Acute Acalculous Cholecystitis

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KEYWORDS

- Acute acalculous cholecystitis
- Percutaneous cholecystostomy • Ultrasound • CT

Acute cholecystitis may develop at any time in the presence of gallstones, especially once symptoms develop. Acute cholecystitis is especially dangerous during a serious illness or following major surgery, however, whether associated with gallstones or more typically not (acute acalculous cholecystitis [AAC]). Now recognized as a complication of serious medical and surgical illnesses,[1–3] increased numbers of critically ill patients, increased awareness, and improved imaging modalities are resulting in the identification of more cases of AAC.[4] The mortality rate remains at least 30% because the diagnosis of AAC remains challenging to make, affected patients are critically ill, and the disease itself can progress rapidly because of the high prevalence of gangrene (approximately 50%) and perforation (approximately 10%).[5]

CLINICAL PATTERNS OF AAC

Reports of acute cholecystitis complicating surgery, multiple trauma, or burn injury are numerous. In patients with gallstones, postoperative cholecystitis affects males and females to a similar degree. More than 80% of patients who develop non–trauma-related postoperative AAC, however, are male.[6] The incidence of AAC following open abdominal aortic reconstruction is 0.7% to 0.9%,[7,8] and has also been reported to complicate endovascular aortic reconstruction.[9]

After cardiac surgery, the incidence of acute cholecystitis is 0.12% (42% AAC) in collected reports encompassing 31,710 patients, with an overall mortality rate of 45%.[6] Although rare following cardiac surgery, those undergoing cardiac valve replacement with or without bypass grafting may be at particular risk[10] because of

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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, 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 from hemorrhagic shock or cardiac arrest[19] have been associated with AAC. End-stage renal disease is associated with AAC, perhaps because both diabetes mellitus and atherosclerosis are commonplace in patients with end-stage renal disease,[20] who often experience low flow on hemodialysis. Hemorrhagic AAC has been reported in end-stage renal disease, related to either uremic thrombocytopathy or frequent exposure to heparinoids to facilitate blood flow through the circuit.[21] 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[22]; or percutaneous transhepatic catheter drainage of extrahepatic biliary obstruction, wherein the catheter in the common bile duct itself may obstruct the cystic duct.[23] Acute acalculous cholecystitis has been reported with acute myelogenous leukemia.[24] In bone marrow transplant recipients, the incidence of AAC is as high as 4%.[25]

Acalculous cholecystitis may also develop as a secondary infection of the gallbladder during systemic sepsis, for example in disseminated candidiasis,[26,27] leptospirosis,[28] in chronic biliary tract carriers of typhoidal[29] and nontyphoidal *Salmonella*,[30] during active diarrheal illnesses, such as cholera[31] or *Campylobacter* enteritis,[32] and tuberculosis (**Box 1**).[33] Also reported are cases of AAC in malaria,[34] brucellosis,[35] Q fever (*Coxiella burnetii*),[36] and dengue fever.[37] Miscellaneous viral pathogens associated with AAC include hepatitis A[38] and B,[39] and Epstein-Barr virus.[40] Extrahepatic biliary obstruction can lead to AAC from infectious or noninfectious causes. Obstructive infectious causes include ascariasis[41] and echinococcal cysts,[42] whereas noninfectious causes of AAC with extrahepatic biliary obstruction include hemobilia (**Fig. 1**),[43] choledochal cyst,[44] and ampullary stenosis.[45]

Acalculous biliary disease occurs in patients with AIDS, and may take either of two forms: cholestasis,[46] which can be impossible to distinguish from bacterial cholangitis in an acutely jaundiced patient, or AAC.[47] Now increasingly rare because of improved antiretroviral therapy, AIDS-associated AAC has been associated with cytomegalovirus infection[48] or infection with *Cryptosporidium* or microsporidial protozoa.[49]

AAC represents 50% to 70% of all cases of acute cholecystitis in children.[50] Acalculous cholecystitis is recognized in young children and neonates,[51] and older children. Dehydration is a common precipitant, as are acute bacterial infections[52] and viral illnesses, such as hepatitis[38] and upper respiratory tract infections. Portal lymphadenitis with extrinsic cystic duct obstruction may be etiologic in viral infections. Recent reports[51] 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. Volume depletion leads to concentration of bile, which can inspissate in the absence of a stimulus for gallbladder emptying (eg, nothing per os). Opioid analgesics increase intralumenal bile duct pressure because of 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

Box 1
Pathogens associated with AAC

- Bacteria
  - *Brucella* spp (etiologic agents of brucellosis)
  - *Campylobacter jejuni*
  - *Coxiella burnetii* (etiologic agent of Q fever)
  - *Leptospira* spp (etiologic agents of leptospirosis)
  - *Mycobacterium tuberculosis, M bovis*
  - *Salmonella* spp
    - *S enterica* subsp *enterica* serovar Enteritidis
    - *S enterica* subsp *enterica* serovar Typhimurium
    - *S typhi* (etiologic agent of typhoid fever)
  - *Vibrio cholerae*
- Yeasts and molds
  - *Candida* spp
- Viruses
  - Hepatitis A virus
  - Hepatitis B virus
  - Epstein-Barr virus
  - *Flavivirus* (serotypes) (etiologic agents of dengue fever and dengue hemorrhagic fever)
- Parasites
  - *Ascaris lumbricoides*
  - *Echinococcus* spp (etiologic agents of echinococcosis)
    - *E granulosus*
    - *E multilocularis*
  - *Plasmodium* spp (etiologic agents of malaria)

ventilation with positive end-expiratory pressure,[53] which also decreases portal perfusion by increasing hepatic venous pressure.

Bile stasis may alter the chemical composition of bile, which may promote gallbladder mucosal injury. Lysophosphatidylcholine has potent effects on gallbladder structure and functional water transport across mucosa.[53] Acute cholecystitis induced in several animal models by lysophosphatidylcholine results in histopathology identical to that of human AAC.[54] Other compounds present in bile (eg, β-glucuronidase) have also been implicated in the pathogenesis of AAC.[55]

Total parenteral nutrition

Fasting and bile stasis may be aggravated by total parenteral nutrition (TPN) in the pathogenesis of AAC.[56] Parenteral nutrition is associated with gallstone formation and AAC in both adults and children. The incidence of AAC during long-term TPN may be as high as 30%.[57] Formation of gallbladder ''sludge'' occurs among 50% of patients on long-term TPN at 4 weeks and is ubiquitous at 6 weeks.[58] Neither

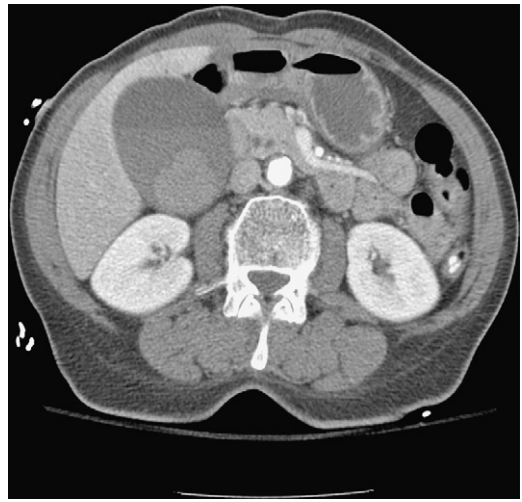

Fig. 1. CT of the abdomen revealing a markedly dilated gallbladder containing a globular density compatible with intralumenal blood clot in a patient with severe coronary artery disease, who was receiving aspirin, clopidogrel, and intravenous unfractionated heparin. No gallstones were visualized. At laparoscopic cholecystectomy an acutely inflamed gallbladder was resected. Clot was present in the lumen, but no stones.

stimulation of gallbladder emptying with cholecystokinin nor enteral alimentation, however, can prevent AAC among critically ill patients.[59]

Gallbladder Ischemia

Gallbladder ischemia is central to the pathogenesis of AAC. An interrelationship between ischemia and stasis has been suggested, leading to hypoperfusion.[60] 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 hypothesis, bacterial invasion of ischemic tissue is a secondary phenomenon.[60] Alternatively, reperfusion injury may be the crucial factor. Prolongation of ischemia was associated with increased mucosal phospholipase A_2 and superoxide dismutase activities, and increased mucosal lipid peroxide content.[61]

It has been hypothesized that the fundamental lesion leading to AAC is failure of the gallbladder microcirculation with cellular hypoxia.[62] 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 humans.[63] 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 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, a potent stimulus of

inflammation and coagulation that mimics clinical sepsis in several respects, produces AAC in several mammalian species, including opossums[64] and cats.[65] In opossums, lipopolysaccharide decreased the contractile response to cholecystokinin and caused a dose-dependent mucosal injury.[62] The dysmotility was abolished by inhibition of nitric oxide synthase. Human gallbladder mucosal cells stimulated in vitro with lipopolysaccharide secrete eicosanoids and platelet-activating factor.[66] Cholecystitis can also be produced by injection of plant polyphenols that activate coagulation factor XII directly and produce immediate spasm of the cystic artery.[67] AAC has also been produced in cats by infusion of platelet-activating factor into the cystic artery.[68] Platelet-activating factor has been implicated in the pathogenesis of splanchnic hypoperfusion in sepsis and other low-flow states. The inflammation seems to be mediated by proinflammatory eicosanoids, because it is inhibited by nonspecific cyclooxygenase inhibitors.[65]

DIAGNOSIS

AAC poses major diagnostic challenges.[68] 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, because 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.[69] Fever is generally present but other physical findings cannot be relied on, 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] Jaundice caused by AAC may be caused most often by sepsis-related cholestasis, or rarely by extrinsic compression of the common duct by the phlegmon (Mirizzi-type syndrome).[70] Other biochemical assays of hepatic enzymes are of little help. The diagnosis of AAC often rests on radiologic studies (**Box 2**).

Ultrasound

Ultrasound of the gallbladder is the most accurate modality to diagnose AAC in the critically ill patient.[71] Although sonography is accurate for detecting gallstones and measuring bile duct diameter, neither is particularly relevant to the diagnosis of AAC. Thickening of the gallbladder wall is the single most reliable criterion,[72–74] with reported specificity of 90% at 3 mm and 98.5% at 3.5 mm wall thickness, and sensitivity of 100% at 3 mm and 80% at 3.5 mm. Accordingly, gallbladder wall thickness greater than or equal to 3.5 mm is generally accepted to be diagnostic of AAC. Other helpful sonographic findings for AAC include pericholecystic fluid or the presence of intramural gas or a sonolucent intramural layer, or ''halo,'' which represents intramural edema (**Fig. 2**).[71] Distention 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, nonshadowing stones, cholesterolosis, hypoalbuminemia, or ascites mimic a thickened gallbladder wall.[73]

Box 2
Imaging criteria for the diagnosis of AAC

Ultrasound

Either two major criteria, or one major criterion and two minor criteria, satisfy the ultrasound diagnosis of AAC

Major criteria

- Gallbladder wall thickening >3 mm
- Striated gallbladder (ie, gallbladder wall edema)
- Sonographic Murphy sign (inspiratory arrest during deep breath while gallbladder is being insonated; unreliable if patient is obtunded or sedated)
- Pericholecystic fluid (absent either ascites or hypoalbuminemia)
- Mucosal sloughing
- Intramural gas

Minor criteria

- Gallbladder distention (>5 cm in transverse diameter)
- Echogenic bile (sludge)

Computed tomography

Either two major criteria, or one major criterion and two minor criteria, satisfy the CT diagnosis of AAC

Major criteria

- Gallbladder wall thickening >3 mm
- Subserosal halo sign (intramural lucency caused by edema)
- Pericholecystic infiltration of fat
- Pericholecystic fluid (absent either ascites or hypoalbuminemia)
- Mucosal sloughing
- Intramural gas

Minor criteria

- Gallbladder distention (>5 cm in transverse diameter)
- High-attenuation bile (sludge)

Hepatobiliary scintigraphy

Nonvisualization or questionable visualization of the gallbladder at 1 hour after administration of 5 mCi of a ^{99m}Tc iminodiacetic acid derivative, in the presence of adequate hepatic uptake of tracer, and excretion into the duodenum

Morphine sulfate, 0.04–0.05 mg/kg intravenously, may be given at 30–40 minutes of nonvisualization to increase specificity at 1 hour

Enhanced accumulation of radiotracer in the gallbladder fossa may be indicative of gallbladder gangrene or perforation

Radionuclide Studies

Although technetium ^{99m}Tc iminodiacetic acid imaging is approximately 95% accurate to diagnose calculous acute cholecystitis,[75] false-negative hepatobiliary scans are problematic when used for diagnosis of AAC in the setting of critical illness,[75,76]

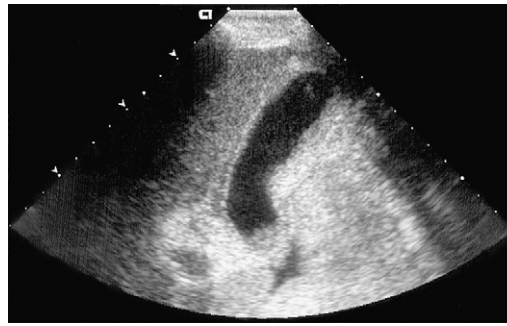

Fig. 2. Gallbladder ultrasound of a patient with sepsis and cholestasis. A thick-walled gallbladder is visible with echogenic bile (sludge) within the neck of the gallbladder, but no stones. There is pericholecystic fluid (the echogenic [bright] area) near the neck of the gallbladder. A "halo" sign (intramural edema) is visible just to the left of the gallbladder in the image.

because of false-positive scans associated with fasting, liver disease, or feeding with TPN.[76] The sensitivity of hepatobiliary imaging for AAC is reportedly as low as 68%.[75] Intravenous morphine (0.04–0.05 mg/kg) given after initial nonvisualization of the gallbladder may increase the accuracy of cholescintigraphy among critically ill patients, by enhanced gallbladder filling caused by increased bile secretory pressure.[77,78] Morphine cholescintigraphy has led to a reappraisal of radionuclide imaging for AAC,[71,79] provided the patient can be transported safely to the nuclear medicine suite and can remain there for the 2 hours or more that it may take to complete morphine cholescintigraphy. False-positive studies are reduced dramatically when morphine cholescintigraphy is performed; sensitivity of 67% to 100% and specificity of 69% to 100% have been reported in collected series of morphine cholescintigraphy for the diagnosis of AAC.[71]

CT

CT seems to be as accurate as ultrasound in the diagnosis of AAC.[80] Diagnostic criteria for AAC by CT are similar to those described for sonography (see **Box 2**; **Figs. 1** and **3**).[81] Only a single retrospective study has compared all three modalities

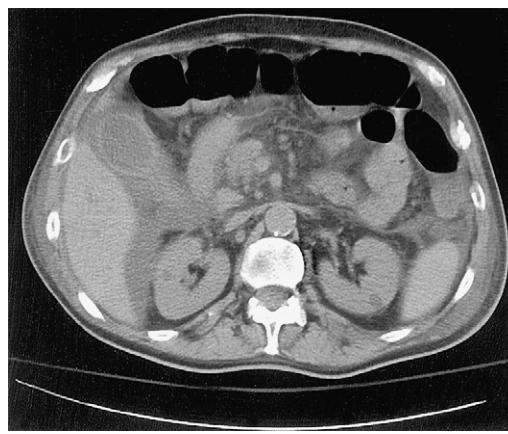

Fig. 3. CT of the abdomen showing AAC. Note the thickened, contrast-enhanced wall of the gallbladder, ventral to the right hepatic lobe, and the large amount of surrounding ascites (pericholecystic fluid). No gallstones were visualized.

(ultrasound, hepatobiliary scanning, and CT)[82]; 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 intensive care unit setting. Preference may be given to CT if other thoracic or abdominal diagnoses are under consideration.

Laparoscopy

Bedside laparoscopy has been used with success for the diagnosis and therapy of AAC,[83–85] but initial enthusiasm has waned because bringing the equipment to the intensive care unit bedside is cumbersome. Laparoscopy can be performed under local anesthesia and intravenous sedation at the bedside, and is possible in patients who have undergone recent abdominal surgery if ''gasless'' techniques are used. Diagnostic accuracy is high,[84] and both laparoscopic cholecystostomy and cholecystectomy are technically possible to perform.

THERAPY

The historic treatment for AAC was cholecystectomy,[2] because of the ostensible need to inspect the gallbladder and perform a resection if gangrene or perforation in AAC are present. Pericholecystic fluid collections can be drained during laparoscopy or celiotomy, and other pathology that may mimic acute cholecystitis (eg, perforated ulcer, cholangitis, pancreatitis) may be identified and managed if the diagnosis of AAC is incorrect. Percutaneous cholecystostomy is now established, however, as a lifesaving, minimally invasive alternative.[86,87] Open cholecystostomy can also be accomplished under local anesthesia through a short right subcostal incision, but the ability to visualize elsewhere in the abdomen is limited. Cholecystostomy by either technique does not decompress the common bile duct if cystic duct obstruction is present; therefore, the common duct must be decompressed in addition by some manner (eg, endoscopic retrograde cholangiopancreatography with sphincterotomy, laparoscopic or open common bile duct exploration) if cholangitis is suspected. Patency of the cystic duct can be determined immediately by tube cholangiography (**Fig. 4**), which should always be performed after the patient has recovered to

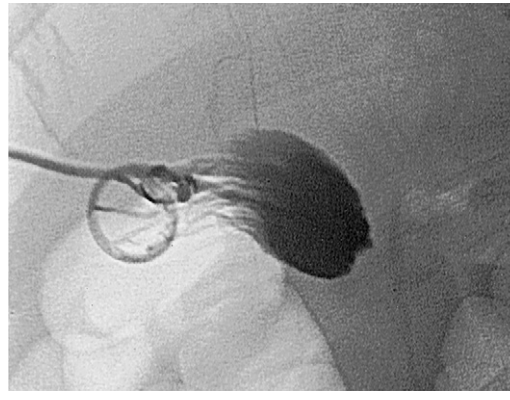

Fig. 4. Tube cholangiography following percutaneous cholecystectomy. Contrast fails to enter the common bile duct (incidence approximately 20%), reflecting cystic duct obstruction. In this circumstance, concomitant cholangitis (which is rare) would not be drained without separate instrumentation of the common bile duct.

determine the presence of gallstones that may not have been detected initially. If gallstones are present an elective cholecystectomy is usually recommended, with the drainage tube remaining in place during the interprocedure interval. Interval cholecystectomy is usually not indicated after true AAC[87]; the cholecystostomy tube can be removed after tube cholangiography confirms that gallstones are absent.

Percutaneous cholecystostomy[88–90] controls AAC in 85% to 90% of patients. The gallbladder is usually intubated under sonographic (occasionally laparoscopic) control by an anterior or anterolateral transhepatic approach (through the right hepatic lobe) to minimize leakage of bile, but transperitoneal puncture has been described. Rapid improvement should be expected when percutaneous cholecystostomy is successful. If rapid improvement does not ensue, the tube may be malpositioned or not draining properly, or the diagnosis of AAC may be incorrect, and an open procedure may be required.

Reported causes of failure include gangrenous cholecystitis, catheter dislodgement, bile leakage causing peritonitis, and an erroneous diagnosis.[91,92] Perforated ulcer, pancreatic abscess, pneumonia, and pericarditis have been discovered in the aftermath of percutaneous cholecystostomy when patients failed to improve. Reported major complications occur after 8% to 10% of procedures, including dislodgment of the catheter, acute respiratory distress syndrome, bile peritonitis, hemorrhage, cardiac arrhythmia, and hypotension caused by procedure-related bacteremia.[90] The 30-day mortality of percutaneous and open cholecystostomy are 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 3 of the 10 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*; antibiotic therapy should be directed against these organisms. Critical illness and prior antibiotic therapy alter host flora, however, and resistant or opportunistic pathogens may be encountered. *Pseudomonas*, staphylococci (including methicillin-resistant strains), *Enterobacter* and related species, anaerobic organisms (eg, *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, is particularly associated with gangrene and perforation. Emphysematous cholecystitis is rare, but shares many traits with AAC; 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 mandates immediate cholecystectomy in view of the fulminant nature of untreated emphysematous cholecystitis (percutaneous cholecystostomy

does not achieve source control reliably enough). *Clostridium* spp, rather than aerobic gram-negative bacilli, are isolated most commonly in emphysematous cholecystitis (45% of cases, with *Clostridium welchii* predominating). *E coli* are recovered from approximately one third of affected patients. Antimicrobial therapy specific for *Clostridium* spp (eg, 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 adjacent duodenum or transverse colon (cholecystoenteric fistula); the subhepatic space, causing abscess formation; 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] The usual immediate cause of death with AAC is severe sepsis with multiple organ dysfunction syndrome.[96] Unusual causes of death from gallbladder perforation in AAC include hemorrhage from the liver[97] and pulmonary bile embolism.[98] Serious complications of gallbladder gangrene without perforation include acute pancreatitis,[99] colon perforation,[100] and obstruction of the common hepatic duct.[101] Empyema of the gallbladder may also complicate AAC.[102]

SUMMARY

AAC should be suspected in every critically ill patient with sepsis in whom the source of infection cannot be found immediately. Suspicion should be especially high if the patient is injured, has undergone recent major surgery, has had a period of hypotension or hypoperfusion for any reason, or becomes jaundiced. The preferred diagnostic modality is ultrasound, which is inexpensive, noninvasive, and can be brought to the bedside of the unstable patient. Once diagnosed, the treatment of choice is percutaneous cholecystostomy, but if the response to drainage is not prompt and favorable, an alternative diagnosis must be considered and 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.

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