3 Pathophysiology and Diagnosis of Acute Acalculous Cholecystitis

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Abbreviat ions

AAC Acute acalculous cholecystitis
ACC Acute calculous cholecystitis

3.1 Introduction

Acute acalculous cholecystitis (AAC) is an acute necro-inflammatory infection of the gallbladder with a multifactorial pathogenesis, in the absence of cholelithiasis, sludge, or cystic duct obstruction on diagnostic imaging [1]. The condition was first described by Duncan in 1844. It accounts for approximately 2–15% of all cases of acute cholecystitis [1, 2] and is associated with high morbidity and mortality rates.

3.2 Epidemiology

AAC occurs in 0.2–0.4% of all critically ill patients [3] with predisposing multifactorial risk factors (Table 3.1). AAC has a predominance in elderly, as well as a male predominance ranging 40–80% and even more [4, 5], affecting patients much older and more predominantly of male sex than acute calculous cholecystitis (ACC) [6, 7]. However, AAC may also occur in young and middle-aged outpatient healthy individuals [2]. In children, AAC represents 50–70% of all cases of acute cholecystitis [8]. The incidence of AAC in outpatients is not well defined. Up to 77% of patients diagnosed with AAC during hospitalization may in fact have the onset at home without evidence of acute illness or trauma, but with significant vascular disease in up to 72% of these cases [9]. Although this would indicate that the actual incidence in outpatients may be in fact much higher than acknowledged, it may be also possible that some of these patients in this condition may have been misdiagnosed as AAC due to failure to reveal gallstones or microcrystals.

3.3 Etiology

AAC occurs more frequently as a complication of severe acute conditions (polytrauma, severe burns, shock, aortic dissection, or non-biliary operations—especially aortic surgery, acute myelogenous leukemia) [10–12]. AAC is also often associated with chronic conditions such as diabetes mellitus, cardiovascular disease, chronic kidney disease, vasculitis, acquired immunodeficiency syndrome, malignant tumors, bone marrow transplantation, and long-term total parenteral nutrition [13, 14]. Patients with cancer are at risk for AAC, including metastasis to the porta hepatis, therapy with interleukin-2, and

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Table 3.1 Risk factors and infections predisposing to acalculous cholecystitis

Risk factors for acalculous cholecystitis	Infections predisposing to acalculous cholecystitis	Risk factors that warrant broad empiric antimicrobial coverage
Systemic diseases: – Acute myelogenous leukemia – Diabetes mellitus – End-stage kidney disease – Immunosuppression – Infections/Sepsis	Bacteria: – *Coxiella burnetiid* – *Campylobacter jejuni* – *Salmonella species* (S. enterica, S typhi) – *Brucella species* – *Leptospira species* – *Mycobacterium tuberculosis* – *Vibrio cholerae*	Factors associated with mortality: – Age > 70 years – Comorbidities (e.g., liver disease, malignancy, chronic malnutrition) – Immunocompromising conditions (e.g., poorly controlled diabetes mellitus, chronic high-dose corticosteroid use, other immunosuppressive agents, neutropenia, advanced AIDS, B or T leukocyte deficiency) – Factors related to acalculous cholecystitis: high severity (i.e., sepsis); extensive peritoneal involvement or diffuse peritonitis; delay in initial intervention (source control) >24 h; inability to achieve adequate debridement or drainage control
Cardiovascular diseases: – Coronary heart disease – Heart failure – Aortic dissection – Hypotension – Cholesterol emboli – Vasculitis	Fungi: – *Candida species* – Isospora	
Iatrogenic factors: – Cardiopulmonary resuscitation – Mechanical ventilation – Nonbiliary surgery – Cystic duct obstruction by a percutaneous transhepatic catheter in the bile duct – Medications (e.g. opiates, sunitinib) – Multiple transfusions – Total parenteral nutrition – Bone marrow transplantation	Parasites: – *Ascaris lumbricoides* – *Echinococcus granulosus* – *Plasmodium species* – *Cryptosporidium*	
Surgical emergencies: – Burns – Major trauma	Viruses: – Cytomegalovirus – Epstein-Barr virus – Flavivirus – Hepatitis A and B – Dengue virus	Factors associated with antibiotic-resistant bacteria: – Nosocomial infections – Travel related: travel to areas with high rates of antibiotic-resistant organisms within the few weeks prior to infection onset; antibiotics received during travel – Known colonization with antibiotic-resistant organisms
HPB diseases: – Ampullary stenosis – Choledochal cyst – Hemobilia – Metastases involving portal vein	Miscellaneous: – Snake bites	
Miscellaneous: – Pregnancy – Childbirth		

lymphokine-activated killer cells for metastatic disease [15]. Local conditions that may often lead to AAC include dehydration, bile stasis, gallbladder dysmotility, or ischemia; systemic conditions that commonly lead to AAC include inflammation mediators [16], systemic bacterial (gram-negative or anaerobic) or viral (EBV, hepatotropic virus) infections, and sepsis [17, 18]. AAC usually develop as a secondary infection of the gallbladder during systemic sepsis, such as disseminated candidiasis, leptospirosis, chronic biliary tract carriers of typhoidal and nontyphoidal Salmonella, cholera, and tuberculosis [19–24], less often malaria, brucellosis, and dengue fever [25–27]. AAC due to extrahepatic biliary obstruction may have infectious, such as ascaria-

sis and echinococcal cysts [28, 29], or noninfectious causes, such as haemobilia, choledochal cyst, ampullary stenosis, or percutaneous transhepatic catheter drainage [30–32]. Rare causes for AAC are photodynamic therapy for duodenal lesions or snakebite [33, 34].

AAC has been reported in 0.7–0.9% of patients following open abdominal aortic reconstruction, in 0.5% of patients following cardiac surgery, and in as many as 4% of patients who have undergone bone marrow transplantation [4, 35, 36].

3.4 Pathogenesis

3.4.1 Gallbladder Wall Ischemia

Although not completely understood, the pathogenesis of AAC is related to blood stasis and ischemia of the gallbladder wall, usually related to hypoperfusion, that lead to a local inflammatory response that induces necrosis of the gallbladder wall [14, 37]. Gallbladder ischemia is central to the pathogenesis of AAC. Hypoperfusion is due to hypotension (e.g., heart failure), dehydration (e.g., fever), and vasoactive drug administration [37].

Prolongation of ischemia has been associated with increased mucosal phospholipase A2, superoxide dismutase activities, and increased mucosal lipid peroxide content, associated with high rates of gallbladder necrosis and perforation [35, 38]. Gallbladder specimen arteriography reveals marked differences between ACC and AAC [39]: ACC is correlated with arterial dilatation and extensive venous filling, while AAC is correlated with multiple arterial occlusions and minimal-to-absent venous filling, underlining the key role of vascular occlusion and microcirculatory disruption in the pathogenesis of AAC. Additionally, reperfusion injury may worsen the ischemic injuries of the gallbladder wall [40].

An interrelationship between ischemia and stasis can result in hypoperfusion [41]. In this model, bacterial invasion of ischemic tissue becomes a secondary phenomenon [41].

3.4.2 Bile Stasis

Another cause of AAC is thought to be bile stasis and increased lithogenicity of bile, proven in both experimental and clinical studies [8]. Hospitalized patients often have bile stasis due to multiple factors including dehydration, absence of oral intake that leads to impaired enterohepatic circulation, long-term total parenteral nutrition, and impaired gut metabolism. Volume depletion leads to bile concentration, thus the bile becomes thick bile or sludge and, in correlation with the absence of a stimulus for gallbladder emptying, may obstruct the cystic duct. Moreover, the use of opioid analgesics induces the spasm of the sphincter of Oddi as adverse effect, increasing the intraluminal bile duct pressure, promoting bile stasis. Bile stasis may also be prompted by mechanical ventilation with positive end-expiratory pressure that also reduces portal perfusion by increasing hepatic venous pressure [42]. Ileus is also thought to induce in bile stasis, but experimental results are conflicting.

Critically ill patients are more predisposed because of increased bile viscosity due to fever and dehydration and because of prolonged absence of oral feeding resulting in a decrease or absence of cholecystokinin-induced gallbladder contraction.

Bile stasis may be aggravated by total parental nutrition [43]. Parenteral nutrition is associated with gallstone formation, as well as AAC, in both adults and children. During long-term total parental nutrition, the incidence of AAC may be as high as 30% [44], while gallbladder “sludge” occurs in 50% of these patients at 4 weeks and is omnipresent at 6 weeks [45]. Neither cholecystokinin administration, to stimulate gallbladder emptying, nor enteral alimentation can completely prevent AAC among critically ill patients [46].

Bile stasis may alter the chemical composition of bile, which may induce gallbladder mucosal injury. For example, lysophosphatidylcholine may induce acute cholecystitis in animal models with identical histopathological features to that of human AAC [47]; lysophosphatidylcholine

has potent effects on gallbladder structure and functional water transport across mucosa [47]. Other bile compounds (e.g., beta-glucuronidase) have also been implicated in the pathogenesis of AAC [44].

3.4.3 Vasoactive Mediators

Vasoactive mediators also play a key role in the pathogenesis of AAC. Bacterial infection is most likely a secondary event, while the phenomena of primary importance seems to be the host response to splanchnic ischemia/reperfusion injury or gram-negative bacteremia. Intravenous injection of *Escherichia coli* lipopolysaccharide, a potent stimulus of inflammation and coagulation, produces AAC in several mammalian species [48, 49]. Human gallbladder mucosal cells stimulated in vitro with the same compound inducing the production of eicosanoids and platelet-activating factor [50]. AAC can also be induced by injecting plant polyphenols that activate factor XII directly and generate spasm of the cystic artery [51]. Platelet-activating factor induces splanchnic hypoperfusion in sepsis and other low-flow states [52]. The inflammation appears to be mediated by pro-inflammatory eicosanoids, as it is inhibited by nonspecific cyclooxygenase inhibitors [49].

In AAC, endothelial injury, gallbladder ischemia, and stasis lead to concentration of bile salts, gallbladder distension, and gallbladder wall necrosis. The majority of patients with AAC have multiple risk factors (Table 3.1) [36, 53–55].

3.4.4 Infection

In some cases, specific primary infections predispose to AAC (Table 3.1). More often, however, these infections cause a cholangiopathy without cholecystitis. Once AAC is established, secondary infection with enteric pathogens, including *Escherichia coli*, *Enterococcus faecalis*, *Klebsiella spp.*, *Pseudomonas spp.*, *Proteus spp.*, and *Bacteroides fragilis* and related strains is common [56]. Perforation occurs in severe cases [57]. AAC is associated with a higher incidence of gangrene and perforation compared to ACC.

Bacteremia is one of the major causes of morbidity and mortality in the ICU [58]. Early diagnosis of bacteremia and prompt initiation of antibiotic therapy improve the clinical outcomes in critically ill patients [14].

The incidence of bacteremia has increased over time despite the availability of suitable antibiotic therapy [59]. The most common bacterial species associated with AAC, identified by blood and/or bile cultures, are gram-negative *Enterobacteriaceae*, such as E. coli and *Klebsiella pneumoniae* [60], [61], followed by *Enterococcus species*, *Staphylococcus spp., Streptococcus spp*., and *Candida spp*. [14]. Particularly, AAC associated with acquired immunodeficiency syndrome (AIDS) or other immunosuppressive conditions may be due to opportunistic infections such as microsporidia, *Cryptosporidium,* or cytomegalovirus [62].

In pediatric patients, AAC occurs in young children and neonates, as well as older children [63]. Common precipitant factors are dehydration, acute bacterial infections, viral diseases, such as hepatitis, upper respiratory tract infections [64], and portal lymphadenitis with extrinsic cystic duct obstruction. Recent studies suggest that the pathogenesis may be similar to that in adults [63].

3.5 Clinical Manifestations

The clinical presentation of AAC varies based on the severity of illness and underlying predisposing conditions (Table 3.1). Early diagnosis is the key to improve prognosis because of the fast progression of AAC due to gangrene and perforation, with dismal prognosis [37]. AAC has to be suspected in a critically ill patient, often intubated and sedated, presenting sepsis or unexplained fever, jaundice, abdominal discomfort, or high transaminases (not justified for other reasons), especially in postoperative setting [6].

The presentation may be similar to ACC, with fever, severe right upper quadrant pain with ten-

derness at palpation, and positive Murphy's sign [6], sometimes presenting with a palpable right upper quadrant mass and/or crepitus (due to emphysematous cholecystitis) and rarely jaundice [9]. Murphy's sign is operator-dependent and involves an alert and cooperative patient; when present, is indicative of gallbladder inflammation. Presentation characterized by recurrent biliary symptoms for months or years usually has gallstone-related disease or functional gallbladder disorder. The presentation may be insidious; therefore, patients may have sepsis, shock, and peritonitis at presentation due to complications including gallbladder necrosis, gangrene, or perforation.

Jaundice typically results from sepsis-related cholestasis, partial biliary obstruction due to inflammation expanding to the common bile duct or due to extrinsic compression of the common bile duct by a phlegmon (Mirizzi-type syndrome).

Nowadays, the diagnosis rate of AAC is increasing due to several factors, such as increased number of severe forms, enhanced awareness on behalf of the medical staff, improved imaging techniques, and consideration of AAC in the differential diagnosis of complications in patients with major comorbidities [37].

As AAC occurs frequently in critically ill patients, it is important to recognize this condition:

- The potentially critically ill patient: is sweaty, anxious, pale, agitated, or confused; responds to moderate stimulation only (loud voice, physical prodding); uses the respiratory accessory muscles at a respiratory rate of 20–30 or under 8; has the heart rate over 100, the systolic blood pressure under 90, and the urinary out is under 0.5 ml/kg/h.
- The critically ill patient: has a severe general status; is dehydrated, unresponsive, or poorly responsive neurologically; has the respiratory rate under 8 or over 30, the heart rate under 50 or over 150, the systolic blood pressure under 60, oliguria or anuria. These patients might not withstand surgery when the Charlson Comorbidity Index (CCI) is at least 6 and the American Society of Anesthesiologists physical status classification (ASA-PS) is at least 3 (patients with severe systemic disease, with one or more moderate to severe diseases, that leads to significant functional limitations with one or more organ dysfunctions) [65–67].

3.6 Laboratory Tests

Laboratory tests in patients with AAC are nonspecific. Leukocytosis is present in 70–85% of patients [68]. Abnormal liver tests include conjugated hyperbilirubinemia and a mild increase in serum alkaline phosphatase and serum aminotransferases [9].

Blood cultures should be acquired in all patients with suspected AAC to guide narrowing of empiric antibiotics (Table 3.1). However, the culture findings may be negative or inconclusive in late-stage disease [13], and bile culture results are negative in nearly 50% of patients with AAC, probably due to concurrent antibiotic therapy.

3.7 Imaging

Imaging in AAC is not specific enough to make a stand-alone diagnosis. Imaging findings must be integrated in the context of clinical presentation.

3.7.1 Ultrasonography

Ultrasonography in patients with suspected AAC is mandatory [56, 69]. Features suggestive of AAC are similar as the ones for ACC, but without gallstones [70]:

- Thick wall (≥3.5–4 mm) (with distended gallbladder of ≥5 cm longitudinally and no ascites)–the most reliable feature seen in patients with AAC but is not specific [71].
- Ultrasonographic Murphy's sign.
- Pericholecystic fluid (halo)/subserosal edema.
- Other signs: intramural gas, mucosal membrane, sludge, hydrops (distension ≥8 cm longitudinally or 5 cm transversely, with clear fluid).

The reported sensitivity of ultrasound for AAC ranges from 30% to 92% [71], while the specificity is 89–100% [3]. False-positive results may be due to hypoalbuminemia, ascites, sludge, non-shadowing stones, or cholesterolosis, which can mimic a thickened gallbladder wall.

3.7.2 Computed Tomography

When diagnosis is uncertain at ultrasound, contrast-enhanced abdominal computed tomography (CT) scan is recommended to confirm AAC and/or to rule out other causes for acute abdominal pain.

CT scan findings in AAC include gallbladder wall thickening (>3 mm), intramural gas, lack of gallbladder wall enhancement, subserosal and/or pericholecystic edema, pericholecystic fluid, mucosal sloughing, hyperdense bile (sludge), and/or gallbladder distention (>5 cm) [71] (Figs. 3.1, 3.2, and 3.3). Of these findings, gas in the gallbladder wall or lumen and pericholecystic edema have the highest specificity for AAC (99, 95, and 92%, respectively), but with poor sensitivity (11, 38, and 22%, respectively). The accuracy of CT scan appears to be like that seen with ultrasonography [72].

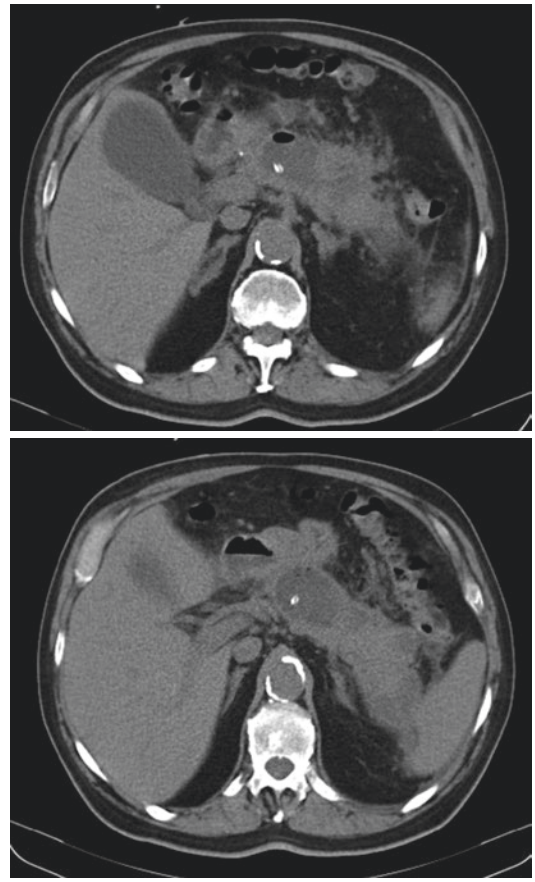

Fig. 3.1 Control CT after percutaneous drainage of an infected pancreatic pseudocyst due to recent episode of acute alcoholic pancreatitis, in a 69-year old patient, with multiple comorbidities (obesity, third degree hypertension, dyslipidemia, hepatic steatosis, acute on chronic kidney condition stage G3a)

3.7.3 Cholescintigraphy

In stable patients with unclear diagnosis at ultrasonography and abdominal CT scan, a hepatic technetium 99 m Tc iminodiacetic acid (HIDA) scan is recommended [73]. As cholescintigraphy (HIDA scan) takes hours to perform, it is not recommended in critically ill patients in whom a delay in therapy can be potentially fatal; other arguments for not recommending it in this setting are the frequent false-negative and false-positive results (due to fasting, liver disease, or total parenteral nutrition) [74].

Failure to opacify the gallbladder at 1 h is considered positive for AAC. Leakage into the pericholecystic space indicates gallbladder perforation. The sensitivity of cholescintigraphy for AAC is 67–100% [74, 75], while the specificity is 58–88% [75].

Cholescintigraphy associated with intravenous morphine administration (0.05 mg/kg) has led to a reappraisal of HIDA imaging for AAC [75, 76], especially when ultrasound is nondiagnostic, increasing the diagnostic accuracy to 95% [75, 77]. AAC is diagnosed if the gallbladder is not visualized in 30 min after morphine injection.

False-negative results are rare occurring in certain conditions, such as cystic duct patency despite a diseased gallbladder, bowel loop simulation of the gallbladder, bile leak from gallblad-

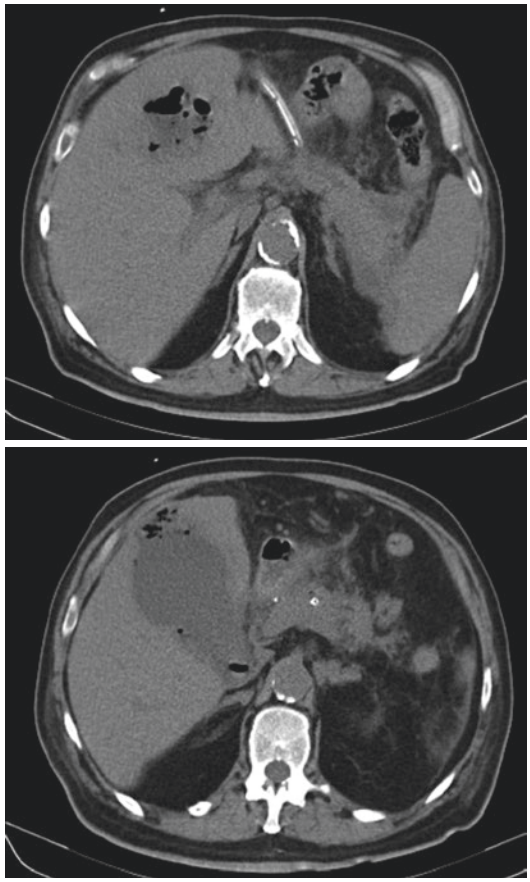

Fig. 3.2 Same patient as in Fig. 3.1: CT at 3 weeks showing gallbladder with significant distension (115/80 mm), with thickened, irregular walls, nonhomogenous mixed fluid, para-fluid and multiple air blob contents, associated with significant densification of the adjacent fat structures, with inflammatory infectious aspect; continuity solution present at the level of the gallbladder fundic area, with intrahepatic penetration in the fourth liver segment, with gaseous, fluid, and parafluid accumulation at this level, approximately 50/45 mm in size axially, without biliary lithiasis—acute acalculous cholecystitis with in-hospital onset, in a critically ill patient, with pericholecystic liver abscess

der perforation, and tracer activity in the kidneys simulating the gallbladder [78]. False-positive results may occur in several conditions, such as fasting, total parenteral nutrition, severe illness, severe hepatocellular disease, hyperbilirubinemia, rapid biliary to bowel transit, biliary sphincterotomy, and/or prior cholecystectomy. Other

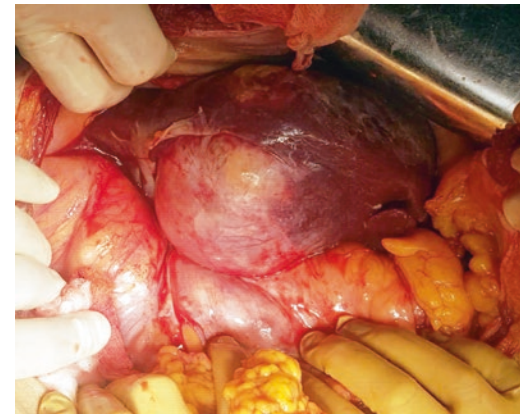

Fig. 3.3 Same patient as in Figs. 3.1 and 3.2: Intraoperative aspect of acalculous cholecystitis with pericholecystic liver abscess (superficialized on the diaphragmatic surface of segments 4–5), for which subtotal cholecystectomy, liver abscess evacuation, and multiple drainage was performed. The patient died in POD 10 due to recurrent acute pancreatitis and multiple peritoneal abscesses, despite ICU aggressive treatment and surgical reintervention

agents (diisopropyl and m-bromothymethyl iminodiacetic acid) used in cholescintigraphy have generally overcome the limitations of morphine cholescintigraphy.

3.7.4 Laparoscopy

Laparoscopy is recommended when the diagnosis of AAC is in question or if percutaneous cholecystostomy has failed to improve the patient's general status [79]. Bedside laparoscopy has been used with certain success for both diagnosis and therapy of AAC, but initial enthusiasm has diminished due to the bulky equipment that has to be brought to the ICU bedside. Nowadays, due to advances in intensive care, most patients will tolerate the transport to the operating room. For severe local forms of AAC, when complete laparoscopic cholecystectomy is not possible in a safe and expedient manner, a laparoscopic damage control procedure such as cholecystostomy or partial cholecystectomy may be performed to treat the patient's condition while minimizing the iatrogenic aggression.

3.8 Diagnosis

3.8.1 Positive Diagnosis

AAC remains difficult to diagnose mainly due to complicated clinical settings [14], the low prevalence, and the complexities to distinguish it from ACC [37].

The diagnosis of AAC is based upon a series of symptoms and clinical signs (e.g., critically ill patients with sepsis without a clear cause or jaundice) correlated with imaging findings that support such diagnosis, and the exclusion of other diagnoses. Imaging in AAC is not specific enough to make the diagnosis alone and must be interpreted in the clinical context. AAC is often diagnosed based on the following:

- Fever, abdominal pain, leukocytosis, and/or elevated liver tests.
- Risk factors for AAC (Table 3.1).
- Imaging features suggesting AAC.
- No evidence of other conditions that explain the clinical and imaging findings.

After diagnosis, imaging has a monitoring role of the development of AAC during medical and interventional treatment. Sometimes, gallstones are discovered by imaging late, during nonsurgical treatment, converting the diagnosis from AAC to ACC, case in which cholecystectomy becomes mandatory (Fig. 3.4).

3.8.2 Differential Diagnosis

The differential diagnosis of AAC includes other causes of sepsis (e.g., pneumonia, urinary tract infection), right upper quadrant pain, and/or jaundice. These include:

- Acute calculous cholecystitis.
- Noninfectious gallbladder hydrops (Fig. 3.5).
- Noninfectious thick gallbladder wall.

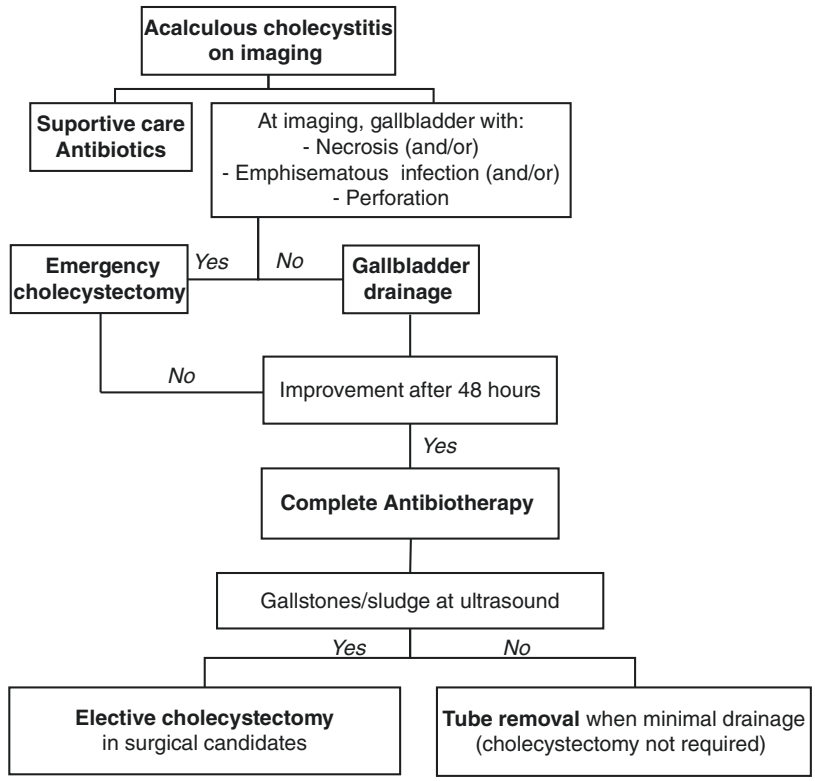

Fig. 3.4 Approach to the management of acalculous cholecystitis

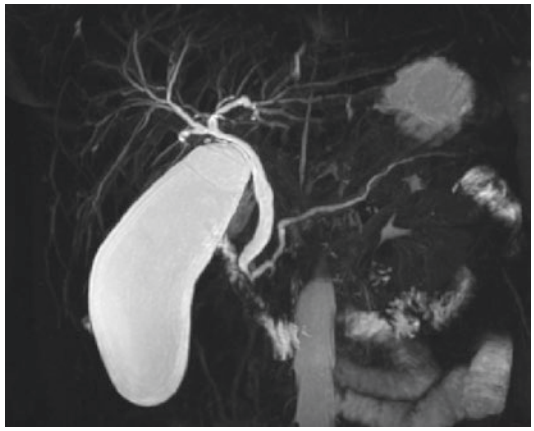
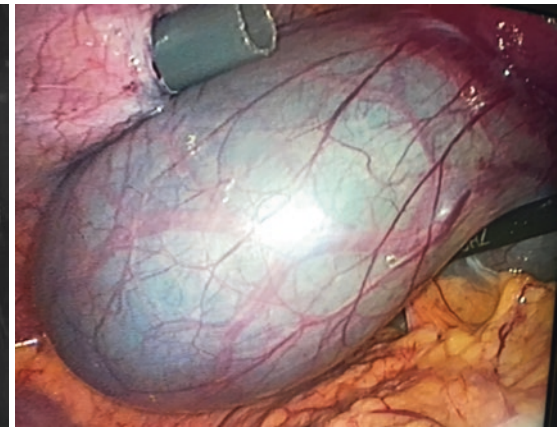

Fig. 3.5 Noninfectious gallbladder hydrops (13 cm) due to stenosis of the terminal common bile duct induced by autoimmune pancreatitis (MRI imaging and intraoperative aspect during laparoscopic cholecystectomy) in a 23-year-old female patient, with Crohn's disease, autoimmune pancreatitis, type 1 ANA autoimmune hepatitis, autoimmune thyroiditis. Surgery consisted in laparoscopic cholecystectomy, with favorable outcome

- Acute pancreatitis.
- Hepatic or subphrenic abscess.
- Right-sided pyelonephritis.
- Right-sided pneumonia.
- Other causes for right upper quadrant pain.
- Other causes for jaundice.
- Other causes for sepsis and abdominal pain.

These conditions can be ruled out by clinical examination, laboratory tests, and imaging also performed for AAC diagnosis. Laboratory evaluation should include a complete blood count, electrolytes, liver tests, and pancreatic enzymes. In addition, a urine analysis to exclude urosepsis, and a chest X-ray or CT scan to exclude pneumonia.

3.8.3 Complications

Because of the potential obscurity of the diagnosis, the underlying illnesses of the affected patients, and the potentially rapid progression of the disease to emphysematous and gangrenous cholecystitis, and gallbladder perforation, complications associated with this condition are frequent and usually severe [53, 69]. Gallbladder necrosis, gangrene, and perforation are frequently present at the time of diagnosis, especially in the critically ill patients, being associated with poor outcome [53, 69]. The incidence of gallbladder gangrene is higher in the AAC than in ACC (31% vs 5%, respectively) [80]. Gallbladder gangrene occurs in approximately 50% of patients with AAC, commonly leading to gallbladder perforation [71]. Particularly, emphysematous cholecystitis increases the risk for perforation. Perforation occurs in approximately 10% of patients with AAC [7, 35] that may result in abscess formation, free perforation with generalized peritonitis or cholecystoenteric fistula. When gallbladder gangrene occurs without perforation, the common complications are acute pancreatitis, obstruction of the main bile duct, and colonic perforation.

The incidence of cerebrovascular accidents is significantly higher in patients with acute AAC than in those with ACC (15% vs 6%) [80].

3.8.4 Mortality

AAC is associated with a high mortality rate, which depends on comorbidities and the swiftness of diagnosis. The cause of death in most patients with AAC is multiorgan failure due to sepsis [81]. The mortality rate is related to the initial clinical severity and a high prevalence of gangrene (approximately 50%) and perforation

(approximately 10%) [37], but always greater than 1% reported in gallstone cholecystitis [70].

With treatment, the overall mortality rate is high (30%) [7, 71, 82], but it increases to up to 75% if diagnosis and treatment are delayed [83]. The mortality rate in critically ill patients is very high, up to 90%, while in outpatient cases may be as low as 10% [71, 84].

3.9 Conclusion

AAC is very difficult to diagnose and should be screened in all critically ill or injured patients with sepsis, especially in cases where the cause of sepsis is not clear, in case of hypoperfusion, onset of jaundice, and/or postoperative setting. Ultrasound is the main diagnostic tool, being repeatable, noninvasive, cost-effective, and bedside available. The diagnosis must be prompt, otherwise mortality increases significantly.

References

1. Treinen C, Lomelin D, Krause C, et al. Acute acalculous cholecystitis in the critically ill: risk factors and surgical strategies. Langenbeck's Arch Surg. 2015;400:421–7. https://doi.org/10.1007/s00423-014-1267-6.
2. Ganpathi IS, Diddapur RK, Eugene H, et al. Acute acalculous cholecystitis: challenging the myths. HPB (Oxford). 2007;9:131–4.
3. Huffman JL, Schenker S. Acute acalculous cholecystitis: a review. Clin Gastroenterol Hepatol. 2010;8:15–22.
4. Cadot H, Addis MD, Faries PL, et al. Abdominal aortic aneurysmorrhaphy and cholelithiasis in the era of endovascular surgery. Am Surg. 2002;68:839.
5. Ganpathi IS, Diddapur RK, Eugene H, Karim M. Acute acalculous cholecystitis: challenging the myths. HPB (Oxford). 2007;9:131.
6. Ryu JK, Ryu KH, Kim KH. Clinical features of acute acalculous cholecystitis. J Clin Gastroenterol. 2003;36:166–9.
7. Kim SB, Gu MG, Kim KH, Kim TN. Long-term outcomes of acute acalculous cholecystitis treated by nonsurgical management. Medicine. 2020;99(7):e19057.
8. Tsakayannis DE, Kozakewich HP, Lillehei CW. Acalculous cholecystitis in children. J Pediatr Surg. 1996;31:127–30.
9. Savoca PE, Longo WE, Zucker KA, et al. The increasing prevalence of AC in outpatients. Results of a 7-year study. Ann Surg. 1990;211:433.
10. Hamp T, Fridrich P, Mauritz W, et al. Cholecystitis after trauma. J Trauma. 2009;66:400.
11. Inagaki FF, Hara Y, Kamei M, Tanaka M, Yasuno M. Acute and chronic acalculous cholecystitis associated with aortic dissection. J Surg Case Rep. 2015;2015(8):rjv101.
12. Topeli A, Demiroglu H, Dundar S. Acalculous cholecystitis in patients with acute leukaemia. Br J Clin Pract. 1996;50:224–5.
13. Tana M, Tana C, Cocco G, Iannetti G, Romano M, Schiavone C. Acute acalculous cholecystitis and cardiovascular disease: a land of confusion. J Ultrasound. 2015;18(4):317–20.
14. Rincon JE, Rasane RK, Aldana JA, Zhang CX, Fonseca RA. Acute acalculous cholecystitis-associated bacteremia has worse outcome. Surg Infect (Larchmt). 2020. https://doi.org/10.1089/sur.2019.297
15. Chung-Park M, Kim B, Marmyola G, et al. Acalculous lymphoeosinophilic cholecystitis associated with interleukin-2 and lymphokine-activated killer cell therapy. Arch Pathol Lab Med. 1990;114:1073–5.
16. Afdhal NH. Acalculous cholecystitis. Up to date. 2016. https://www.uptodate.com/contents/acalculous cholecystitis?source=search_result&search=acalculouscholecystitis&selectedTitle=1~28.
17. Souza LJ, Braga LC, Rocha Nde S, Tavares RR, et al. Acute acalculous cholecystitis in a teenager with hepatitis A viral infection: a case report. Braz J Infect Dis. 2009;13:74–6.
18. Basar O, Kisacik B, Bozdogan E, et al. An unusual cause of acalculous cholecystitis during pregnancy: hepatitis a virus. Dig Dis Sci. 2005;50(8):1532.
19. Mandak JS, Pollack B, Fishman NO, et al. Acalculous candidal cholecystitis: a previously unrecognized complication after cardiac transplantation. Am J Gastroenterol. 1995;90:1333–7.
20. Baelen E, Roustan J. Leptospirosis associated with acute acalculous cholecystitis. Surgical or medical treatment? J Clin Gastroenterol. 1997;25:704–6.
21. Khan FY, Elouzi EB, Asif M. Acute acalculous cholecystitis complicating typhoid fever in an adult patient: a case report and review of the literature. Travel Med Infect Dis. 2009;7:203–6.
22. McCarron B, Love WC. Acalculous nontyphoidal salmonellal cholecystitis requiring surgical intervention despite ciprofl oxacin therapy: report of three cases. Clin Infect Dis. 1997;24:707–9.
23. West BC, Silberman R, Otterson WN. Acalculous cholecystitis and septicemia caused by non-01 Vibrio cholerae: first reported case and review of biliary infections with Vibrio cholerae. Diagn Microbiol Infect Dis. 1998;30:187–91.
24. Vallejo EA. Acute tuberculous cholecystitis. Gastroenterology. 1950;16:501–4.

25. Abreu C, Santos L, Poínhos R, Sarmento A. Acute acalculous cholecystitis in malaria: a review of seven cases from an adult cohort. Infection. 2013;41(4):821–6.
26. Ashley D, Vade A, Challapali M. Brucellosis with acute acalculous cholecystitis. Pediatr Infect Dis J. 2000;19:1112–3.
27. Bhatty S, Shaikh N, Fatima M, Sumbhuani AK. Acute cholecystitis in dengue fever. J Pak Med Assoc. 2009;59:519–21.
28. Kuzu MA, Ozturk Y, Ozbek H, Soran A. Acalculous cholecystitis: ascariasis as an unusual cause. J Gastroenterol. 1996;31:747–9.
29. Mansour K. Acute cholecystitis with echinococcal cyst obstruction of the common bile duct. Postgrad Med J. 1963;39:542–3.
30. Sandblom P. Hemorrhage into the biliary tract following trauma: "Traumatic hemobilia". Surgery. 1948;24:571–86.
31. Lin SL, Shank M, Hung YB, et al. Choledochal cyst associated with acute acalculous cholecystitis. J Pediatr Gastroenterol Nutr. 2000;31:307–8.
32. Lillemoe KD, Pitt HA, Kaufman SL, et al. Acute cholecystitis occurring as a complication of percutaneous transhepatic drainage. Surg Gynecol Obstet. 1989;168:348–56.
33. Savoye G, Michel P, Hochain P, et al. Fatal acalculous cholecystitis after photodynamic therapy for high-grade dysplasia of the major duodenal papilla. Gastrointest Endosc. 2000;51:493–5.
34. Cello JP. AIDS cholangiopathy: spectrum of disease. Am J Med. 1989;86:539–46.
35. Hagino RT, Valentine RJ, Clagett GP. Acalculous cholecystitis after aortic reconstruction. J Am Coll Surg. 1997;184:245.
36. Wiboltt KS, Jeffrey RB Jr. Acalculous cholecystitis in patients undergoing bone marrow transplantation. Eur J Surg. 1997;163:519.
37. Soria-Aledo V, Galindo-Iñíguez L, Flores-Funes D, Carrasco-Prats M, Aguayo-Albasini JL. Is cholecystectomy the treatment of choice for acute acalculous cholecystitis? A systematic review of the literature. Rev Esp Enferm Dig. 2017;109(10):708–18.
38. Barie PS. Acalculous and postoperative cholecystitis. In: Barie PS, Shires GT, editors. Surgical intensive care. Boston: Little, Brown; 1993. p. 837–57.
39. Hakala T, Nuuiten PJ, Ruokonen ET, Alhava E. Microangiopathy in acute acalculous cholecystitis. Br J Surg. 1997;84:1249–52.
40. Taoka H. Experimental study on the pathogenesis of acute acalculous cholecystitis, with special reference to the roles of microcirculatory disturbances, free radicals and membrane-bound phospholipase A2. Gastroenterol Jpn. 1991;26:633–44.
41. Orlando R, Gleason E, Drezner AD. Acute acalculous cholecystitis in the critically ill patient. Am J Surg. 1983;145:472–6.
42. Parkman HP, James AN, Bogar LJ, et al. Effect of acalculous cholecystitis on gallbladder neuromuscular transmission and contractility. J Surg Res. 2000;88:186–92.
43. Lin KYK. Acute acalculous cholecystitis: a limited review of the literature. Mt Sinai J Med. 1986;53:305–9.
44. Kouromalis E, Hopwood D, Ross PE, et al. Gallbladder epithelial acid hydrolases in human cholecystitis. J Pathol. 1983;139:179–91.
45. Messing B, Bories C, Kuntslinger F, et al. Does total parenteral nutrition induce gallbladder sludge formation and lithiasis? Gastroenterology. 1983;84:1012–9.
46. Merrill RC, Miller-Crotchett P, Lowry P. Gallbladder response to enteral lipids in injured patients. Arch Surg. 1989;124:301–2.
47. Niderheiser DH. Acute acalculous cholecystitis induced by lysophosphatidyl choline. Am J Pathol. 1986;124:559–63.
48. Cullen JJ, Maes EB, Aggarwal S, et al. Effect of endotoxin on opossum gallbladder motility: a model of acalculous cholecystitis. Ann Surg. 2000;232:202–7.
49. Kaminski DL, Feinstein WK, Deshpande YG. The production of experimental cholecystitis by endotoxin. Prostaglandins. 1994;47:233–45.
50. Kaminski DL, Amir G, Deshpande YG, et al. Studies on the etiology of acute acalculous cholecystitis: the effect of lipopolysaccharide on human gallbladder mucosal cells. Prostaglandins. 1994;47:319–30.
51. Ratnoff OD, Crum JD. Activation of Hageman factor by solutions of ellagic acid. J Lab Clin Med. 1964;63:359–77.
52. Rehman T, Deboisblanc BP. Persistent fever in the ICU. Chest. 2014;145(1):158–65.
53. Shapiro MJ, Luchtefeld WB, Kurzweil S, et al. Acute acalculous cholecystitisin the critically ill. Am Surg. 1994;60:335.
54. Gofrit O, Eid A, Pikarsky A, et al. Cholesterol embolisation causing chronic AC. Eur J Surg. 1996;162:243.
55. Schwesinger WH, Diehl AK. Changing indications for laparoscopic cholecystectomy. Stones without symptoms and symptoms without stones. Surg Clin North Am. 1996;76:493.
56. Wang AJ, Wang TE, Lin CC, et al. Clinical predictors of severe gallbladder complications in acute acalculous cholecystitis. World J Gastroenterol. 2003;9(12):2821–3. https://doi.org/10.3748/wjg.v9.i12.2821.
57. Venkataramani A, Strong RM, Anderson DS, et al. Abnormal duodenal bile composition in patients with acalculous chronic cholecystitis. Am J Gastroenterol. 1998;93:434.
58. Nasa P, Juneja D, Singh O, et al. Incidence of bacteremia at the time of ICU admission and its impact on outcome. Indian J Anaesth. 2011;55:594–8.
59. Lachhab Z, Frikh M, Maleb A, et al. Bacteraemia in intensive care unit: clinical, bacteriological, and prognostic prospective study. Can J Infect Dis Med Microbiol. 2017;2017:4082938.
60. Ozyer U. Long-term results of percutaneous cholecystostomy for definitive treatment of acute acalcu-

lous cholecystitis: a 10-year single center experience. Acta Gastroenterol Belg. 2018;81:393–7.
61. Kuo CH, Changchien CS, Chen JJ, et al. Septic acute cholecystitis. Scand J Gastroenterol. 1995;30:272–5.
62. Wind P, Chevallier JM, Jones D, et al. Cholecystectomy for cholecystitis in patients with a cquired immune deficiency syndrome. Am J Surg. 1994;168:244.
63. Imamoglu M, Sarrhan H, Sari A, Ahmetoglu A. Acute acalculous cholecystitis in children: diagnosis and treatment. J Pediatr Surg. 2002;37:36–7.
64. Parithivel VS, Gerst PH, Banerjee S, et al. Acute acalculous cholecystitis in young patients without predisposing factors. Am Surg. 1999;65:366–8.
65. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373–83. https://doi.org/10.1016/0021-9681(87)90171-8.
66. Mayhew D, Mendonca V, Murthy BVS. A review of ASA physical status – historical perspectives and modern developments. Anaesthesia. 2019;74:373–9.
67. Okamoto K, Suzuki K, Takada T, et al. Tokyo Guidelines 2018: flowchart for the management of acute cholecystitis [published correction appears in J Hepatobiliary Pancreat Sci. 2019 Nov;26(11):534]. J Hepatobiliary Pancreat Sci. 2018;25(1):55–72.
68. Trowbridge RL, Rutkowski NK, Shojania KG. Does this patient have acute cholecystitis? JAMA. 2003;289:80.
69. Kalliafas S, Ziegler DW, Flancbaum L, Choban PS. Acute acalculous cholecystitis: incidence, risk factors, diagnosis, and outcome. Am Surg. 1998;64:471.
70. Javier BA, Eloísa SGC, Raquel GG, Carolina JA. Acute alithiasic cholecystitis: a not so rare disease. Rev Esp Enferm Dig. 2014;106(7):487–90.
71. Barie PS, Eachempati SR. Acute acalculous cholecystitis. Gastroenterol Clin N Am. 2010;39:343.
72. Mirvis SE, Whitley NO, Miller JW. CT diagnosis of acalculous cholecystitis. J Comput Assist Tomogr. 1987;11:83.
73. Westlake PJ, Hershfield NB, Kelly JK, et al. Chronic right upper quadrant pain without gallstones: does HIDA scan predict outcome after cholecystectomy? Am J Gastroenterol. 1990;85:986.
74. Shuman WP, Roger JV, Rudd TG, et al. Low sensitivity of sonography and cholescintigraphy in acalculous cholecystitis. AJR Am J Roentgenol. 1984;142:531–4.
75. Mariat G, Mahul P, Prévt N, et al. Contribution of ultrasonography and cholescintigraphy to the diagnosis of acute AC in intensive care unit patients. Intensive Care Med. 2000;26:1658.
76. Krishnamurthy S, Krishnamurthy GT. Cholecystokinin and morphine pharmacological intervention during 99mTc-HIDA cholescintigraphy: a rational approach. Semin Nucl Med. 1996;26:16–24.
77. Ziessman HA. Hepatobiliary scintigraphy in 2014. J Nucl Med Technol. 2014;42(4):249–59.
78. Dillehay G, Bar-Sever Z, Brown M, Brown R, Green R, Lee M, Lim K, et al. Appropriate use criteria for Hepatobiliary Scintigraphy in abdominal pain: summary and excerpts. J Nucl Med. 2017;58:9N.
79. Ceribelli C, Adami EA, Mattia S, Benini B. Bedside diagnostic laparoscopy for critically ill patients: a retrospective study of 62 patients. Surg Endosc. 2012;26(12):3612–5.
80. Gu MG, Kim TN, Song J, Nam YJ, Lee JY, Park JS. Risk factors and therapeutic outcomes of acute acalculous cholecystitis. Digestion. 2014;90(2):75–80.
81. Barie PS, Hydo LJ, Pieracci FM, et al. Multiple organ dysfunction syndrome in critical surgical illness. Surg Infect. 2009;10:369.
82. Eachempati SR, Barie PS. Acute acalculous cholecystitis. In: Eachempati SR, Reed II RL, editors. Acute Cholecystitis. Cham: Springer; 2015. https://doi.org/10.1007/978-3-319-14824-3_15.
83. Cornwell EE 3rd, Rodriguez A, Mirvis SE, Shorr RM. Acute acalculous cholecystitis in critically injured patients. Preoperative diagnostic imaging. Ann Surg. 1989;210:52.
84. Unal H, Korkmaz N, Kirbas I, Selcuk H, Yilmaz U. Acute acalculous cholecystitis associated with acute hepatitis B infection. Int J Infect Dis. 2009;13:e310–2.