but offers the benefits of additional information and potential therapy. For these reasons, ERCP is often employed as a follow-up procedure in the United States when choledocholithiasis is suspected. Imaging the biliary tree during ERCP is accomplished with retrograde cholangiography via cannulation of the ampulla of Vater. Advantages of ERCP include favorable test performance characteristics for diagnosing choledocholithiasis, (sensitivity 89–90 % and specificity is 98–100 % [53, 54]) and the ability to perform therapeutic interventions such as stone lithotripsy, extraction, and sphincterotomy. Additional diagnostic maneuvers such as CBD brushings may also be accomplished. The main disadvantages of ERCP include availability, cost, and invasiveness. ERCP is usually performed under conscious sedation, although general anesthesia is sometimes required. Concomitant therapeutic interventions may lead to important morbidities, such as bleeding, pancreatitis, and biliary or bowel perforation. Andriulli et al. published the most comprehensive review of prospective ERCP morbidity and mortality data in 2007—including 16,855 patients in 21 studies. The cumulative rate of complications was 6.85 % (CI 6.46–7.24 %), with pancreatitis being the most common event (3.47 %) and infections and bleeding being second and third (1.62 % and 1.34 % respectively). Perforations occurred infrequently at 0.6 % and deaths occurred in 0.33 % of patients. Mortalities were caused by pancreatitis, infection, bleeding, and perforation at approximately equal rates. There were additional complications related to cardiovascular events or anesthesia-related effects that brought the pooled complication rate up to 8 % [55].

The potential risk of complications related to ERCP illustrates the importance the importance of considering less invasive imaging modalities for choledocholithiasis and other biliary pathology when evaluating patients for possible ERCP intervention. When first described in the 1960s, ERCP represented an exciting, minimally invasive alternative to both imaging and instrumenting the biliary tree in the pre-laparoscopy era [56]. However, with the advent of advanced laparoscopy, and in particular laparoscopic approaches to the CBD, enthusiasm for ERCP at our center and others has waned (see treatment) [57, 58].

MRCP is an imaging technique that uses the high water content in bile to produce 2D or 3D images of the biliary tree similar to those obtained with more invasive methods such as ERCP [59]. MRCP can image the biliary tree with high precision because bile and pancreatic secretions have high water content and appear white on heavily T_2-weighted images against a dark background of suppressed high-fat tissues. Importantly, MCRP images can be captured without the use of contrast or dyes [60]. In two separate meta-analyses, MRCP was found to have 85–92 % sensitivity and 93–97 % specificity for the detection of CBD stones [61, 62]. MRCP has also been shown to be equivalent to ERCP, for diagnosing biliary tree obstructions [63]. Despite these findings, MRCP is limited in detecting both smaller stones

(<5 mm) and sludge. Furthermore, MRCP is challenging in individuals with a body mass index >40 kg/m^2 [64–66]. Cost, time, frequent lack of availability, and inability to provide interventions all limit the utility of MRCP as a first-line imaging modality for the detection of choledocholithiasis. The greatest benefit from MRCP occur in cases of either laboratory or sonographic evidence of ductal obstruction without confirmation of choledocholithiasis or in cases in which ERCP is technically difficult or impossible (e.g., following rouy-n-y gastric bypass surgery) or unavailable.

Endoscopic ultrasound (EUS) uses specially designed echoendoscopes that take advantage of the close proximity of the duodenum and stomach to the biliary tree for imaging of the extrahepatic biliary anatomy. Three separate meta-analyses published between 2006 and 2008 reported pooled sensitivities of 89–94 % and specificities of 94–96 % for detecting CBD stones [61, 67, 68]. Although more invasive than MRCP, EUS remains safer than ERCP as a diagnostic modality. A prospective study by Canto and colleagues of 64 consecutive patients found EUS had a complication rate of 1.6 % versus 9.4 % for diagnostic ERCP [69]. The use of EUS before ERCP has been shown to significantly reduce the need for ERCP and its subsequent complications with the main drawback being the need for two procedures in the stone-positive EUS group [70]. Many endoscopists can perform ERCP if EUS is positive at same setting. EUS has also been shown to have value in finding undetected stones in patients at intermediate risk of choledocholithiasis [71]. In general, cost, availability of resources, and clinician experience will generally guide decisions on whether to employ ERCP or EUS in particular circumstances, as they have both been shown to have equivalent sensitivity and specificity [61].

Conventional and helical (spiral) CT scanning as well as CT cholangiography have been studied for the detection of choledocholithiasis. However, the utilization of radiation and contrast exposure in these studies have limited the use of these diagnostic modalities. Conventional CT scans have been found to be superior to the United States for diagnosing CBD stones, however these studies are more than 20 years old and most US hospitals now employ more advanced US imaging as well as spiral CT scanners [50, 52, 72]. In a 2000 study of 51 patients with suspected choledocholithiasis, Soto and others showed that oral contrast-enhanced CT cholangiography had 92 % sensitivity for detecting CBD stones, compared to 96 % for MR cholangiography—significantly better than the 65 % sensitivity of unenhanced helical CT [73]. The most recent study using multidetector helical CT scanning technology, published in 2013, found that unenhanced helical CT is 85 % sensitive for the detection of CBD stones with the primary limitations being radiopacity of stones and stone size less than 5 mm [74]. A 2006 study of combined unenhanced and contrast-enhanced helical CT found 71 % sensitivity in detecting CBD stones, however less than half of the cholesterol stones were detected by CT, leading the authors to conclude that CT might not be the ideal detection modality in Western countries where cholesterol stones are most common [75]. Additionally, coronal reconstruction does not improve the diagnostic efficacy of CT [76]. Given the expense, and radiation/dye exposure, the role of CT in diagnosing suspected CBD stones will likely remain limited. Clinicians should not rule out a small or radiolucent stone in a symptomatic patient where CT scans are negative.

In addition to the aforementioned nonoperative imaging techniques, both IOC and intraoperative laparoscopic ultrasound (LUS) may be performed during the course of cholecystectomy to diagnose choledocholithiasis. IOC involves the injection of iodinated contrast dye into the extrahepatic biliary tree via either the cystic duct or gallbladder for fluoroscopic imaging. Although methods for delineating the anatomy of the biliary tree were published as early as 1919, Mirizzi first described IOC in the 1930s as a way to visualize retained stones and other defects during open cholecystectomy [77, 78]. Mirizzi and other authors in the 1930s recognized that IOC was also useful for diagnosing iatrogenic bile duct injuries [78, 79].

Despite the early recognition of the value of IOC, it remained a technique routinely utilized by

only a quarter of surgeons into the 1970s, due in large part to the time that it added to open cholecystectomy procedures [80, 81]. IOC is not particularly technically challenging (either open or laparoscopically), but the 20–30 min it took to setup, take, and develop the static films was a major hurdle to widespread adoption. This limitation was at least partially mitigated by the advent of mobile C-arm high-resolution image intensifier fluoroscopic units, which took total procedure time down to a mean of 16 min and significantly improved image accuracy [81–83]. Yet, a 2012 study of 177,000 cholecystectomies performed in Texas found drastically wide variation in the use of IOC, both among individual surgeons (2.4–98.4 % of cases) and hospitals (3.7–94.8 % of cases), with an overall IOC rate of 44 %[84].

There are two issues to consider when evaluating IOC in patients with suspected choledocholithiasis: (1) Does routine IOC improve the overall safety of LC? and (2) What is the utility of IOC in patients with suspected choledocholithiasis? The first question remains highly debated because the data are mixed as to whether IOC identification of biliary structures improves safety. A recent meta-analysis of eight randomized studies with 1715 patients found that there was insufficient level-one evidence to support or abandon the use of IOC. This finding resulted largely due to the studies being underpowered for detecting differences in bile duct injury rates, which occur only a fraction of one percent of the time [83]. In fact, it has been suggested that a randomized trial would have to include between 12,000 and 30,000 patients in order to be sufficiently powered to detect this difference [85, 86]. It is therefore unlikely that a definitive answer to this question will ever be found. Instead, other authors have looked at nonrandomized population-based trials. One recent review of six large nonrandomized studies found that the data is conflicting in that half of the studies showed a safety benefit, while half did not [87]. However, the largest studies suggest that routine IOC could prevent one ductal injury in every 500 operations, thereby roughly halving the risk of ductal injury during cholecystectomy [87]. This data point is particularly interesting because the rate of iatrogenic bile duct injuries in *open* cholecystectomies was reportedly 0.2 % and the LC duct injury rate is 0.3–0.6 % or about double that figure [88–91].

A separate issue involves the role of IOC in diagnosis and treatment of patients with suspected choledocholithiasis. The data suggests that IOC is very effective at identifying stones in the CBD as demonstrated in a recent meta-analysis, which found IOC had a pooled sensitivity of 0.87 (95 % CI 0.77–0.93) and a pooled specificity of 0.99 (95 % CI 0.98–0.99) [92]. Since the advent of endoscopic techniques for stone removal, the most commonly employed method for management of suspected choledocholithiasis has been a two-stage approach, where ERCP is performed first to find and remove CBD stones and a follow-up LC is performed for definitive treatment of the gallbladder disease [93]. In this context, the value of IOC is limited, since its use would be in detecting rare retained stones after ERCP or stones that had subsequently migrated into the CBD in the interval between ERCP and LC. However, several recent papers have shown equivalent clinical results and superior economics with a single-stage approach where LC is combined with IOC and subsequent laparoscopic common bile duct exploration (LCBDE) [94] (discussed below). In our view, the best role for IOC and LUS is in complete laparoscopic management of CBD stones.

In experienced hands, laparoscopic ultrasonography (LUS) can certainly play a similar though less invasive role in single-stage treatment of CBD stones. In LUS, an ultrasound transducer is introduced through a 12 mm port during LC, where it is used to identify biliary tree structures and stones in the CBD. Although it requires specialized laparoscopic ultrasound equipment, compared to IOC, LUS is faster, less expensive, less invasive, and avoids the risks of radiation and iodinated dye exposure [95]. For detection of CBD stones, LUS is equivalent to IOC with a recent meta-analysis showing pooled sensitivity of 0.87 (95 % CI 0.80–0.92) and a specificity of 1.00 (95 % CI 0.99–1.00) [92]. LUS has also been utilized successfully as a routine intraoperative prescreening tool for determining which patients get selective IOC [85]. Finally, LUS has

demonstrated the capacity of avoiding intraoperative bile duct injuries [85]. In this case, LUS is superior to IOC in that a ductotomy (potentially of a misidentified CBD) is not necessary to delineate biliary anatomy.

In summary, abdominal US should be the first imaging modality used in all patients with suspected biliary pathology, regardless of suspicion for choledocholithiasis. Additional imaging and diagnostic modalities should be chosen based upon risk, index of suspicion for cCDL and availability of local expertise. The routine use of ERCP as a diagnostic modality is not justified due to its cost and invasiveness and because both IOC and LUS at surgery may be just as effective at identifying choledocholithiasis. The advantages and limitations of the aforementioned imaging modalities are summarized in Table 14.1.

Clinical Decision Making and Treatment

Fundamentally in cases of suspected or documented choledocholithiasis, the goals of treatment are to clear the CBD of stones if present and to remove the gallbladder. The first step in the aforementioned process involves determining the likelihood of choledocholithiasis [96, 97]. The literature is replete with predictive models for choledocholithiasis [6, 29, 31–33, 48, 98–101]. For a thorough example of such an algorithm, the reader is referred to the 2010 ASGE recommendations [24]. In these recommendations, Maple and co-authors present three predictor categories: *very strong*, *strong*, or *moderate*. Clinical factors such as patient demographics, physical exam findings, labs, and imaging, fit into these predictor categories (Table 14.2). Risk of CBD stone is categorized as *high*, *medium*, or *low,* based on the presence of various predictors (Table 14.3). Treatment is then advised based upon the risk stratification [24].

Despite these and other expert recommendations, there is currently no consensus approach to patients with suspected choledocholithiasis. Rather, management of these patients is based upon index of suspicion for CBD stones, availability of both resources and expertise, and local referral patterns (Fig. 14.2). Fundamentally, three strategies may be identified. The first option involves inpatient admission of patients at mild to moderate risk of choledocholithiasis (as evidenced primarily by laboratory derangements) for serial laboratory evaluation. ERCP is performed in patients with either persistent or worsening laboratory derangements. By contrast, patients in whom laboratory derangements improve are taken for LC without CBD imaging (the presumption being that the CBD stone has passed). This particular strategy is lengthy, costly, and dissatisfying to patients, who must be admitted, additional blood work obtained, and definitive surgery delayed. Furthermore, multiple studies have shown that patients classified as high likelihood of CBD stone (by ASGE recommendations) have a 40–80 % rate of actual stone on EUS or ERCP, with faster timing being postulated as the reason for better results [102, 103].

The second management strategy, or the "two-stage approach," involves both routine ERCP and LC as separate procedures. In this strategy, ERCP functions to access, interrogate, and clear the CBD, including various combinations of techniques such as cholangiography, stone extraction, lithotripsy, and biliary sphincterotomy. Typically, ERCP is performed first and routinely, followed by LC. However, ERCP may also be used selectively following cholecystectomy in patients with IOC findings suggestive of choledocholithiasis. Although this latter approach carries the possibility of a third, open surgery being needed in the case of failed ERCP, this risk is exceedingly low, as contemporary technology is highly effective at clearing even larger (e.g., 8–10 mm) stones endoscopically [104–106]. US national healthcare survey data indicate that greater than 90 % of patients with CBD stones are managed using the two-stage approach. Although the order of the procedures is not clear, data suggest that ERCP first is the most popular method [107, 108].

The main advantage to the two-stage approach involves endoscopic clearance of the CBD. Prior to laparoscopic surgery, there was no advantage to pre-cholecystectomy stone removal because open bile duct clearance was common and either

Table 14.1 Imaging modalities for detection of CBD stones

Imaging modality	Advantages	Disadvantages	Recommended application	Refs.
Transabdominal ultrasound	• Least invasive • Lowest cost • Highly sensitive for CBD dilation	• Poor sensitivity for visualizing stones in CBD	Use in all patients with suspected CBD stones	[24, 44–52]
MRCP	• Less invasive • No contrast • Highly sensitive and specific	• Expensive • Time consuming • Limited utility in obese patients • Limited ability to detect small stones • Limited availability	Use when labs and/or US suggest obstruction in the absence of gallstones or when ERCP is difficult or impossible	[60–65]
CT scan	• Fast • Widely available • Moderate sensitivity and specificity	• Expensive • Radiation exposure • Contrast exposure • Limited ability in cholesterol stones	Not recommended for use and negative CT should not rule out CBD stone	[71–73]
Endoscopic ultrasound	• Safer than ERCP as diagnostic modality • Highly sensitive and specific • Optional immediate intervention	• More invasive than MRCP • Requires sedation and experienced endoscopist • 1.6 % complication rate	Use in combination with ERCP only when ERCP is chosen first treatment modality	[60, 66–68]
ERCP	• Gold standard for imaging the biliary tree • Highly sensitive and specific • Immediate intervention	• Most invasive nonoperative approach • Requires sedation and experienced endoscopist • 8 % complication rate	Imaging and intervention in acute cholangitis or gallstone pancreatitis complicated by cholangitis and/or biliary obstruction	[53–55]
Laparoscopic ultrasound	• Equivalent to IOC without dye or radiation • Faster than IOC • Highly sensitive and specific	• Requires specialized equipment and training • Time consuming in OR	Alternative to IOC or screening tool for IOC during complete laparoscopic management of CBD stone	[84, 91, 94]
Intraoperative cholangiography	• Highly sensitive and specific • May improve safety of LC	• Highly invasive • Time consuming in OR • Dye exposure • Radiation exposure	Use during complete laparoscopic management of CBD stone	[80–82, 86, 91]

MRCP magnetic resonance cholangiopancreatography, *CBD* common bile duct, *US* ultrasound, *ERCP* endoscopic retrograde cholangiopancreatography, *CT* computed tomography, *IOC* intraoperative cholangiography, *OR* operative room

Table 14.2 Predictors of choledocholithiasis

Very strong	Strong	Moderate
CBD stone on transabdominal US	Dilated CBD on US >6 mm with gallbladder in situ	Abnormal liver biochemical test other than bilirubin
Clinical ascending cholangitis	Total bilirubin 1.8–4 mg/dL	Age older than 55 years
Total bilirubin >4 mg/dL		Clinical gallstone pancreatitis

CBD common bile duct, *US* ultrasound. Adapted from Maple et al. [24]

Table 14.3 Risk of common bile duct stone

High (>50 %)	Moderate (10–50 %)	Low (<10 %)
Presence of any very strong predictor	Presence of any combination of predictors other than those for high	No predictors present
Presence of both strong predictors		

Adapted from Maple et al. [24]

as good or better than ERCP at clearing CBD stones [109, 110]. However, the advent of LC rendered the CBD inaccessible by traditional means. As a result, preoperative or postoperative stone clearance with ERCP gained popularity as LC became more common.

However, as both the practice and efficacy of laparoscopic CBD clearance increased, the primary advantage of the two-stage approach has come under scrutiny. Because the two-stage approach involves at least two separate procedures, time, resources, costs, and complications are increased. The main risks of ERCP have been discussed earlier and involve duodenobiliary reflux, pancreatitis due to accidental cannulation of the pancreatic duct, duodenal perforation, and intraluminal massive hemorrhage from injury to the gastroduodenal artery.

Furthermore, as many as 65–80 % of patients with suspected choledocholithiasis will be negative for stones on ERCP/EUS, rendering the procedure unnecessary [103, 102]. Even after stones have been confirmed intraoperatively with IOC, only 50 % of post-LC ERCPs are positive for CBD stones [111], presumably because either the stone has passed in the interim or was misdiagnosed by IOC.

Finally, as many as one-third of patients managed with the two-stage, ERCP first approach, never end up having a cholecystectomy. Although biliary sphincterotomy may prevent further episodes of cCDL, both biliary colic and cholecystitis are still possible as long as the gallbladder remains in situ. The incidence of recurrent biliary symptoms is significantly higher in patients following endoscopic sphincterotomy who are discharged with gallbladder in situ versus those who receive same admission cholecystectomy [112, 113]. A prospective study of patients who had LC within 72 h of ERCP versus those who waited 6–8 weeks found that the group who waited had a 36 % rate of repeat complications compared to 2 % in the LC within 72 h group [114]. In a retrospective study at our institution, our colleagues showed that of 24 patients discharged after medical management of gallstone pancreatitis with specific instructions to return for LC, only seven (29 %) returned for definitive treatment of their gallstone disease [112].

The final strategy is referred to as the "single-stage" approach. This approach involves immediate LC on all patients with cholelithiasis, regardless of preoperative probability of choledocholithiasis (with three important exceptions, discussed below). In patients in whom choledocholithiasis is suspected preoperatively (either dilated CBD on transabdominal US or direct hyperbilirubinemia), one or both LUS and IOC are performed. If choledocholithiasis is confirmed on these imaging modalities, a laparoscopic CBD exploration (LCBDE) is performed, with definitive clearance of the CBD.

The technique of LCBDE was originally described in the 1990s and has undergone several recent modifications, including improvements in both technique and equipment. A choledochoscope is introduced though a laparoscopic port and the CBD is cannulated either through a cystic ductotomy (prior to cholecystectomy) or a primary choledochotomy; both approaches have been reported to be safe [115]. Various devices,

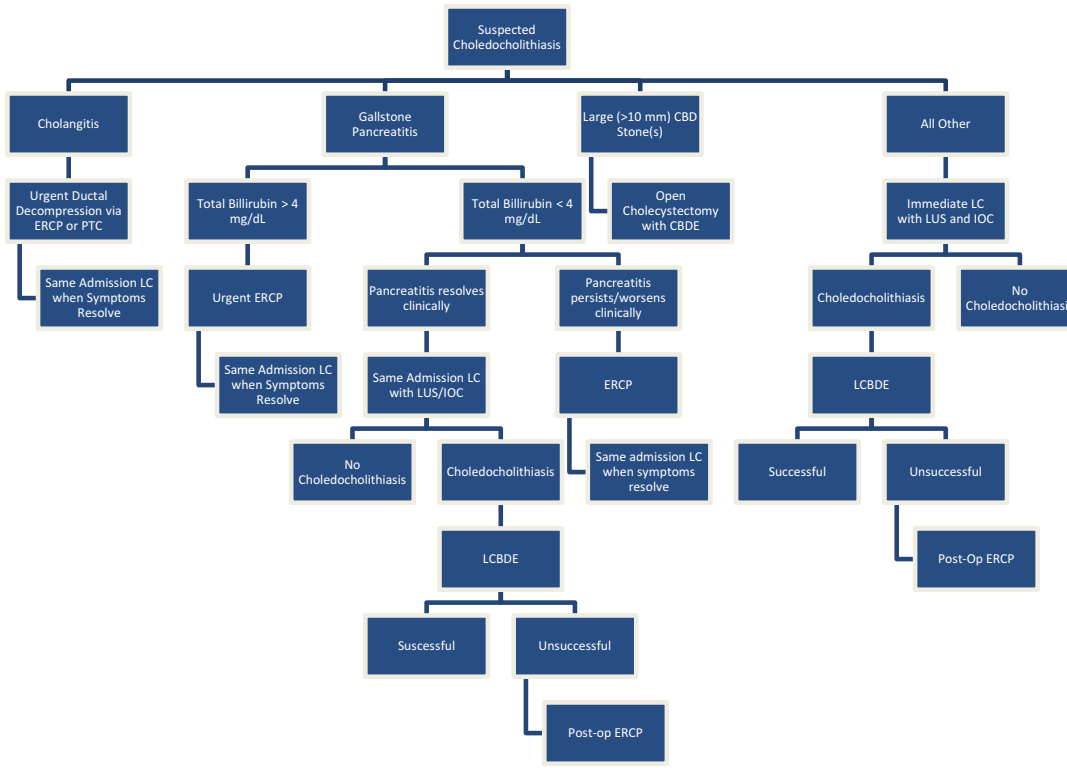

Fig. 14.2 Algorithm for management of suspected choledocholithiasis. Choledocholithiasis is suspected in the presence of cholelithiasis plus (1) jaundice, (2) direct hyperbilirubinemia or (3) dilated common bile duct diameter. *ERCP* endoscopic retrograde cholangiopancreatography, *PTC* percutaneous transhepatic cholangiostomy, *LC* laparoscopic cholecystectomy, *LUS* laparoscopic ultrasound, *IOC* intraoperative cholangiogram, *CBDE* common bile duct exploration, *LCBDE* laparoscopic common bile duct exploration

including power irrigators, balloons, baskets, and lithotripsy devices, are then introduced through the working channel of the choledochoscope to achieve ductal clearance.

The single-stage approach has several potential advantages. First, if either the IOC disproves choledocholithiasis, or the LCBDE is successful, ERCP is avoided. Second, definitive treatment of choledocholithiasis, i.e., cholecystectomy, is accomplished during the same procedure. Finally, when ERCP is unavailable in a timely fashion (or at all), the single-stage approach minimizes delays in definitive treatment. The primary disadvantage of the single-stage approach is the relative lack of availability and expertise in LCBDE. Another potential disadvantage is the need for postoperative ERCP in the case of failed LCBDE, however, the necessity of a second procedure occurs by definition in the two-stage approach—making this situation equivalent.

Several RCTs have suggested the superiority of a single-stage approach in terms of time to definitive care, number of procedures, length of stay, and costs [106, 116–120]. Single-stage treatment has also been shown to be safe in elderly patients [121]. The results of these trials must be interpreted cautiously, as the LCBDEs were performed by surgeons with additional training in advanced laparoscopy at high volume centers. However, one group recently reported favorable outcomes following adoption of the single-stage approach by a group of acute care surgeons with less ERCPs, higher same admission cholecystectomy, and fewer gallbladder-related

readmissions [122]. The cost-effectiveness of LC plus ERCP vs. LC plus LCBDE has been studied specifically with most studies suggesting the single-stage approach is superior [123]. Depending on the local success rate of LCBDE, the single-stage approach may frequently in essence become a two-stage approach if the laparoscopic clearance methods prove unsuccessful.

A recent addition to the single-stage management pathway has been termed the "rendezvous approach," and involves simultaneous LC and ERCP. Intraoperative ERCP may be used routinely in cases of choledocholithiasis documented by either IOC or LUS or alternatively, it may be employed selectively in cases of failed LCBDE. Although outcomes data regarding the rendezvous approach remain scant, initial reports have been favorable [124–126]. This technique represents a potential step forward in the management of choledocholithiasis and a viable option for surgeons who do not practice LCBDE but want to manage cCDL during one procedure [126].

Although the vast majority of patients with suspected choledocholithiasis will be eligible for management via the single-stage approach, several important exceptions warrant discussion. Cholangitis involves bacterial infection of the biliary tree, most commonly with associated sepsis, and occasionally with both bacteremia and shock. Early biliary decompression is paramount to successful management of this disease [127]. Surgical stress, including induction of general anesthesia, pneumoperitoneum, bleeding, and tissue trauma, exacerbate the effects of cholangitis. As such, biliary decompression should occur by the least invasive means possible; usually in the form of either ERCP or percutaneous transhepatic cholangiostomy (PTC). Patients with acute cholangitis should generally not be managed using a single-stage approach. Once sepsis has resolved following biliary ductal decompression, LC may be performed safely.

Interesting, recent data have challenged the aforementioned, traditional management strategy for patients with cholangitis. Chan et al. reported favorable outcomes for a small group of patients with cholangitis managed with a single-stage approach, including immediate LC plus LCBDE [128]. However, we believe that a larger experience is necessary prior to recommend a change in practice, and biliary decompression via ERCP or PTC remains the safest option for patients with cholangitis.

Acute pancreatitis is characterized by intense retroperitoneal inflammation, resulting in the systemic inflammatory response syndrome, diffuse tissue edema, and, in particular, obscuring of biliary anatomy. Patients often require resuscitation using both volume expansion and vasopressors. In light of this, gallstone pancreatitis has been managed traditionally by bowel rest and watchful waiting until clinical markers of inflammation, including abdominal pain and tenderness, have resolved. Patients who present with gallstone pancreatitis should not be taken for immediate LC. Moreover, the rare patients with gallstone pancreatitis and coexisting cholangitis or biliary obstruction (TB > 4 mg/dL) benefit from urgent ERCP [129]. LC may then be performed safely following ERCP, and during the same admission.

Finally, bypassing both LC and ERCP to initial surgery should be considered in cases of larger (e.g., >10 mm) CBD stones as these may not be amenable to ERCP-guided stone removal. Imaging of such patients may be quite impressive, showing giant CBD stones, as well as a massively dilated gallbladder and CBD (Fig. 14.3). Although no formal size threshold exists, patients with one or more CBD stone >10 mm should be considered for open CBD exploration, choledochotomy, and stone clearance. Important technical points of this operation include utilizing a longitudinal incision to preserve blood supply to the CBD, placement of the incision near the confluence of the common hepatic and cystic ducts, utilization of stay sutures on the duct, and Kocherization of the duodenum to palpate and manipulate distal CBD stones. Following removal of all CBD stones both proximal and distal to the choledochotomy, the incision is closed over a large T-tube to allow for subsequent imaging and intervention of the biliary tree if needed.

Large stones that are impacted at the ampulla may be impossible to remove. In the case of a

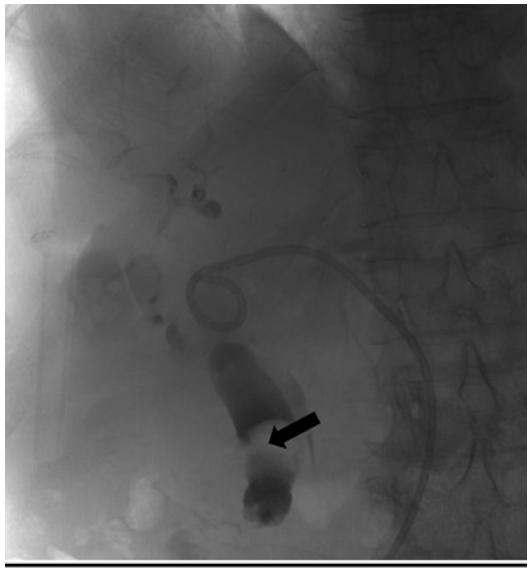

Fig. 14.3 Large common bile duct stone. Percutaneous transhepatic cholangiogram from an 88-year-old woman who presented with ascending cholangitis. A large, 2.5 cm stone (*arrow*) is seen within a massively dilated common bile duct. Following ductal decompression via PTC, her sepsis resolved and she underwent an open cholecystectomy, common bile duct exploration, stone extraction, and T-tube placement. *Source*: FM Pieracci

dilated CBD and absent pancreatitis, a choledochoenterostomy may be performed, utilizing either the Kockerized duodenum (choledochodoudenostomy) or a Roux limb of jejunum (choledochojejunostomy). In the case of a normal sized CBD or recurrent pancreatitis from the impacted stone, an open, transduodenal sphincterotomy may be performed. For an excellent description of these operations, the reader is referred to Gliedman's Atlas of Surgical Techniques [130].

One final clinical scenario involving symptomatic choledocholithiasis is the post gastric bypass patient. Management options include LC with LCBDE, laparoscopic-assisted, transgastric remnant ERCP, or traditional, transoral ERCP using an extra-long endoscope. Selection of a technique will depend upon patient anatomy and operator expertise.

Although treatment discussions thus far have addressed either suspected or confirmed choledocholithiasis, one final discussion point involves management of incidentally discovered choledocholithiasis. This situation arises most commonly during routine IOC for elective cholecystectomy. In institutions where either IOC or LUS are used routinely, surgeons should expect incidental findings of CBD stones in a small minority of low-risk patients—studies have suggested between 2 and 12 % [7, 131, 132]. Although once believed to be benign, recent studies of patients in whom small CBD stones were found incidentally have suggested that approximately 25 % of these patients go on to experience symptoms related to their choledocholithiasis [133]. Thus, when choledocholithiasis is found intraoperatively, regardless of the clinical scenario, we advocate for clearance of the CBD.

Conclusion

Choledocholithiasis commonly complicates cholelithiasis. It is suspected in the presence of jaundice, direct hyperbilirubinemia, and dilation of the CBD on transabdominal US. Whether CBD stones are found incidentally or in symptomatic patients, many advocate a policy of routine ductal clearance. The optimal means by which to achieve this remains controversial, and is dependent upon operator expertise and resource availability. If local expertise allows, many recommend a single-stage approach, to include immediate LC in all patients regardless of the level of suspicion of choledocholithiasis, followed by both LUS and IOC, and finishing with LCBDE in cases of confirmed choledocholithiasis. Important exceptions include cholangitis, acute gallstone pancreatitis, and relatively large, impacted CBD stones. Continued advancements in technology, as well as more universal training in minimally invasive surgical approaches to CBD clearance will refine management strategies.

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Acute Acalculous Cholecystitis

15

Philip S. Barie and Soumitra R. Eachempati

Introduction

Acute cholecystitis may develop at any time when gallstones are present. The likelihood of this disease developing appears to accelerate once symptoms develop. Acute acalculous cholecystitis (AAC) is now a well recognized complication of serious medical and surgical illnesses [1–3] and is being diagnosed more frequently in critically ill patients [4]. The mortality rate of AAC remains at least 30 % because of the potential obscurity of the diagnosis, the underlying illnesses of the affected patients, and because of the potential rapid progression of the disease to gangrenous cholecystitis and gallbladder perforation (~10 %) [5].

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Clinical Patterns of AAC

Reports of acute cholecystitis complicating surgery, multiple trauma, or burn injury abound in the literature. While the patients with AAC generally harbor some major acute or chronic illness, clinicians have tried to detect more precise patterns of the disease's frequency. More than 80 % of patients who develop non-trauma-related postoperative AAC are male [6]. The incidence of AAC after open abdominal aortic reconstruction is 0.7–0.9 % [7, 8] and the disease has also been reported to complicate endovascular aortic reconstruction [9].

The incidence of acute cholecystitis is 0.12 % after cardiac surgery (42 % AAC) in collected reports encompassing 31,710 patients with an overall mortality rate of 45 % [6]. Those undergoing cardiac valve replacement with or without bypass grafting may be at particular risk [10] because of associated cardiomyopathy. Postoperative cholecystitis, regardless of the antecedent operation, is as likely to develop in the presence of gallstones as in their absence [11]. Patients with trauma [12, 13] or burns [14] have a striking predilection to develop AAC and again mostly among male patients.

The development of AAC is not limited to surgical or injured patients, or even to critical illness. Diabetes mellitus, abdominal vasculitis [15, 16], congestive heart failure, cholesterol embolization of the cystic artery [17, 18], and resuscitation

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from hemorrhagic shock or cardiac arrest [19] have been associated with AAC. Hemodialysis is associated with AAC, perhaps because both diabetes mellitus and atherosclerosis are commonplace in patients with end-stage renal disease [20]. Patients with cancer are also at risk for AAC, including metastasis to the porta hepatis, therapy with interleukin-2 and lymphokine-activated killer cells for metastatic disease [21], or percutaneous transhepatic catheter drainage of extrahepatic biliary obstruction [22]. AAC has been reported with acute myelogenous leukemia [23]. In bone marrow transplant recipients, the incidence of AAC is as high as 4 % [24].

Acalculous cholecystitis may also develop as a secondary infection of the gallbladder during systemic sepsis, for example, in disseminated candidiasis [25, 26], leptospirosis [27], in chronic biliary tract carriers of typhoidal [28] and nontyphoidal *Salmonella* [29], cholera [30], and tuberculosis [31]. Also reported are cases of AAC in malaria [32], brucellosis [33], and dengue fever [34]. Extrahepatic biliary obstruction can cause AAC from infectious or noninfectious causes. Obstructive infectious causes include ascariasis [35] and echinococcal cysts [36], whereas noninfectious causes of AAC with extrahepatic biliary obstruction include hemobilia [37], choledochal cyst [38], ampullary stenosis [39], or rarely snakebite [40].

Acalculous biliary disease presents in patients with the acquired immunodeficiency syndrome (AIDS), as either cholestasis [40–42], which can be sometimes difficult to distinguish from bacterial cholangitis, or AAC [43, 44]. Now increasingly rare, AIDS-associated AAC has been associated with cytomegalovirus (CMV) infection [43], EBV infection [44], or infection with *Cryptosporidium* or microsporidial protozoa [44–46].

AAC represents 50–70 % of all cases of acute cholecystitis in children [47]. Acalculous cholecystitis is recognized in young children and neonates [48], as well as older children. Dehydration is a common precipitant, as are acute bacterial infections [49] and viral illnesses such as hepatitis and upper respiratory tract infections. Portal lymphadenitis with extrinsic cystic duct obstruction may be etiologic in viral infections. Recent reports [48] suggest that the pathogenesis may be similar to that in adults.

Pathogenesis

Bile Stasis

Bile stasis has been implicated in the pathogenesis of AAC in both experimental and clinical studies [47]. Hospitalized patients are potentially prone to this situation due to multiple factors including dehydration, fasting leading to impaired enterohepatic circulation, total parenteral nutrition (TPN), and impaired gut metabolism. Volume depletion additionally leads to concentration of bile, which can become inspissated in the absence of a stimulus for gallbladder emptying. Opioid analgesics increase intraluminal bile duct pressure due to spasm of the sphincter of Oddi. Several early clinical studies suggested that ileus can result in bile stasis, but experimental results are conflicting. Bile stasis may also be induced by mechanical ventilation with positive end-expiratory pressure (PEEP), which also decreases portal perfusion by increasing hepatic venous pressure [50–52].

Bile stasis may alter the chemical composition of bile, which may promote gallbladder mucosal injury. Lysophosphatidyl choline has potent effects on gallbladder structure and functional water transport across mucosa [53]. Acute cholecystitis induced by lysophosphatidyl choline in several animal models results in histopathology identical to that of human AAC [53]. Other compounds present in bile (e.g., beta-glucuronidase) have also been implicated in the pathogenesis of AAC [54].

Total Parenteral Nutrition

Fasting and bile stasis may be aggravated by TPN in the pathogenesis of AAC [55]. Parenteral nutrition is associated with gallstone formation as well as AAC in both adults and children. The incidence of AAC during long-term TPN may be as high as 30 % [54]. Formation of gallbladder "sludge" occurs among 50 % of patients on long-

term TPN at 4 weeks and is ubiquitous at 6 weeks [56, 57]. However, neither stimulation of gallbladder emptying with cholecystokinin nor enteral alimentation can completely prevent AAC among critically ill patients [58].

Gallbladder Ischemia

Gallbladder ischemia is central to the pathogenesis of AAC. An interrelationship between ischemia and stasis can result in hypoperfusion [59]. Perfusion is decreased by hypotension, dehydration, or the administration of vasoactive drugs, whereas intraluminal pressure is increased by bile stasis, thereby decreasing gallbladder perfusion pressure. In this model, bacterial invasion of ischemic tissue becomes a secondary phenomenon [59]. Additionally, reperfusion injury may exacerbate an already tenuous situation [60]. Prolongation of ischemia has been associated with increased mucosal phospholipase A_2, superoxide dismutase activities, and increased mucosal lipid peroxide content.

Numerous clinical observations of hypoperfusion leading to AAC support this hypothesis [6, 8, 10, 16, 17], as does the pathologic observation of high rates of gallbladder necrosis and perforation. Gallbladder specimen arteriography reveals marked differences between acute calculous and AAC in human beings [61]. Whereas gallstone-related disease is associated with arterial dilatation and extensive venous filling, AAC is associated with multiple arterial occlusions and minimal-to-absent venous filling, reiterating the central role of vascular occlusion and microcirculatory disruption in the pathogenesis of AAC.

Mediators of Inflammation, Sepsis, and AAC

Vasoactive mediators also play a role in the pathogenesis of AAC. Although bacterial infection is likely a secondary phenomenon, the host response to gram-negative bacteremia or splanchnic ischemia/reperfusion injury may be of primary importance. Intravenous injection of *Escherichia coli* lipopolysaccharide (LPS), a potent stimulus of inflammation and coagulation, produces AAC in several mammalian species, including opossums [62] and cats [63]. In opossums, LPS decreased the contractile response to cholecystokinin and causes a dose-dependent mucosal injury [62]. The dysmotility was abolished by inhibition of nitric oxide synthase. Human gallbladder mucosal cells stimulated in vitro with LPS secrete eicosanoids and platelet-activating factor (PAF) [64]. Cholecystitis can also be produced by injection of plant polyphenols that activate Factor XII directly and produce immediate spasm of the cystic artery [65]. PAF has been implicated in the pathogenesis of splanchnic hypoperfusion in sepsis and other low-flow states [66]. The inflammation appears to be mediated by pro-inflammatory eicosanoids, as it is inhibited by nonspecific cyclooxygenase inhibitors [63].

Diagnosis

AAC poses major diagnostic challenges [66, 67]. Most afflicted patients are critically ill and unable to communicate their symptoms. Cholecystitis is but one of many potential causes in the differential diagnosis of systemic inflammatory response syndrome or sepsis in such patients. Rapid and accurate diagnosis is essential, as gallbladder ischemia can progress rapidly to gangrene and perforation. Acalculous cholecystitis is sufficiently common that the diagnosis should be considered in every critically ill or injured patient with a clinical picture of sepsis or jaundice and no other obvious source.

Physical examination and laboratory evaluation are unreliable [67]. Fever is generally present but other physical findings cannot be relied upon, particularly physical examination of the abdomen [12]. Leukocytosis and jaundice are commonplace, but nonspecific in the setting of critical illness. The differential diagnosis of jaundice in the critically ill patient is complex and context sensitive, including intrahepatic cholestasis from sepsis or drug toxicity and "fatty liver" induced by TPN, in addition to AAC [68]. Other

biochemical assays of hepatic enzymes are of little help. The diagnosis of AAC thus often rests on radiologic studies.

Ultrasound

Ultrasound of the gallbladder is the most accurate modality to diagnose AAC in the critically ill patient. Although sonography is accurate for detecting gallstones and measuring biliary duct diameter, neither is particularly relevant to the diagnosis of AAC. Thickening of the gallbladder wall is the single most reliable criterion [69, 70], with reported specificity of 90 % at 3.0 mm and 98.5 % at 3.5 mm wall thickness, and sensitivity of 100 % at 3.0 mm and 80 % at 3.5 mm. Accordingly, gallbladder wall thickness ≥3.5 mm is generally accepted to be diagnostic of AAC. Other helpful ultrasonographic findings for AAC include pericholecystic fluid or the presence of intramural gas or a sonolucent intramural layer, or "halo," that represents intramural edema [71, 72]. Distension of the gallbladder of more than 5 cm in transverse diameter has also been reported [71]. False-positive ultrasound examinations have been reported, and may occur in particular when conditions including sludge, non-shadowing stones, cholesterolosis, hypoalbuminemia, or ascites mimic a thickened gallbladder wall [70].

Radionuclide Studies

Although technetium ^{99m}Tc iminodiacetic acid imaging is approximately 95 % accurate to diagnose calculous acute cholecystitis [73], false-negative hepatobiliary scans frequently occur when used for diagnosis of AAC in the setting of critical illness [74, 75], due to false-positive scans associated with fasting, liver disease, or feeding with TPN [75]. The sensitivity of hepatobiliary imaging for AAC is reportedly as low as 68 % [75]. Intravenous morphine (0.05 mg/kg) given after initial non-visualization of the gallbladder may increase the accuracy of cholescintigraphy among critically ill patients, by enhanced gallbladder filling due to increased bile secretory pressure [76, 77]. Morphine cholescintigraphy has led to a reappraisal of radionuclide imaging for AAC [78], especially when a screening ultrasound has been non-diagnostic (86 % accuracy was reported in one study) [78].

Computed Tomography

Computed tomography (CT) appears to be as accurate as ultrasound in the diagnosis of AAC (Fig. 15.1) [79]. Diagnostic criteria for AAC by CT are similar to those described for sonography [80]. Only a single retrospective study has compared all three modalities (ultrasound, hepatobiliary scanning, and CT) [81]. In this study, sonography and CT were comparably accurate and superior to hepatobiliary imaging. Low cost and the ability to perform sonography rapidly at the bedside make it the preferred diagnostic modality in possible AAC in the ICU setting. Preference may be given to CT if other thoracic or abdominal diagnoses are under consideration.

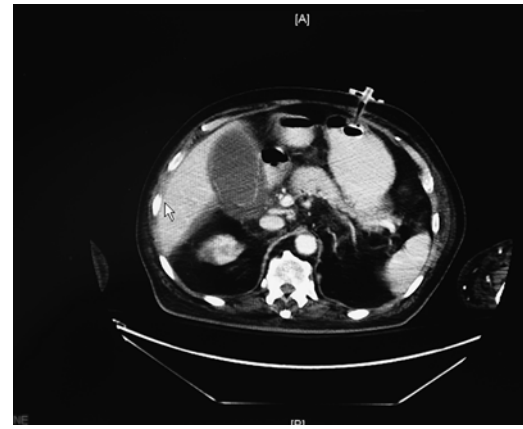

Fig. 15.1 A patient who has been diagnosed with acute acalculous cholecystitis. The gallbladder has a characteristic thickened wall with dependent sludge in the gallbladder. The patient was successfully treated with percutaneous drainage

Laparoscopy

The primary utility of laparoscopy for AAC is when the diagnosis is in doubt or if percutaneous cholecystostomy has failed to correct the patient's illness [82–85]. Bedside laparoscopy has been used with some success for the diagnosis and therapy of AAC but initial enthusiasm has waned because bringing the equipment to the ICU bedside is cumbersome. Nowadays due to advances in critical care anesthesia, most patients will tolerate the transport to the operating room as well as the physiologic effects of the anesthetic. Importantly, for severely inflamed gallbladders where complete laparoscopic cholecystectomy is not possible in an expedient manner, a laparoscopic damage control procedure may be performed to treat the patient's pathology while minimizing the physiologic insult.

Therapy

In the past, the treatment for AAC was cholecystectomy [2], due to the ostensible need to inspect the gallbladder and perform a resection if gangrene or perforation was present. Other pathology that could mimic acute cholecystitis (e.g., perforated ulcer, cholangitis, pancreatitis) could also be identified at this time during open or laparoscopic operation if the diagnosis of AAC were incorrect. However, percutaneous cholecystostomy is now established as a lifesaving, minimally invasive alternative [86, 87]. Cholecystostomy by either technique will not decompress the common bile duct if cystic duct obstruction is present. Therefore the common duct must be decompressed in addition by some manner if cholangitis is suspected. Patency of the cystic duct can be determined immediately by tube cholangiography after cholecystostomy but this is usually not necessary. If gallstones are present an elective cholecystectomy is usually recommended in a delayed fashion whereas interval cholecystectomy is not generally indicated after AAC [87] and the cholecystostomy tube can be removed after tube cholangiography confirms that gallstones are absent.

Percutaneous cholecystostomy [88–90] controls the AAC in 85–90 % of patients. The gallbladder is usually intubated under sonographic (occasionally laparoscopic) control via an anterior or anterolateral transhepatic approach (through the right hepatic lobe) in order to minimize leakage of bile, but transperitoneal puncture has also been described. Rapid improvement should be expected when percutaneous cholecystostomy is successful. If rapid improvement does not ensue, suspicion should arise that the tube may be malpositioned and not draining properly, or the diagnosis of AAC may be incorrect. Perforated ulcer, pancreatic abscess, pneumonia, and pericarditis have been discovered in the aftermath of percutaneous cholecystostomy when patients failed to improve. Rarely, in genuine AAC, the patient will fail to improve due to gangrenous cholecystitis and an open procedure may be required [91, 92].

Reported major complications occur after 8–10 % of procedures, including dislodgment of the catheter, acute respiratory distress syndrome (ARDS), bile peritonitis, hemorrhage, cardiac arrhythmia, and hypotension due to procedure-related bacteremia [90]. The 30-day mortality of percutaneous and open cholecystostomy is similar, and influenced heavily by the underlying severity of illness.

Empiric percutaneous cholecystostomy has been advocated for patients who have sepsis absent a demonstrable source. In one report of 24 patients receiving vasopressor therapy for septic shock, 14 patients (58 %) improved as a result of cholecystostomy [89]. Pneumonia was diagnosed subsequently in three of the ten nonresponders, but an infection was never found in the other seven patients. Such an approach is not recommended routinely, but the importance of considering AAC in the differential diagnosis of occult sepsis is underscored.

Antibiotic therapy does not substitute for drainage of AAC, but is an important adjunct. The most common bacteria isolated from bile in acute cholecystitis are *E. coli*, *Klebsiella* spp., and *Enterococcus faecalis*, thus antibiotic therapy should be directed against these organisms. However, critical illness and prior antibiotic

therapy alter host flora, and resistant or opportunistic pathogens may be encountered. *Pseudomonas*, staphylococci (including methicillin-resistant strains), *Enterobacter* and related species, anaerobic organisms (e.g., *Clostridium* spp., *Bacteroides* spp.), or fungi may be recovered. Anaerobes are particularly likely to be isolated from bile of patients with diabetes mellitus, in those older than 70 years of age, and from patients whose biliary tracts have been instrumented previously.

Complications

The prevalence of gallbladder gangrene in AAC exceeds 50 %, and leads to additional morbidity, including gallbladder perforation. One variant, emphysematous cholecystitis (Fig. 15.2), is particularly associated with gangrene and perforation. Emphysematous cholecystitis is rare, but shares many traits with AAC, as 28 % of patients with emphysematous cholecystitis have acalculous disease. More than 70 % of cases of emphysematous cholecystitis occur in men, and 20 % of patients have diabetes mellitus. Crepitus to palpation of the right upper abdomen or radiographic identification of gas in patients with acute cholecystitis warrants consideration for immediate cholecystectomy in view of the fulminant nature of untreated emphysematous cholecystitis. In this scenario, percutaneous cholecystostomy does not frequently achieve source control reliably enough and should only be used as temporizing measure in select circumstances. Importantly, if the patient does not improve, urgent cholecystectomy is needed.

Clostridium spp., rather than aerobic gram-negative bacilli, are isolated most commonly in emphysematous cholecystitis (45 % of cases, with *C. welchii* predominating). *Escherichia coli* is recovered from approximately one-third of affected patients. Antimicrobial therapy specific for *Clostridium* (such as penicillin G) may be added to agents directed against the typical bacteria flora of acute cholecystitis.

Perforation of the gallbladder occurs in 10 % or more of cases of AAC [8], either localized into the subhepatic space or free perforation with generalized peritonitis. Perforation into the liver or biliary tract has been reported rarely in AAC [93, 94], as is perforation into the retroperitoneum with iliopsoas abscess [95]. Unusual causes of death from gallbladder perforation in AAC include hemorrhage from the liver [96, 102] and pulmonary bile embolism [97]. Serious complications of gallbladder gangrene without perforation include acute pancreatitis [98], colon perforation [99], and obstruction of the common hepatic duct [100]. Empyema of the gallbladder may also complicate AAC [101].

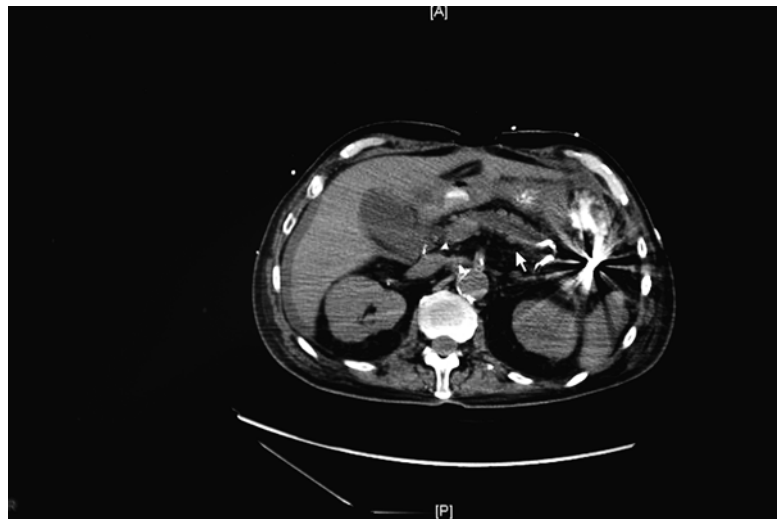

Fig. 15.2 A patient with emphysematous changes in acute acalculous cholecystitis. The gallbladder has a rim of air in the wall of the gallbladder adjacent to the liver bed

Conclusion

AAC should be suspected in every critically ill or injured patient with sepsis in whom the source of infection cannot be found immediately. Suspicion should be especially high if the patient has undergone recent major surgery, has had a period of hypoperfusion or becomes jaundiced. The preferred diagnostic modality is ultrasound, which is inexpensive, noninvasive, and can be brought to the bedside of the critically ill or unstable patient. Once diagnosed, the treatment of choice is percutaneous cholecystostomy. If the response to drainage is not prompt and favorable, an alternative diagnosis must be considered or abdominal exploration may be required. If percutaneous drainage is successful and the patient truly has no gallstones, then no further treatment may be necessary and the catheter may be removed after the patient has improved from the critical illness.

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Management of Gallstones in the Pediatric Patient

16

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Introduction

Infant and pediatric cholelithiasis, as well as other related gallbladder diseases, are becoming increasingly more common due to heightened awareness and the increased incidence of childhood obesity [1–5]. The prevalence of biliary sludge and gallstones in the pediatric population is estimated to be 1.46 % and 1.9 %, respectively, and the incidence is slightly higher in children undergoing abdominal sonogram for abdominal pain [4, 6]. Cholelithiasis in pediatric patients usually presents between the ages of 7 and 10, but this age range is changing as the childhood obesity epidemic continues [3, 4, 7, 8].

The majority of cases of childhood cholelithiasis are believed to be idiopathic. Only 20 % of gallstones are related to hematologic diseases including hereditary spherocytosis, sickle cell disease (SCD), and thalassemia [7, 9, 10]. Other risk factors for infantile and pediatric cholelithiasis and choledocholithiasis include total parenteral nutrition (TPN), ileal resection, inflammatory bowel disease, obesity, hereditary gallstones, cystic fibrosis, biliary tract anomalies, Gilbert's syndrome, and various medications (such as oral contraceptives, cyclosporine, or ceftriaxone) [4, 5, 7, 11–16].

In adults, cholelithiasis is often associated with obesity, and it is believed that the incidence of childhood obesity is associated with gallstones in children. According to the National Health and Nutrition Examination Survey, childhood and adolescent obesity increased to 17.1 % in 2003–2004 and is likely much higher today [17]. The incidence of severe obesity in children has tripled over the last 25 years [18]. Mehta and colleagues [19] reported on 404 children undergoing cholecystectomy, 16 % were overweight, 24 % were obese, and 15 % were severely obese. In a case control study there was a strong relation between the prevalence of obesity and increased

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cholelithiasis-related hospitalizations in children [20]. In addition, Hispanic ethnicity and obesity strongly correlate with symptomatic gallbladder disease [19]. In this study, Hispanic children were also more likely to have obstructive gallbladder disease [19].

Gallstones can be classified as pigmented, cholesterol, or mixed-type stones. Pigment stones are typically associated with hemolytic disorders, but can be associated with inflammatory bowel disease, ileal resection, and Gilbert's syndrome [5]. Alternatively, cholesterol and mixed-type stones are commonly seen in obese children and adolescents [5, 19, 21].

Symptomatic gallstones in children present most commonly with right upper quadrant pain (75–85 %), followed by nausea or vomiting in 60 %. Jaundice is less frequently seen and epigastric tenderness is found in only one third of the patients. Jaundice is a more common clinical presentation in infants less than 1 year [1, 2, 7]. Gallstones can be asymptomatic in up to 17 % of children [4, 7]. Medical therapy is ineffective in children with symptomatic cholelithiasis and laparoscopic cholecystectomy is now the treatment of choice [7, 22, 23]. Complications of pediatric gallstone disease include choledocholithiasis, acute cholecystitis, chronic cholecystitis, cholangitis, and gallstone pancreatitis. In this chapter, we will predominantly focus on the diagnosis and management of acute cholecystitis in children; however, we will also touch upon acalculous cholecystitis, the management of gallstones with certain associated comorbid conditions that are unique to the pediatric population, and lastly the management of biliary dyskinesia in the pediatric population.

Acute Cholecystitis

Acute cholecystitis is relatively infrequent in the pediatric population in comparison to adults, but again this may be changing in light of the childhood obesity epidemic (Fig. 16.1). In children with symptomatic gallbladder disease, it is estimated that the prevalence of acute cholecystitis is 10 % with the vast majority of patients suffering solely from biliary colic [24]. Children commonly present with abdominal pain in the right upper quadrant (85–94 %) and less frequently in the epigastrium (34 %) [3, 24]. Accompanying symptoms include nausea and vomiting in up to 60 % of patients [5, 24]. Acute cholecystitis may also be associated with fever.

Laboratory investigations should include hepatic aminotransferases which are commonly elevated in the early course of biliary obstruction. In addition, serum bilirubin, alkaline phosphatase, and gamma-glutamyl transferase are elevated in patients with cholestatic disease. These patients may also have a normal or elevated white blood cell count (WBC). While children may have an atypical presentation of acute cholecystitis,

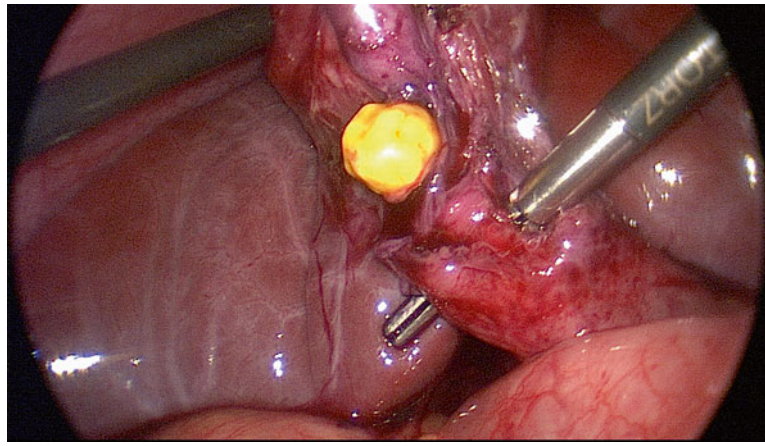

Fig. 16.1 Large gallbladder calculus in adolescent patient with severe acute cholecystitis. The patient had no risks for stone disease such as hemolytic disease or hypercholesterolemia. *Photo courtesy of Dr. Shaun Steigman*

right upper quadrant/epigastric pain along with a transabdominal ultrasound depicting gallstones or sludge, gallbladder wall thickening, an enlarged/distended gallbladder, pericholecystic fluid, and/or a sonographic Murphy's sign confirms or at least solidifies the diagnosis. Normal gallbladder wall thickness in children under 16 years of age is ≤3 mm [25]. The positive predictive value of ultrasound in pediatric cholecystitis is reported to be 67–87 % [26]. Tsai et al. [26] reported that 80 % of their pathological specimens after a cholecystectomy in children revealed chronic cholecystitis indicating that previous episodes of gallbladder inflammation occurred and thus children may have less severe episodes of cholecystitis when compared to adults.

The incidence of asymptomatic cholelithiasis in children is unclear. It is reported that up to 17 % of children are diagnosed with gallstones [4, 7]. Several authors have highlighted the incidence of acute cholecystitis as an initial presentation of gallstones. In one study, Bogue et al. [24] evaluated 194 asymptomatic children with cholelithiasis. Of these patients, nine suffered a complication of their gallstones including six patients with choledocholithiasis, two who suffered from gallstone pancreatitis, and one patient with acute cholecystitis. Six of these patients eventually underwent cholecystectomy, representing approximately a 3 % surgery rate. However, Tannuri et al. [27] found a slightly higher complication rate in their series where 56 of 223 (25.1 %) patients presented with a complication of cholelithiasis including 16 with acute cholecystitis. Overall, the progression to symptoms in children with incidentally diagnosed asymptomatic cholelithiasis is relatively low. Therefore it is advisable that asymptomatic gallstones in a pediatric patient without comorbidities be followed clinically, reserving an operation for only those patients who suffer from a complication or symptoms of their gallstones.

Laparoscopic Cholecystectomy

Laparoscopic cholecystectomy (LC) has become a mainstay in the management of cholecystitis in children, as it has in adults. Several authors have examined the safety, efficacy, and cost effectiveness of this procedure in the pediatric population. Holcomb and colleagues [28] were the first to report the safety and efficacy of LC for the management of acute cholecystitis in children. In this series, there were no complications during the follow-up period of 16 months (range 2–24 months). In addition, children undergoing elective LC had shorter length of stay, reduced analgesics, and decreased total hospital charges. Tannuri et al. [27] reported on 16 children with acute cholecystitis treated with LC. The authors reported conversion to open in two patients with acute cholecystitis and portal hypertension early in their series. This suggests that surgeon experience may reduce conversion rate, which has been found to be the case in adults. Similarly, this study also had no complications or bile duct injuries. LC is now the standard of care in managing gallstone disease in children.

The single port laparoscopic cholecystectomy has been reported in the literature for children with symptomatic gallstone disease. Ostlie et al. [29], in a prospective randomized trial, reported that the single port LC had a longer operating time and increased level of difficulty when compared to the traditional four port LC. There was no significant difference in hospital length of stay. Nonetheless single incision LC is considered to be a safe alternative to a standard LC in children with cholecystitis [30–32], although it is not the authors' preference. Its use is not widespread among pediatric surgeons.

The complication rate of LC is less than 5 %, with trocar site infections being the most common complication [3, 33, 34]. Children undergoing LC for acute cholecystitis and those with hemolytic disorders or other significant comorbid conditions have higher complication rates [8, 35]. The complication rate in those with SCD is 39 % in one series and the complications were mainly associated with the hemolytic disorder [36]. These patients had a higher incidence of respiratory compromise and readmission to the hospital for abdominal pain. Children undergoing LC with cardiac disease have a higher prevalence of multi-system organ failure [8, 37]. Bile duct

injury following LC in children is rare. In a large retrospective series, Kelley-Quon et al. [38] found a 0.36 % incidence of bile duct injury. Zeidan and colleagues [34] reported no bile duct injuries in 202 children undergoing LC. Thus, LC is safe and effective in children and there is no age-specific reason for children to be subjected to an open procedure.

Endoscopic Retrograde Cholangiopancreatography and Intraoperative Cholangiogram

Endoscopic retrograde cholangiopancreatography (ERCP) may be performed preoperatively or postoperatively if choledocholithiasis is present, depending on surgeon and endoscopist preferences. In children from ages 1 month to 18 years ERCP is a diagnostic and therapeutic tool with up to a 95 % success rate [39–42]. Post-ERCP pancreatitis occurs in up to 8 % of children and the incidence increases in children undergoing therapeutic ERCP. Hemorrhage and perforation are relatively rare and are observed in 0.3–2 % of children undergoing ERCP [40]. ERCP is considered to be safe and efficacious before, during, or after laparoscopic cholecystectomy with common bile duct (CBD) clearance attained in 95 % of the patients [7, 15, 43, 44]. Newman et al. [45] suggested that preoperative ERCP may be more efficacious if preoperative assessment demonstrates choledocholithiasis. An increased operative time by 86 % has been seen with concomitant ERCP and LC and therefore may impact operative costs, although this approach may be more desirable than two separate general anesthetics [23].

Intraoperative cholangiography (IOC) may be performed in children with CBD stones without the need for the additional general anesthesia required for ERCP. Holcomb et al. [23] performed IOC in 57 patients undergoing LC and had an 86 % success rate for completing the procedure, with an overall increase in operative time by 29 %. Kumar et al. [7] reported a 100 % success rate without any complication related to the IOC. In an effort to determine the role of IOCs in children with biliary stone disease, Waldhausen and colleagues [43] performed 63 IOCs in 100 children undergoing LC of which there were 55 positive studies, by their criteria. However, only 18 children were found to have CBD stones. IOC did not result in any complications, though it increased operative time by 35 % [43]. Based on their findings, Waldhausen et al. [43] recommended that routine IOC should be completed in children undergoing LC although whether this conclusion is supported by their data is debatable. Furthermore, they argued IOC could help avoid unnecessary ERCP and the obligatory second anesthetic. More recently there has been some controversy in the need for routine IOC at the time of LC since it often yields negative results and thus may not be necessary for the diagnosis of CBD stones in the vast majority of pediatric patients [27, 46]. In addition, the biliary tract can be delineated preoperatively in most children through ultrasonography [27]. Thus routine IOC at the time of LC is not routinely performed at our institution and many others around the country. Whether it is superior to merely obtaining the critical view for preventing injury to the CBD in children is unknown.

Acalculous Cholecystitis

Acute acalculous cholecystitis (AAC) in children is uncommon although the incidence is increasing. In children with cholecystitis, AAC accounts for up to 21.4 % of cases [47]. AAC is commonly associated with an infectious disease; however, it may be seen in previously healthy children as well. AAC has been associated with hepatitis, typhoid fever, sepsis, Epstein–Barr virus, cytomegalovirus, and pneumonia in children [48–53]. Children with AAC clinically present similar to acute calculous cholecystitis with RUQ and/or epigastric pain, fever, nausea, and vomiting. Occasionally, a palpable mass in the right upper quadrant is present. AAC may be associated with an elevated WBC and normal or slightly abnormal serum hepatic aminotransferase levels.

Abdominal ultrasound has a high specificity in diagnosing diseases of the biliary system, and gallbladder wall thickening in the absence of

gallstones is the most common ultrasonographic sign seen in children with AAC. Additionally, gallbladder distention, debris, and pericholecystic fluid may also be seen on sonogram. While computed tomography has a low sensitivity for cholelithiasis it can detect gallbladder perforation and visualization of the entire abdomen and pelvis, and thus is sometimes useful in the diagnosis of AAC.

Laparoscopic cholecystectomy is the treatment of choice for AAC in children. Alternatively, critically ill children may receive antibiotics, with or without a cholecystostomy, and an interval LC once their acute illness resolves. Karkera et al. [53] recommend an interval cholecystectomy in children with AAC, which is now becoming standard of care unless the child was otherwise healthy upon presentation with AAC.

Neonatal and Infantile Gallstones

Gallstones have been found in up to 0.5 % of newborns. Most patients are asymptomatic and the majority of infants have no recognized predisposing factor [54, 55]. However, associated risk factors include prematurity, Down's syndrome, polycythemia, hemolysis, biliary tract anomalies, phototherapy for jaundice, maternal morphine addiction, TPN, and nephrocalcinosis [12, 56–59]. Symptomatic infants have been treated successfully utilizing ERCP, open or laparoscopic cholecystectomy with or without ERCP, and CBD exploration [7, 34, 60, 61]; however, most patients can be treated with cholecystectomy alone if symptoms arise.

Up to 50 % of infants will have spontaneous resolution of gallstones [54, 56, 62, 63]. Several studies have recommended treating infants with choledocholithiasis conservatively with antibiotics and ursodeoxycholic acid [59, 64]. Although rare, there have been reported cases of acute cholecystitis in infants [65]. Fatal complications in infants including perforation, obstruction, and peritonitis have been reported [66]. Based on these findings, Jawad et al. [60] recommended observation of asymptomatic infants for 3–6 months. If there is failure of resolution or the presence of calcified stones, then LC is recommended by these authors [60]. Others suggest continuing to observe until symptoms present.

Hematologic Disorders and Biliary Stone Disease

Excess bilirubin due to hemolysis can coalesce in the gallbladder to form stones or sludge. The incidence of gallstones associated with hemolytic disorders has been reported as high as 41 %. However, most studies report an incidence closer to 20 % [3, 7, 8]. Hematological conditions associated with excessive hemolysis and the development of cholelithiasis or sludge are most commonly SCD or hereditary spherocytosis (HS) (≤43 %), and the thalassemia disorders (≤23 %) [10].

Laparoscopic cholecystectomy has been safely performed in children with hemolytic disorders and symptomatic gallstones. Children with SCD and gallbladder disease often receive preoperative packed red blood cell transfusions to achieve a hemoglobin level of 10 g/dL, or exchange transfusion to reduce the concentration of hemoglobin S to a level <50 % [35, 67, 68], to help prevent acute chest syndrome or a sickle cell crisis as a complication of general anesthesia. In addition, simultaneous elective laparoscopic cholecystectomy and splenectomy have been safely performed in children with SCD [69, 70].

Suell et al. [71] in a study of 83 children with SCD with ultrasonographic evidence of stones or sludge found that only 12 had clinical symptoms of cholecystitis. Of these, 54 patients underwent cholecystectomy, and 45/54 patients underwent packed red blood cell transfusion or exchange transfusion prior to the procedure. A total of 93 % of the patients who underwent cholecystectomy had chronic cholecystitis diagnosed in the pathologic specimen irrespective of their preoperative symptomatology. Surgical complications occurred in two patients: one patient suffered from an intra-abdominal hemorrhage requiring re-exploration, and the second patient developed

pancreatitis. Children with SCD who underwent elective cholecystectomy had a shorter hospital stay than those who underwent operation during an inpatient admission and also experienced fewer SCD crises. Based upon their findings, Suell et al. [71] suggested that elective LC should be considered at the time of initial gallstone diagnosis. Moreover, LC is the treatment of choice in children with SCD and acute cholecystitis [35].

The role of cholecystectomy in patients with HS and gallstones has not been as clearly delineated, but most authors recommend cholecystectomy in patients who are undergoing splenectomy, especially if they are symptomatic [10, 72, 73]. Marchetti et al. [74] determined that prophylactic splenectomy and cholecystectomy provide a gain in quality-adjusted life expectancy in patients with HS and asymptomatic cholelithiasis over the age of 6 years. Furthermore, this improvement may be enhanced by using the laparoscopic approach [75, 76]. There is no role for prophylactic cholecystectomy in patients with normal gallbladders undergoing splenectomy for HS [77].

Pigment stones form in children with beta-thalassemia due to bile stasis, causing an enlarged gallbladder and impaired emptying [78]. Patients with thalassemia or HS and co-inherited Gilbert's syndrome have a higher incidence of cholelithiasis, suggesting that children with concomitant disease should have early gallbladder ultrasonography and closer follow-up [79, 80]. As in patients with SCD, concomitant cholecystectomy with splenectomy has been successfully performed in patients with beta-thalassemia [81]. Feretis et al. [82] suggest that patients with beta-thalassemia undergo simultaneous splenectomy and prophylactic cholecystectomy; however, this recommendation has not been further studied.

Transplantation

Children after solid organ and bone marrow transplantation have a higher incidence of gallstones than non-transplant patients. This increase may be related to drug therapy (ceftriaxone, cyclosporine A, octreotide, and clofibrate), sepsis, parenteral nutrition, or surgical complications [83]. Hoffmeister et al. [84] followed 1,325 patients who underwent hematopoietic stem cell transplant in childhood and were followed for 40 years. There was an incidence of gallstones in 6.9 % after transplant. Of the 56 who underwent cholecystectomy, 20 had acute and/or chronic cholecystitis. Safford et al. reported the development of gallstones in 20/235 (8.5 %) children after bone marrow transplant [85]. Sakopoulos et al. [86] reported an overall rate of gallstone formation in children undergoing cardiac transplantation between 3.2 and 8 % in infants transplanted under the age of 3 months. Elective cholecystectomy is recommended for cardiac transplant patients with cholelithiasis regardless of symptomatology [87].

Biliary Dyskinesia

Biliary dyskinesia is characterized by biliary colic without evidence of cholelithiasis or acute cholecystitis. The diagnosis can be aided by demonstrating a gallbladder ejection fraction (EF) of <35 % on cholecystokinin hepatobiliary iminodiacetic acid scanning (CCK-HIDA) [5, 88, 89]. The incidence of biliary dyskinesia is increasing and reflects improved ability to diagnose the disease. The optimal management of biliary dyskinesia is unclear; however, laparoscopic cholecystectomy has more frequently become the treatment of choice. In fact, Lacher et al. [90] suggested that LC should be performed in all children with biliary dyskinesia and an EF <15 %. LC has up to a 95 % success rate in the treatment of biliary dyskinesia [91]. Histological examination often reveals an abnormal gallbladder with sludge and acute or chronic inflammation [92]. However other studies show a variable rate of resolution of symptoms in patients with biliary dyskinesia after LC: reports have suggested that anywhere from 44 to 96 % of children's symptoms resolved after LC for biliary dyskinesia [90, 93, 94]. Thus the true role of LC for biliary dyskinesia in children has yet to be definitively determined.

Summary

Childhood and adolescent obesity along with improved detection of gallstones has lead to an increased incidence of the diagnosis of acute cholecystitis in children. Laparoscopic cholecystectomy is safe, efficacious, and is the treatment of choice for acute and chronic cholecystitis, acalculous cholecystitis, and perhaps biliary dyskinesia. Similarly, laparoscopic cholecystectomy at the time of splenectomy can be performed in children with hematological disorders, with blood or exchange transfusion being highly recommended preoperatively. Cholecystectomy for biliary colic or acute cholecystitis is recommended in neonates and infants if symptoms do not resolve within 3–6 months or in previously asymptomatic infants when symptoms develop. ERCP for CBD stones or gallstone pancreatitis in infants and children has a high success rate and should be part of the treatment algorithm usually prior to laparoscopic cholecystectomy. In contrast, the utility of IOC as a routine practice in the pediatric population is unclear.

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Gallbladder Cancer Presenting as Acute Cholecystitis

17

Maureen Moore and Benjamin Golas

Introduction

There are 8,500 new cases of carcinoma of the gallbladder diagnosed each year [1]. The majority of these cases (70 %) are found incidentally when the patient is receiving cholecystectomy. In these circumstances, the diagnosis either occurs when the surgeon intraoperatively examines the gallbladder at the time of cholecystectomy or when the pathologist postoperatively examines the gallbladder. The next highest numbers of patients (30 %) are diagnosed for symptoms related to advanced gallbladder cancer [1, 2].

Overall, gallbladder cancer widely portends a poor prognosis for the patient due to the advanced stage at which carcinoma of the gallbladder is often diagnosed. The cancer-specific mortality of patients with gallbladder carcinoma following simple cholecystectomy is directly correlated with the T and N stages of the tumor (Table 17.1) [3]. While nearly all patients obtain long-term survival with simple cholecystectomy for T1a tumors, the 5-year survival for T1b and greater tumors drops precipitously without further intervention. Those patients diagnosed with early stage have the greatest likelihood of long-term survival if provided with a complete R0 resection [1, 2].

Presentation

With incidental gallbladder cancer representing the majority of all gallbladder cancer in the USA, one must question why it is not discovered more often preoperatively [4]. Patients are often symptomatic with right upper quadrant pain that appears to be due to cholelithaisis or acute/chronic cholecystitis. Imaging usually notes the gallstones and may also suggest thickening of the gallbladder wall usually without peri-cholecystic edema. Gallstones represent the most prevalent risk factor with over 75 % of patients with gallbladder cancer having associated gallstones [3, 5]. This association leads to the lack of preoperative diagnosis since the incidence of gallbladder cancer in resected cholecystectomies is only 1 % [6]. Certainly, the presence of gallstones is a risk factor for gallbladder cancer. In another series, 90 % of cases of incidentally discovered GBCA had gallstones compared to only 13 % of non-incidental [4].

Incidentally found gallbladder cancer is much more likely to be early stage than cases diagnosed preoperatively using ultrasound, computed

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Table 17.1 AJCC TNM staging

Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor invades lamina propria or muscular layer
T1a	Tumor invades lamina propria
T1b	Tumor invades muscular layer
T2	Tumor invades perimuscular connective tissue; no extension beyond serosa or into liver
T3	Tumor perforates the serosa (visceral peritoneum) and/or directly invades the liver and/or one other adjacent organ or structure, such as the stomach, duodenum, colon, pancreas, omentum, or extrahepatic bile ducts
T4	Tumor invades main portal vein or hepatic artery or invades at least two extrahepatic organs or structures
Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastases to nodes along the cystic duct, common bile duct, hepatic artery, and/or portal vein
N2	Metastases to periaortic, pericaval, superior mesenteric artery, and/or celiac artery lymph nodes

abdominal tomography, magnetic resonance imaging, or magnetic resonance cholangiopancreatography scans. Right upper quadrant ultrasound, routinely used for evaluation of symptomatic patients, might show a polypoidal gallbladder mass and potentially invasion of adjacent structures. The presence of gallbladder calcification, also known as "porcelain gallbladder," may also be noted preoperatively. Wall thickness greater than 3 mm and increased vascularity of the gallbladder are considered sonographic features that can also signify possible malignancy [7].

During open routine cholecystectomy, which was standard procedure decades ago, surgeons might have felt an area of abnormality in the gallbladder during the operation and send the tissue for frozen section examination. Laparoscopic cholecystectomy often misses the incidental cancer during cholecystectomy due to the inability of the operator to actually "feel" the gallbladder and note focal abnormalities during removal. The tactile feedback afforded by a surgeon's hands appreciating a thickened, infiltrated, incidentally malignant gallbladder is lost in the laparoscopic technique. Unless the surgeon, thoroughly exams the gallbladder upon its removal, the diagnosis is not made for several days when the histologic examination of the tissue is complete.

If gallbladder cancer is not detected while the gallbladder is in situ, the treatment may be compromised. Adenocarcinoma of the gallbladder, in its early focal growth pattern invades into the lamina propria, followed by invasion into the deeper submucosal area and then advances diffusely throughout the gallbladder in the subserosal plane. If the surgeon does not suspect the diagnosis intraoperatively and perform a deep, wide excision of the gallbladder, the subsequent dissection may occur in the subserosal plane and leave cancer cells behind upon separation of the gallbladder from the liver. When this event occurs, incidentally discovered gallbladder cancer patients should undergo careful evaluation to determine the margins and likelihood of recurrence to determine the next best form of management after they have undergone a potentially incomplete cancer operation. Having a high risk for residual disease in the gallbladder fossa and a major risk of cancer seeding of the abdomen at the time of cholecystectomy should be considerations when further extirpative surgery is contemplated.

Detection of Incidentally Discovered Gallbladder Cancer

The surgeon's diagnosis of incidental carcinoma of the gallbladder intraoperatively is rare (0.1 %), especially when the procedure is performed laparoscopically. In a retrospective review of 3,050 patients undergoing laparoscopic cholecystectomy for cholelithiasis, carcinoma of the gallbladder was discovered during or after laparoscopic cholecystectomy in 10 patients. Interestingly, laparoscopy was converted to an open procedure in only three patients after pathologic diagnosis was confirmed using frozen section [6]. If signs of malignancy are encountered during laparoscopic cholecystectomy, the surgeon should convert to an open procedure [3, 6]. As noted above, the lack of tactile sensation during laparoscopic cholecystectomy makes

intraoperative assessment of malignancy quite difficult. A retrospective review of nearly 300 cases of laparoscopic cholecystectomy in which there was suspicion of gallbladder cancer, and frozen section was performed, the incidence of gallbladder cancer was only 1.3 %.

A thickened, infiltrated, or porcelain gallbladder should raise an index of suspicion for the surgeon. Preoperative imaging demonstrating porcelain gallbladder or polypoid lesions of the gallbladder are indications to examine the gallbladder closely intraoperatively for the possibility of malignancy. Among patients presenting with polypoid lesions of the gallbladder, the incidence of cancer is reported to range from 4 to 18 % [8]. Because of this association, patients with porcelain gallbladders should undergo frozen section examination of the gallbladder upon removal if a tumor is not detected intraoperatively by the surgeon.

If an early malignancy (pT1) is diagnosed intraoperatively, no additional resection is required if there has not been a perforation of the gallbladder. If inadvertent gallbladder perforation occurs during its removal, the peritoneal recurrence rate of gallbladder cancer is likely to be increased. In patients with pT2 (into perimuscular fibers) and beyond, hepatic resection of the gallbladder fossa, segmental hepatic resection, and complete dissection of the lymph nodes along the hepato-duodenal ligament (around the bile ducts, hepatic arteries, and portal vein from the hilus of the liver to behind the duodenum and pancreas) is indicated [6, 8, 9]. There are multiple issues to be considered in this situation such as obtaining operative consent for a much larger and unanticipated procedure, the patient's existing comorbidities and the skill required by the operating surgeon to perform this more complex procedure. Due to these issues, the operating surgeon should decide whether the better option is to perform an open radical resection or whether to close without attempts of resection. When faced with an unexpectedly malignant gallbladder, it is highly recommended that the operating surgeon obtain additional help from a specialty-trained surgeon if the original surgeon is not trained in the more complex surgery. The patient must then be referred for further oncologic work up and potential operative planning for resection (Fig. 17.1).

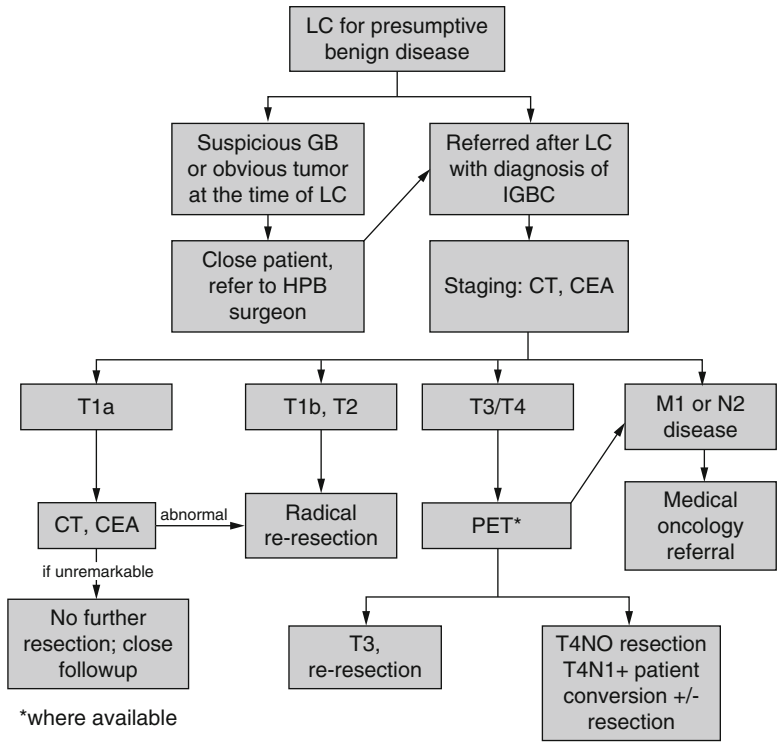

Fig. 17.1 Management algorithm for patients with incidental gallbladder carcinoma. *LC* laparoscopic cholecystectomy, *BG* gallbladder, *IGBC* incidentally discovered gallbladder cancer, *HPB* hepato-pancreatico-biliary, *CT* computed tomography, *CEA* carcinoembryonic antigen, *PET* positron emission tomography. Used with permission: Belin, Laurence J., Christina E. Lewis, and Yuman Fong. "Management of Incidental Gallbladder Carcinoma." Carcinoma of the Gallbladder: The Current Scenario. New Delhi: Elsevier, 2014. 54–66. Print. ECAB Clinical Update Surgical Gastroenterology and Liver Transplantation

Incidentally Discovered Gallbladder Cancer by Pathologic Review

Most commonly, incidental gallbladder cancer is diagnosed after histologic examination of the gallbladder by the pathologist postoperatively. In many cases, the patient has already been discharged from the hospital and has expected no further gallbladder treatment (see Fig. 17.2 and its description of what is a typical case). For the pathologist and the surgeon, the site of the malignancy in the gallbladder and the pathologic stage must be carefully determined to counsel the patient on appropriate further therapy. Review of the histology by another experienced pathologist or at a tumor board is critical because some stages of disease do not require further surgical therapy. For example, patients with pT1a tumors do not benefit from additional treatment as their prognosis is good. Additional operative resection in patients with stage pT1a incidental gallbladder cancer did not result in better survival when compared with patients who had the initial cholecystectomy performed without additional treatment. Patients with more advanced stages of disease (pT2 or greater), however, may well benefit from additional treatment such as re-resection [10].

Because of the rarity of this malignancy, there are no prospective, randomized trials available to provide Level 1 evidence as to the benefits of additional surgical resection as compared to observation or use of adjuvant chemoradiotherapy in those with incidental gallbladder cancer. However, multiple retrospective reports have recommended that patients undergo an additional resection if gallbladder cancer (>pT1) is diagnosed postoperatively after laparoscopic cholecystectomy [10]. In one report, less than a third of these patients diagnosed postoperatively received an additional resection as described above with segmental liver resection and hepatoduodenal nodal dissection with or without bile duct excision and hepatico-jejunostomy because of extensive disease [11]. If the invasion of the gallbladder cancer is limited to the mucosa or subserosa, the 5-year survival rate is over 95 % [12]. The 5-year survival for T1b and greater tumors drops precipitously without further intervention. Duffy et al. found that over half of the patients undergoing a second operation after incidental gallbladder cancer found initially were noted to have much more extensive disease in their liver, peritoneum, and hepatoduodenal nodes [10].

Due to a lack of prospective, randomized data regarding results of aggressive resection following incidentally discovered gallbladder cancer, no consensus surrounds the extent of necessary resection for this scenario. Importantly, no radical procedure is recommended after postoperative diagnosis of incidental pT1a (through lamina propria). T1a tumors with a normal CT and CEA may therefore be closely monitored without reexploration. If after the index laparoscopic or open cholecystectomy, pathology reveals tumor infiltration beyond the lamina propria and muscularis (>pT1a and pT1b), computed tomographic scans should be done to evaluate for residual and disseminated disease. For all T1 tumors with a positive cystic node and all tumors T1b or greater, reexploration and radical resection for accurate staging and potential cure are indicated [9]. If the patient has a normal carcinoembryonic antigen (CEA) level and CT scan showing no evidence of unresectable disease, additional resection in pT1b have been recommended based on retrospective series suggesting that further resection has been associated with improved survival compared with patients that did not undergo further surgery [13]. As described above, the recommended procedure is that of gallbladder fossa segmental hepatic resection (segments IVb and V) combined with hepato-duodenal lymph node dissection.

Other authors give guidelines for further workup and aggressive tissue resection after diagnosis of advanced stage gallbladder cancer. Certain authors from Asia have recommended complete bile duct resection, hepatic-jejunostomy to proximal hepatic ducts along with caudate lobe resection [12]. For patients with T2 and T3 tumors, a staging computed tomographic scan with and without contrast is recommended to evaluate for residual disease in the liver and peritoneum as well as suspicious lymphadenopathy. In accordance with the >50 % probability of lymph node involvement in T3+ tumors, PET-CT scan may offer additional information for staging purposes. Magnetic resonance imaging with

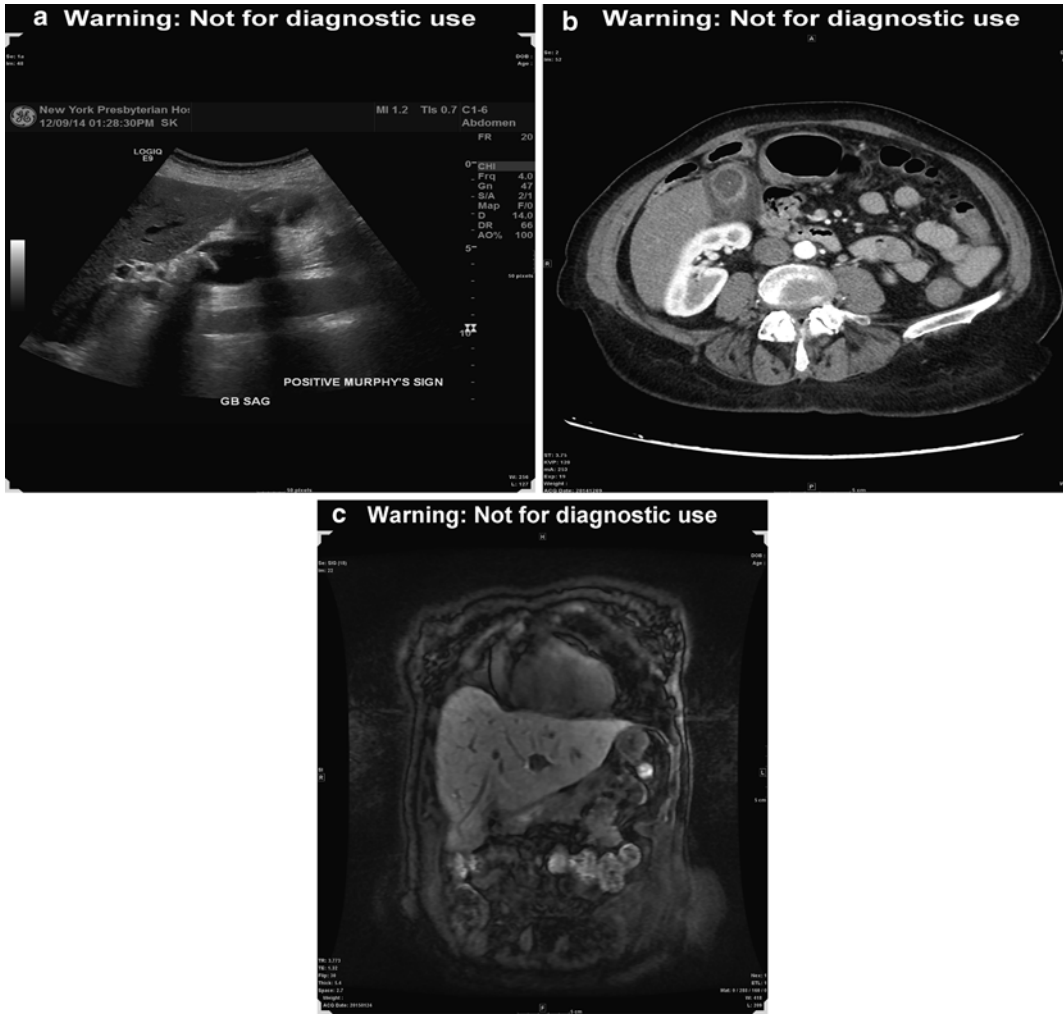

Fig. 17.2 Seventy-three-year-old female presenting with right upper quadrant pain initially thought to be acute cholecystitis. Patient underwent laparoscopic cholecystectomy. Pathology revealed invasive adenocarcinoma of the gallbladder with high-grade dysplasia and invasion of perimuscular connective tissue (T2, Nx). (**a**) Preoperative right upper quadrant ultrasound image showing thickened gallbladder wall (9 mm), multiple gallstones, and sludge with normal intraheptatic ducts. Impression read as acute cholecystitis. (**b**) Preoperative axial CT-scan of abdomen showing 2.0 cm gallstone within the gallbladder neck. This is associated with gallbladder wall thickening/edema and pericholecystic fluid. Mild enhancement of the hepatic parenchyma adjacent to the gallbladder was also noted. No intra- or extra-biliary ductal dilatation was seen. (**c**) Postoperative coronal MRCP image after the patient was found to have incidental gallbladder cancer with acute cholecystitis. Slightly abnormal signal in the subcapsular portion of hepatic segment 5 in the gallbladder fossa, possible tumor invasion. No clear residual tumor at the level of the cystic duct remnant. No tumor involvement of the common hepatic or common bile duct was noted on pathology

magnetic resonance cholangiopancreatography and serum CEA and CA19-9 levels, which are 93 % and 79.4 % sensitive for gallbladder cancer when elevated, respectively, may also be obtained [9]. The presence of T4 disease is often regarded as widely disseminated through vascular invasion and/or metastasis, thus rendering the disease unresectable. No reexploration is recommended in those patients if there is any evidence of metastatic disease and the patient should be referred to medical oncology for therapies. Some of these advanced stage patients may require palliative surgery or interventional radiologic drainage for certain conditions such as jaundice or bowel

obstruction but these procedures should be individualized based on the symptoms, prognosis, disease state, and the wishes of the patient or health care agent.

Reexploration for Incidentally Discovered Gallbladder Cancer Identified After Simple Cholecystectomy?

The fundamental basis of reexploration surrounds the observation that gallbladder cancer carries a poor prognosis, with the only chance for cure lying in early detection and complete surgical resection. Additionally, as many as 50 % of patients reexplored for incidental gallbladder cancer had residual disease following laparoscopic cholecystectomy [13]. As noted, re-resection of patients with early stage incidental gallbladder cancer may result in long-term survival, but workup of these patients must be thorough to avoid unnecessary reexploration as there is a risk of peritoneal or port-site seeding leading to metastatic disease. After diagnosis of gallbladder cancer, a high theoretical risk of residual disease exists after the initial operation. Also, the staging is usually incomplete as the original surgery rarely has complete nodal dissection performed.

As T stage increases, the likelihood of residual disease on reexploration increases.

In another large, multicenter retrospective review, the incidence of residual disease at the second operation was 61 % which correlated directly with T stage and indirectly with long-term outcome [13]. Bartlett et al. reported a 5-year survival rate is 69 % for T2 disease after radical resection as compared to the best results for simple cholecystectomy, a 5-year survival rate of 40 % being reported [14]. In the same report, Bartlett et al. went on to describe a 5-year survival rate of 67 % for T3 disease after complete resection.

Prognosis After Re-resection

As is common with most carcinomas of the gastrointestinal tract, the incidence of regional lymph node metastases increases with the T stage of the primary tumor, increasing from 12 to 45 % for patients with T1 to T3 primary tumors. Similarly, as is found with other gastrointestinal malignancies, the presence and extent of positive regional nodes adversely affects 5-year survival (26 % with nodal metastasis vs. 73 % in patients with no nodal involvement) [13]. Any planned secondary surgery should be done in an attempt to remove remaining cancer either in regional nodes or at adjacent primary sites. Thus, the underlying rationale for re-resection is to excise residual tumor and nodal tissue and thereby obtain a possibility of long-term survival or cure.

Incidentally discovered cases of gallbladder cancer have a significantly longer median survival (16 months) than those with a diagnosis established preoperatively (5 months) [15]. Patients with incidentally discovered gallbladder cancer who undergo reexploration and resection have a significantly improved median survival compared with those who are reexplored and cannot undergo resection and those who never have a re-laparotomy. This observation derives from retrospective studies and parallels similar findings to those examining results of re-resection for other areas of the gastrointestinal tract. In all retrospective series, re-resection for cancer occurs at the judgment of the attending surgeon and is dependent on factors such as initial tumor staging, patient age and comorbidities and other factors suggestive a high degree of patient selection bias. Outcomes of re-resection are dependent on the T stage of the tumor with an excellent chance of long-term survival possible in early-stage tumors. Important prognostic variables associated with prognosis after re-resection includes T, N, and M stages, tumor differentiation, and re-resection margin status. As patient selection has improved due to more extensive radiologic evaluation, there has been an increase in R0 resections from 14 to 40 %, a decrease in operative mortality from 24 to 5 %, and an improvement in overall median survival from 3 to 12 months [10]. Thus, it is critically important to thoroughly assess the patient's performance status, comorbidities, and initial tumor biology to make the correct choices regarding reoperation.

In patients with T3 or T4 tumors, counseling must be provided noting lack of intervention essentially precludes any chance of long-term survival.

Stage for stage, re-resection for incidentally discovered gallbladder cancer is safe and equivalent to initial definitive resection. In one retrospective study from Memorial Sloan Kettering, no significant differences were noted in regards to mortality, postoperative complication rate, or long-term outcomes between patients with incidental gallbladder cancer and preoperatively diagnosed cases undergoing definitive re-resection. In addition, prior surgical resection was not statistically associated with a decreased likelihood of obtaining an R0 resection and, in fact, was less likely to be associated with metastatic disease [16].

Extent of Re-resection

At the time of reexploration for patients with initial T1b, T2, and T3 tumors, thorough examination of the abdomen for peritoneal disease should occur. As has been done for patients with gastric and pancreatic cancers, peritoneal lavage for cytology should be performed with cytologic results reported by immediate analysis if possible. The planned operation should include resection of the gallbladder fossa (liver segments IVb and V) along with a complete lymphadenectomy of the hepatoduodenal ligament. Some have suggested that major hepatectomy, common bile duct (CBD) excision, and resection of adjacent organs improves patient survival, but only small retrospective studies support this concept. Tumor biology often trumps the extent of surgical resection especially when dealing with secondary surgery. Major hepatic and CBD resections should not be performed routinely, and are only necessary when these structures are directly involved with residual tumor. A microscopically positive cystic duct margin, however, is an indication for common duct resection as greater than one-third patients have residual disease in the resected common duct compared to <5 % of those with a negative cystic duct margin [13].

Tumor Seeding and Port Site Metastases

Retrospective reviews have described the potential risk of tumor seeding during the laparoscopic cholecystectomy prior to the cancer diagnosis. Peritoneal carcinomatosis is observed during follow-up of patients with gallbladder carcinoma, suggesting that tumor seeding of the peritoneum, port sites, and subcutaneous tissues occurs as a result of gallbladder perforation, bile and stone spillage, and perhaps seeding of laparoscopic instruments. Perforation may occur at the time of dissection of the gallbladder initially or during removal from the umbilical port site.

Port site recurrence rates after laparoscopic cholecystectomy can occur in up to 40 % of patients, but most reports put the number in single digits, as higher incidences are associated with known gallbladder perforation. Some clinicians have suggested that port-site resection be done routinely since doing so removes a potential site of tumor seeding or peritoneal disease [16]. At present, conflicting evidence makes it difficult to determine whether to routinely remove all port sites at the secondary laparotomy. A retrospective study out of the Memorial Sloan Kettering Cancer Center examined their incidence of port site metastasis [17]. In their study, 113 incidentally discovered gallbladder cancer patients who presented after laparoscopic cholecystectomy for definitive oncologic resection over a 17-year period were reviewed. Of the 69 patients who had undergone port-site resection, 13 (19 %) patients had port-site metastases. These patients all had T2 or T3 primary tumors. These findings significantly correlated with the development of peritoneal metastasis. After adjustment for T and N stage, however, port-site resection was not associated with overall or recurrence-free survival when compared to patients who did not undergo port-site resection. However, median survival of T2/T3 patients in whom port-site metastases were confirmed was 17 months compared to 42 months in patients with negative port sites. Thus, port-site resection may be useful for accurate staging of metastatic disease and have implications for prognosis and adjuvant therapies.

Of note, the management of bile spillage during the initial operation and the entity of free gallstones found within the peritoneal cavity at reoperation for incidental gallbladder carcinoma is unclear. Most would advocate removal of the residual stones and careful localized washout of the abdomen when possible but there is little evidence that doing so improves long-term outcome or prognosis of the patient.

Conclusion

In summary, incidentally discovered gallbladder carcinoma often leads to an early stage presentation of the cancer and treatment has the potential for cure. Patients with the earliest stages (pT1a) do not require further reoperation. For patients with Stage T1b, controversy exists as to the benefits of reoperation, but many surgeons would recommend reoperation in the young, fit, healthy patient without serious comorbidities. In patients with Stage T2 and T3 tumors discovered incidentally at the time of their initial operation, complete radiologic work-up should proceed including obtaining serum CEA and Ca 19-9 levels. In the absence of known metastatic disease, reoperation should be done unless patient factors preclude a more extensive procedure. The true benefits of adjuvant therapies such as chemotherapy and radiotherapy are unclear from the current data.

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Index

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