Infectious Considerations in Complicated Acute Cholecystitis

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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),

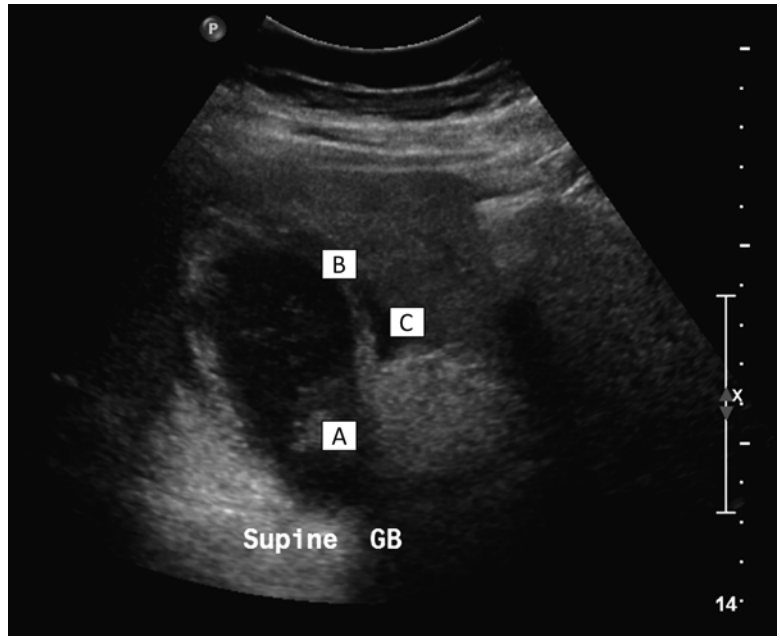

Fig. 9.1 Ultrasound image of acute cholecystitis. The gallbladder is significantly distended. Heterogeneous echotexture within the gallbladder lumen, which contains numerous stones and sludge (**a**). The gallbladder wall is thickened (**b**), measuring approximately 10 mm and there is a small amount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

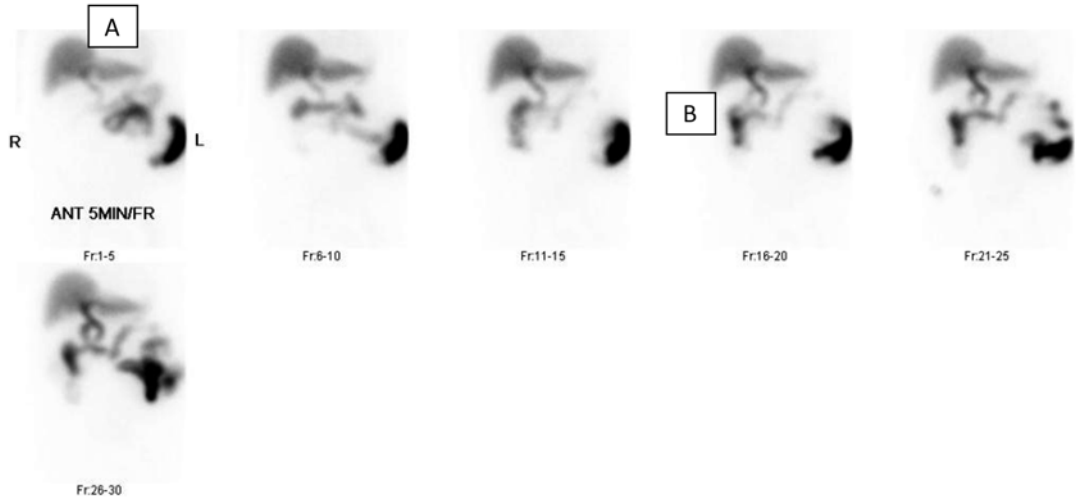

Fig. 9.2 Hepatobiliary Iminodiacetic Acid imaging of an unobstructed hepatobiliary tree. There is prompt uptake of the radiotracer by the liver (**a**). Normal excretion of the radiotracer into the intra- and extra-hepatic biliary tree (**b**). There is no filling of the gallbladder by 60 min. There 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

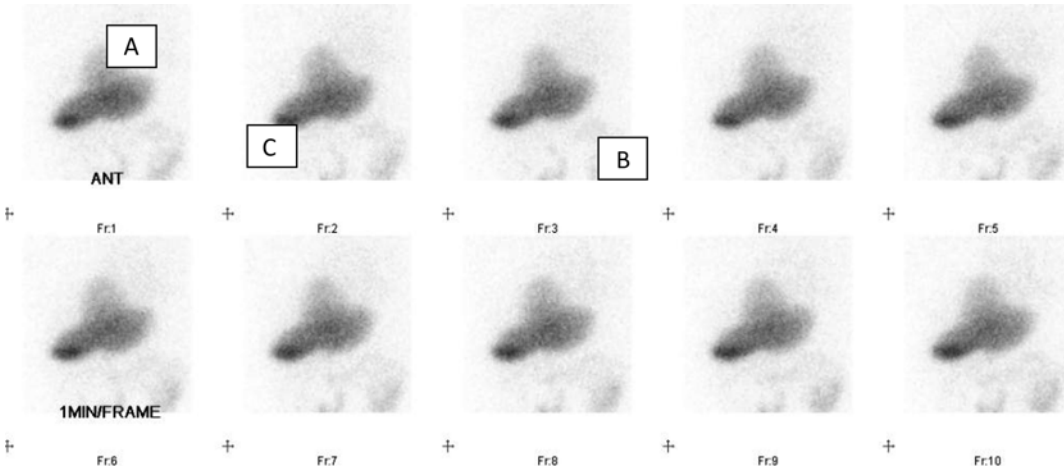

Fig. 9.3 Hepatobiliary Iminodiacetic Acid imaging of an obstructed hepatobiliary tree. There is prompt uptake of the radiotracer by the liver (**a**). There was no excretion into the common bile duct (**b**). There is delayed uptake within the gallbladder at 4 h (**c**)

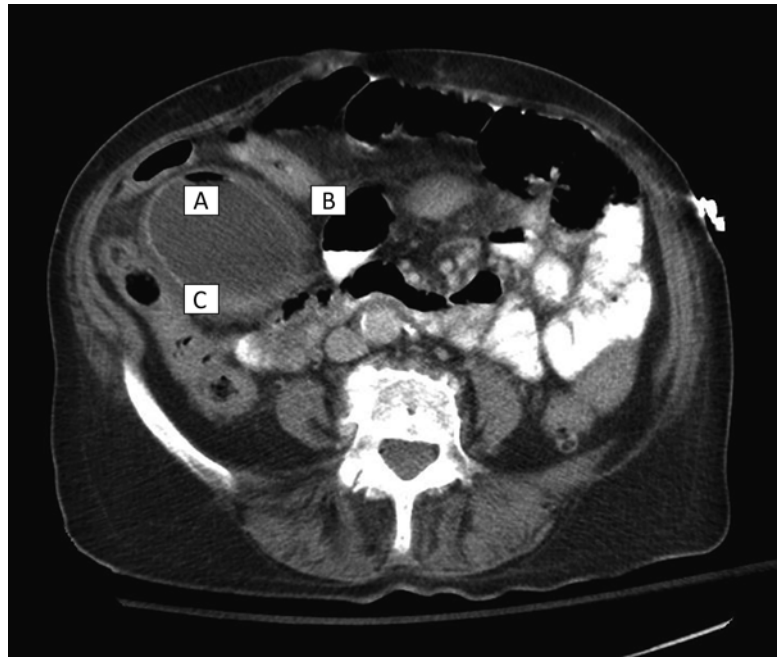

Fig. 9.4 Computed Tomography Imaging of Emphysematous Cholecystitis. (**a**) Gas trapping within the gallbladder lumen. (**b**) Pericholecystic fluid. (**c**) Thickened gallbladder wall. Evidence of acute cholecystitis with air within the gallbladder lumen (**a**) suggestive of early acute emphysematous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

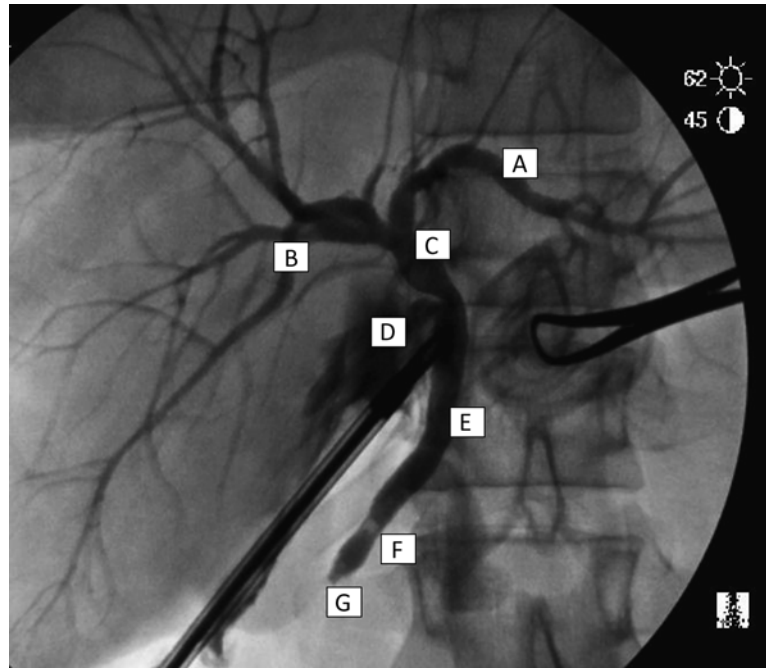

Fig. 9.5 Intraoperative Cholangiography with Retained Stone. (**a**). Left hepatic duct. (**b**) Right hepatic duct. (**c**) Common hepatic duct. (**d**) Cystic duct stump. (**e**) Common bile duct. (**f**) Retained stone. (**g**) Distal obstruction of the common bile duct. Intraoperative cholangiogram 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**)

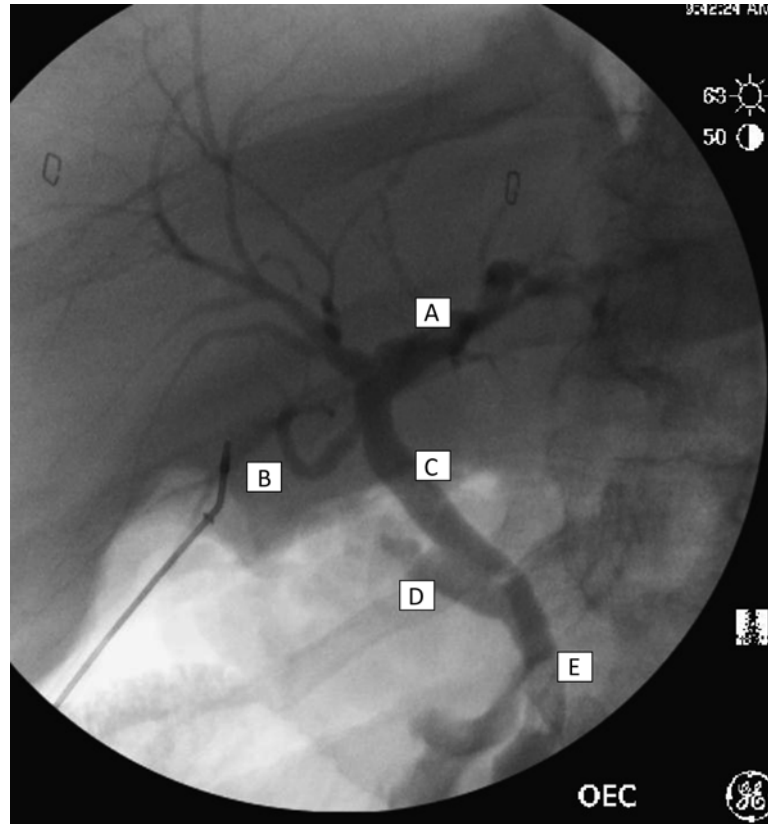

Fig. 9.6 Intraoperative Cholangiography of Right Hepatic Duct Injury. (**a**) Left hepatic duct. (**b**) Injured right hepatic duct. (**c**) Common hepatic duct. (**d**) Cystic duct stump. (**e**) Common bile duct. A transected right hepatic duct is opacified (**b**) showing anomalous insertion of the 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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