Treatment of acute calculous cholecystitis

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INTRODUCTION

Acute cholecystitis is a syndrome of right upper quadrant pain, fever, and leukocytosis associated with gallbladder inflammation. It typically occurs in patients with gallstones (ie, acute calculous cholecystitis [ACC]), while acalculous cholecystitis accounts for a minority (5 to 10 percent) of cases. Complications of acute cholecystitis include gallbladder gangrene or perforation, which can be life-threatening.

Patients with ACC usually present with severe and steady abdominal pain in the right upper quadrant or epigastrium, fever, and leukocytosis. A positive Murphy's sign on physical examination supports the diagnosis. In most cases, the diagnosis can be established with an abdominal ultrasound or a cholescintigraphy if the ultrasound is equivocal. (See "Acute calculous cholecystitis: Clinical features and diagnosis".)

Cholecystectomy is the mainstay of treatment for ACC. Poor surgical candidates may benefit from initial nonoperative management with antibiotics and a gallbladder drainage procedure; those whose surgical risk improves after resolution of the acute inflammation should undergo elective gallbladder surgery to prevent recurrent symptoms.

The treatment of ACC will be reviewed here. Other topics on gallstone diseases and their treatment include:

- The approach to patients with asymptomatic gallstones. (See "Overview of gallstone disease in adults" and "Approach to the management of gallstones".)

- The approach to the pregnant patient with gallstones. (See "Gallstone diseases in pregnancy".)

- The clinical manifestations and diagnosis of cholecystitis. (See "Acute calculous cholecystitis: Clinical features and diagnosis".)

- The diagnosis and management of acalculous cholecystitis. (See "Acalculous cholecystitis: Clinical manifestations, diagnosis, and management".)

- Xanthogranulomatous cholecystitis. (See "Xanthogranulomatous cholecystitis".)

- Techniques of cholecystectomy. (See "Laparoscopic cholecystectomy" and "Open cholecystectomy".)

- The approach to choledocholithiasis. (See "Choledocholithiasis: Clinical manifestations, diagnosis, and management" and "Surgical common bile duct exploration".)

SUPPORTIVE CARE

Patients diagnosed with acute calculous cholecystitis (ACC) should be admitted to the hospital and provided with supportive care including [1]:

- Intravenous hydration.

- Correction of any electrolyte abnormalities.

- Pain control.

- Intravenous antibiotics.

- Patients should be kept fasting, and although uncommonly needed, those who are vomiting should have placement of a nasogastric tube. (See "Inpatient placement and management of nasogastric and nasoenteric tubes in adults".)

Pain control — Pain control in patients with ACC can usually be achieved with nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids.

We prefer ketorolac for patients with biliary colic. Treatment usually relieves symptoms within 20 to 30 minutes. Opioids, such as morphine, hydromorphone, or meperidine, are appropriate therapy for patients who have contraindications to NSAIDs or who do not achieve adequate pain relief with an NSAID, which may be more common in patients with acute cholecystitis compared with those with uncomplicated biliary colic.

Although meperidine was traditionally the opioid of choice in patients with gallstone disease because it was thought to have less of an effect on sphincter of Oddi motility than morphine [2-4], a systematic review found that all opioids increase sphincter of Oddi pressure [3]. Thus, there are insufficient data to avoid morphine, especially considering that morphine requires less frequent dosing than meperidine.

Antibiotics — For patients with complicated ACC, broad-spectrum antibiotics are required. For those with uncomplicated ACC, we also suggest administering antibiotics. Once started, antibiotic therapy should continue until either the gallbladder is removed or the cholecystitis clinically resolves.

ACC is primarily an inflammatory process, but secondary infection of the gallbladder can occur as a result of cystic duct obstruction and bile stasis [5,6]. The rate of gallbladder empyema and pericholecystic abscess is overall low, but patients can easily develop life-threatening gram-negative sepsis from uncomplicated, acute cholecystitis. Thus, antibiotics are commonly administered prophylactically to protect against sepsis and wound infection [7]. However, since data are conflicted as to whether antibiotics are required for the treatment of uncomplicated acute cholecystitis [5,6,8-10], some clinicians do not use antibiotics in very mild cases.

In the PEANUT II trial, 457 patients with mild-to-moderate ACC (immediate cholecystectomy indicated) received cefazolin before incision or no antibiotic prophylaxis [11]. The number of surgical site infections was significantly higher in the no-prophylaxis group (5.3 versus 12.1 percent; P = 0.010). Other complications or length of stay were not different.

Regardless, it is generally agreed that antibiotics are indicated for all complicated ACC (ie, gallbladder gangrene/necrosis, rupture, or emphysematous cholecystitis) and for uncomplicated ACC in patients who are frail, have diabetes, or are immunocompromised [8,12].

When empiric antibiotic therapy is indicated, the chosen agent(s) should cover the most common pathogens of the *Enterobacteriaceae* family, including gram-negative rods and anaerobes [6]. In a study of 467 patients, including a control group of 42 with normal biliary trees, positive bile cultures were found in 22 percent of patients with symptomatic gallstones and 46 percent of patients with acute cholecystitis [13]. The most frequent isolates from the gallbladder or common bile duct were *Escherichia coli* (41 percent), *Enterococcus* (12 percent), *Klebsiella* (11 percent), and *Enterobacter* (9 percent). Whenever possible, the chosen agent(s) should also achieve adequate concentrations in bile.

We recommend the following antibiotic regimens for acute cholecystitis based on the patient's individual risk category [8]:

- For patients with community-acquired acute cholecystitis of low risk (table 1)
- For patients with community-acquired acute cholecystitis of high risk (table 2)
- For patients with health-care-associated acute cholecystitis (table 3)

The Tokyo Guidelines 2018, an international reference commonly cited for the treatment of acute cholangitis and acute cholecystitis, agreed with the recommendations above in general but included additional agents in each patient category (eg, ertapenem) (table 4) [14].

The choosing of an antibiotic regimen within each patient category is governed by local practices, taking into consideration the antibiogram and formulary of each institution. The chosen agents should subsequently be tailored to culture and susceptibility results when they become available [5].

The duration of antibiotic therapy is generally tailored to the clinical situation. For patients undergoing cholecystectomy for uncomplicated cholecystitis, we discontinue antibiotics the day after the cholecystectomy. Our practice is supported by results from several randomized trials:

- A multicenter trial randomly assigned 414 patients hospitalized for mild or moderate calculous cholecystitis to continue their preoperative antibiotic regimen for five days (2 g amoxicillin-clavulanate, three times daily) or to receive no antibiotics following cholecystectomy [15]. No significant differences in postoperative infection rates (17 versus 15 percent) were found.
- A single-center trial randomly assigned 195 patients who underwent laparoscopic cholecystectomy for mild-to-moderate calculous cholecystitis to receive either amoxicillin-clavulanate or placebo for five days [16]. Similar numbers of patients developed postoperative infectious complications (5.8 percent placebo versus 6.6 percent antibiotics), and there were no differences in other outcomes (eg, hospital stay, readmission, and reoperation).

Clinical judgment should dictate antibiotic management in more complicated scenarios, such as in the septic postoperative patient. The duration of antibiotic therapy for high-risk patients managed nonoperatively is discussed separately. (See 'Antibiotic therapy' below.)

Antibiotic therapy for intra-abdominal infections, including acute cholecystitis, is also discussed in detail elsewhere. (See "Antimicrobial approach to intra-abdominal infections in adults".)

INDICATIONS FOR EMERGENCY CHOLECYSTECTOMY

Despite supportive care, emergency cholecystectomy is indicated in a minority of patients in the presence of:

Complicated acute cholecystitis — Complicated acute cholecystitis, including gallbladder gangrene/necrosis, perforation, and emphysematous cholecystitis, may be fatal without emergency cholecystectomy. Gallbladder perforation (image 1 and image 2) and emphysematous cholecystitis (image 3) can usually be detected on imaging studies.

Gallbladder gangrene/necrosis is more difficult to distinguish from nongangrenous cholecystitis by radiology. There is no imaging sign that is specific for gallbladder gangrene/necrosis [17]. Multiple models have been proposed to predict gallbladder gangrene based on patient history (old age, male sex, coronary artery disease, diabetes), physical examination (tachycardia, guarding on abdominal palpation), laboratory values (leukocytosis, elevated levels of C-reactive protein, bilirubin, urea, and creatinine), and imaging findings (gallbladder wall thickening, pericholecystic fluid) [18-21]. Despite all that, surgeons diagnosed gangrenous cholecystitis preoperatively in only 9 percent of cases [21].

Disease progression — Progressive symptoms and signs such as high fever, hemodynamic instability, or intractable pain in spite of best supportive care (including antibiotics and gallbladder drainage) indicate disease progression, which is a sign of gallbladder gangrene and an indication for emergency cholecystectomy to prevent further complications (eg, gallbladder perforation) or sepsis. (See 'Ineffective drainage' below.)

RISK STRATIFICATION

Laparoscopic cholecystectomy is the gold-standard treatment for patients with acute calculous cholecystitis (ACC). Patients who do not require emergency surgery for complicated ACC should be risk stratified to determine if they should undergo early (same-admission) or delayed gallbladder surgery after initial nonoperative management.

Several systems have been developed to risk stratify patients with ACC with the goals of determining the need and candidacy for early cholecystectomy. As examples, the Tokyo Guidelines (TG) 2013 and 2018 classify patients into grade I (mild), II (moderate), or III (severe) cholecystitis [22]; the American Association of Surgery of Trauma (AAST) system grades patients from I to V [23]. However, a 2020 systematic review and meta-analysis found that none of the prognostic factors and risk prediction models can be relied upon to accurately predict outcomes of ACC [24]. The prognostic factors evaluated include patient sex, age, TG2013 severity class, previous upper abdominal surgery, diabetes, hypertension, and C-reactive protein value.

Nevertheless, with improvements in experience, surgical technique, and instrumentation, the hesitation to safely perform laparoscopic cholecystectomy in patients with ACC has waned over the years. The contemporary trend emphasizes the pivotal role of early (same-admission) laparoscopic cholecystectomy in the management of ACC, even in high-risk patients:

- TG2018 widened the indications for laparoscopic cholecystectomy when compared with TG2013 [25] by supporting same-admission laparoscopic cholecystectomy for patients with all three severity grades of acute cholecystitis [1].

- The 2020 World Society of Emergency Surgery (WSES) guidelines stated that laparoscopic cholecystectomy should be attempted in cases of ACC except in critical patient conditions, such as septic shock or anesthetic contraindications [26].

Contemporary studies have further addressed certain patient populations who are traditionally considered high risk for cholecystectomy [26,27]. These include:

- **Patients with liver cirrhosis** – In cirrhotic patients, the morbidity associated with laparoscopic cholecystectomy is directly related to the liver disease [28]. For Child A and B patients (or Model for End-stage Liver Disease [MELD] score <15), laparoscopic cholecystectomy should be the first choice for ACC. In such patients, however, there remains a risk of hepatic decompensation postcholecystectomy and more frequent need for conversion to an open cholecystomy [29]. For patients with Child C or uncompensated cirrhosis, cholecystectomy should be avoided in favor of conservative management [30]. It should be noted that there has been no study on ACC in cirrhotic patients, and the above suggestions are made by extrapolating data from elective cholecystectomy. (See "Managing the difficult gallbladder", section on 'Cirrhosis'.)

- **Older adult patients** – Initial nonoperative management with delayed cholecystectomy has traditionally been used as an alternative strategy to immediate cholecystectomy for older patients (eg, >65 years) [31]. However, data have consistently shown that outcomes following early laparoscopic cholecystectomy in octogenarians are comparable with those for younger patients [32-35]. According to the 2017 WSES and Italian Society for Geriatric Surgery guidelines for older patients with ACC, early laparoscopic cholecystectomy can be performed in older adult patients with ACC, even in those >80 years of age [36].

  - In a United Kingdom (UK) retrospective study of 47,500 patients >80 years who were admitted as an emergency with acute cholecystitis, early cholecystectomy was associated with higher 30 day mortality rate (11.6 versus 9.9 percent) but lower one-year mortality rate (20.8 versus 27.1 percent) and readmission rate compared with conservative management [37]. Cholecystostomy was associated with higher mortality than both cholecystectomy and conservative management (13.4 and 35 percent at 30 days and one year). Laparoscopic cholecystectomy was associated with lower 30 day mortality than open cholecystectomy (odds ratio [OR] 0.16, 95% CI 0.10-0.25).

- A separate database study of 29,818 older adult patients (aged ≥66 years) with acute cholecystitis found a higher mortality over the following two years in patients who were discharged without surgery compared with patients who underwent cholecystectomy in the initial hospitalization (hazard ratio [HR] 1.56, 95% CI 1.47-1.65). In addition, 38 percent of patients who were discharged without cholecystectomy were readmitted within two years for gallstone-related events, compared with 4 percent who underwent cholecystectomy during the index admission [38].

Other studies reported that cholecystectomy can be performed in octogenarian patients with ACC, albeit at higher morbidity and mortality rates (up to 41 and 5 percent, respectively) compared with younger patients [32,39,40]. (See 'Morbidity and mortality' below.)

- **Patients who are pregnant** – Following supportive care including antibiotic therapy, gallbladder surgery is indicated for any pregnant patient with acute cholecystitis and can be safely performed during any trimester (algorithm 1). For patients near term, a reasonable alternative is to defer gallbladder surgery until after delivery, assuming that symptoms can be controlled with antibiotics and supportive care. However, the risk of persistent, worsening, or recurrent symptoms in such patients is unknown. For pregnant patients who undergo cholecystectomy, we suggest a laparoscopic approach rather than open surgery, when feasible and available. Laparoscopic surgery has been shown to improve patient outcomes without increasing surgical, maternal, or fetal complication rates. (See "Gallstone diseases in pregnancy".)

As such, the decision to perform early cholecystectomy in patients with uncomplicated ACC comes down to whether the surgeon considers them suitable surgical candidates. Besides the obvious reasons not to perform cholecystectomy (eg, septic shock or anesthetic contraindication), the criteria for a suitable surgical candidate have not been universally defined and depend on the judgment of the surgeon and anesthesia provider (algorithm 2). As examples, high-risk patients were defined as having APACHE scores between 7 and 14 in the CHOCOLATE trial, and such patients did better with cholecystectomy than percutaneous cholecystostomy [41]. Alternatively, the American Society of Anesthesiology (ASA) physical status classification may be used to help stratify patients for surgery risk, with ASA class I to III considered good surgical candidates and class IV or V considered poor candidates. Local clinical pathways should be developed to define the patient criteria that fit local needs and expertise [26].

GOOD SURGICAL CANDIDATES

For good surgical candidates with acute calculous cholecystitis (ACC) but without indications for emergency cholecystectomy, we recommend cholecystectomy during the initial hospitalization (algorithm 2). Early cholecystectomy has been shown to eliminate recurrent gallstone-related diseases that occur in one-third to one-half of those ACC patients who are managed conservatively, and it can be safely performed in patients traditionally considered high risk. (See 'Risk stratification' above.)

No randomized trials have been performed that directly compared early cholecystectomy with conservative management in patients with ACC [26]. In a randomized trial that compared **delayed** cholecystectomy with observation with a median follow-up of 67 months, about 30 percent of patients treated conservatively developed recurrent gallstone-related complications, compared with 3 percent of those who underwent cholecystectomy, and 60 percent of patients required cholecystectomy subsequently [42]. The study only included 33 patients in the observation group and had a high risk of bias [43].

Early cholecystectomy has been compared with cholecystostomy in another randomized trial (CHOCOLATE). One hundred and forty-two patients with symptoms of ACC for fewer than seven days and who were at high risk for surgery (defined by an APACHE II score between 7 and 14) were randomly assigned to immediate laparoscopic cholecystectomy or percutaneous catheter drainage [41]. Cholecystectomy was completed laparoscopically in 83 percent; 17 percent converted to open. Major complications occurred in 12 percent of patients who underwent surgery, including bile duct injury in 6 percent. By contrast, major complications occurred in 65 percent of those treated with percutaneous drainage, of which the majority were related to recurrent biliary disease (53 percent) or drain malfunction. The one-year mortality rate was 3 and 9 percent after cholecystectomy and percutaneous drainage, respectively ($p = 0.27$).

In a 2022 systematic review and meta-analysis of six studies, compared with laparoscopic cholecystectomy, percutaneous drainage was associated with higher rates of mortality (relative risk [RR] 7.47, 95% CI 1.88-29.72), morbidity (RR 3.71, 95% CI 1.78-7.75), readmission (RR 7.91, 95% CI 3.80-16.49), and longer length of hospitalization (weighed mean difference [WMD] 6.92, 95% CI 5.89-7.95) [44].

Although Tokyo Guidelines (TG) 2013 grade 3 ACC was associated with higher mortality than grade I ACC when treated with cholecystectomy [24], a retrospective case series reported success with immediate cholecystectomy in 93 percent of patients with grade II (moderate) and 64 percent with grade III (severe) acute cholecystitis according to the 2013 TG; the surgical morbidity and mortality rates were comparable between grade I (mild) and II patients [45]. For patients with severe ACC, transfer to high-volume or specialized centers may be warranted and has been shown to reduce complication and mortality rates [46,47].

Timing of cholecystectomy — For suitable surgical candidates, laparoscopic cholecystectomy should be performed as early as possible during the hospitalization. Although all agree that earlier cholecystectomy is associated with lower perioperative morbidity and mortality, there is no consensus as to how early surgery needs to happen. Various authors or societies have advocated performing cholecystectomy within 3, 7, and 10 days of admission or symptom onset or else delaying surgery for a period of time (eg, 45 days) to allow inflammation to subside. The authors of this topic prefer to perform surgery within the first three days.

The timing of cholecystectomy in patients presenting with ACC has been under intense investigation, with "early" cholecystectomy variably defined in the literature as gallbladder surgery performed within 3, 7, or 10 days of symptom onset and "delayed" cholecystectomy as that performed 7 or 45 days, or six weeks, after initial diagnosis [48]. Evidence from large database reviews and randomized trials generally associates cholecystectomy performed early during the initial hospitalization with better outcomes and a lower cost [38,49-60].

- A 2016 systematic review and meta-analysis included seven meta-analyses comparing early (within seven days of the onset of symptoms) with delayed laparoscopic cholecystectomy (at least one week after initial conservative treatment) for ACC published between 2004 and 2015 [61]. Although the seven individual meta-analyses (all of which only included randomized trials [ranging from 3 to 15]) reported discordant results [62,63], the "meta-meta-analysis" concluded that no differences in mortality, bile duct injury, bile leakage, overall complications, or conversion to open surgery were seen. However, early cholecystectomy was associated with a significant reduction in wound infection, length of hospitalization, and duration of surgery and improvement in quality of life.

- A large administrative database study of over 15,000 cholecystectomies for acute cholecystitis provided even more granular data on how the timing of cholecystectomy can impact patient outcomes [64]. In that study, the rate of intraoperatively detected biliary injury was the lowest in patients who underwent surgery on the day of admission; the rate increased day by day thereafter. The rates of other intraoperative adverse events (eg, bleeding), as well as 30 and 90 day mortality rates, were lower in patients who underwent surgery on the first or second day after admission than either on the day of admission or after the second day after admission. The authors of the study advocated operating within two days of admission, but after patients have been adequately resuscitated, and when the most qualified surgeon becomes available. Although there were no data, they speculated that the slightly higher rate of nonbiliary adverse events that occurred when patients underwent surgery on the day of admission compared with the day after was due to under-resuscitation of the patient or a lack of laparoscopic surgical expertise. Alternatively, the rate of adverse events may be influenced by the duration of symptoms rather than hospitalization.

- Similarly, a 2020 study of more than 109,862 cholecystectomies performed in New York State found that patients who underwent cholecystectomy <72 hours from admission had a lower conversion rate to an open procedure (7.5 versus 13.8 percent, P<0.001) than those who underwent cholecystectomy >72 hours after admission [65].

Early surgery is easier to perform as local inflammation increases after 72 hours from the initial onset of symptoms, making dissection less precise, increasing the severity of surgical complications, and making open conversion more likely.

Nevertheless, there are data to suggest that surgery is still safe even after 72 hours from symptom onset, albeit with a higher rate of conversion from laparoscopic to open technique [57,66-68]. In a randomized trial of 86 patients with acute cholecystitis who had more than 72 hours of symptoms, early laparoscopic cholecystectomy during the index admission was safe [69]. Of 42 patients who received early surgery, only one required conversion to open surgery; none had a bile leak or bile duct injury. Compared with surgery delayed for six weeks, early surgery reduced the overall morbidity rate from 39 to 14 percent. Given that the postoperative complication rates (15 percent early versus 17 percent delayed) were similar, the difference in morbidity was almost entirely attributed to complications that occurred while patients who underwent delayed surgery were waiting for surgery (3 failed initial treatment; 10 required unplanned readmission while awaiting surgery). The length of stay (four versus seven days), duration of antibiotic therapy (2 versus 10 days), and total hospital cost (€9349 versus €12,361) were also in favor of early surgery. The authors of this trial argued that the degree of inflammatory changes associated with acute cholecystitis may not be time dependent as previously thought [70] and therefore suggested that early laparoscopic cholecystectomy may be offered to patients with acute cholecystitis regardless of the duration of symptoms.

Although the 2013 Tokyo Guidelines suggested that surgery be performed within 72 hours of symptom onset, it is not always practical, as some patients present after more than three days of symptoms [25]. The updated 2018 Tokyo Guidelines concluded that in patients for whom more than 72 hours has passed since symptom onset, there are still benefits to performing cholecystectomy early, and recommended early cholecystectomy in low-risk patients with ACC regardless of how much time has passed since symptom onset [1].

The 2020 World Society of Emergency Surgery (WSES) guidelines recommended early laparoscopic cholecystectomy for ACC as long as it can be completed within 7 days of admission and 10 days of symptom onset [26]. Patients who have had symptoms for longer than 10 days should not undergo early cholecystectomy unless their disease progresses; delaying cholecystectomy beyond six weeks is a safer option for those patients to allow inflammation to subside.

Surgical approach — For surgical treatment of patients with ACC, we recommend laparoscopic cholecystectomy rather than open cholecystectomy. Laparoscopic cholecystectomy should be attempted unless there is an absolute anesthetic contraindication to laparoscopy or a lack of requisite surgical expertise.

In a systematic review and meta-analysis of 10 trials comparing open versus laparoscopic cholecystectomy for acute cholecystitis, laparoscopic surgery was associated with lower mortality (odds ratio [OR] 0.2), morbidity (OR 0.46), postoperative wound infection (OR 0.54) and pneumonia rates (OR 0.51), and hospital length of stay (median difference -4.74 days) [71]. There were no significant differences in the bile leakage rate, intraoperative blood loss, and operative times. Conversion rate ranged from 8 to 35 percent.

However, laparoscopic cholecystectomy for acute cholecystitis can be more technically demanding than surgery for other gallbladder diseases (eg, biliary colic). When faced with severe inflammation, adhesion, or bleeding in the Calot's triangle, or suspected bile duct injury, surgeons should be prepared to perform an alternative technique, such as subtotal cholecystectomy, top-down cholecystectomy, or conversion to open surgery, to ensure safe dissection [72-74]. Techniques that can be used to manage a "difficult" gallbladder are discussed in another topic. (See "Managing the difficult gallbladder".)

Although other minimally invasive techniques such as single-incision laparoscopy, mini-laparoscopy, robotic-assisted laparoscopy, and natural orifice transluminal endoscopic surgery (NOTES) have been used to treat patients with symptomatic cholelithiasis, their role in the treatment of patients with acute cholecystitis is limited due to the technically demanding dissection caused by severe inflammation as well as technical challenges associated with the adoption of these new technologies [74,75]. (See "Laparoscopic cholecystectomy", section on 'Abdominal access'.)

POOR SURGICAL CANDIDATES

For poor surgical candidates with acute calculous cholecystitis (ACC) but without indications for emergency cholecystectomy, we suggest initial nonoperative management rather than immediate cholecystectomy (algorithm 2). As examples, conservative management with or without cholecystostomy is required for patients who are in septic shock or have cardiopulmonary contraindications to anesthesia. Best medical therapy is likely to be safe but may incur a high incidence of recurrent disease [42].

Nonoperative management consists of antibiotics for all patients and gallbladder drainage for some patients. Septic patients should undergo urgent gallbladder drainage; removing the infected bile or pus from the gallbladder could potentially reverse sepsis. Patients who fail to improve with antibiotic therapy for one to three days also require gallbladder drainage. Failure to improve after three days of biliary drainage requires careful reassessment for drain positioning or development of new infectious pockets of liver abscess, and patients may require cholecystectomy despite the high risk or else face a dismal prognosis. (See 'Ineffective drainage' below.)

Once cholecystitis resolves, the patient's risk for surgery should be reassessed. Patients who have become reasonable candidates for surgery should undergo delayed (elective) cholecystectomy [76]. Others with a higher operative risk can be considered for percutaneous gallstone extraction with or without mechanical lithotripsy (see "Overview of nonsurgical management of gallbladder stones"). Medical management with interval cholecystectomy only for recurrent acute cholecystitis may also be appropriate [31]. (See 'Effective drainage' below.)

Antibiotic therapy — Cholecystectomy in high-risk patients carries a mortality rate of up to 19 percent [77]. In such patients, the potential risk of cholecystectomy likely outweighs its benefits, and an initial nonoperative approach should be undertaken that includes antibiotic therapy and bowel rest. (See 'Supportive care' above.)

Appropriate antibiotics should be administered to patients in septic shock within one hour of diagnosis and to others within six hours [14]. The primary goals of antimicrobial therapy in acute cholecystitis are to limit both the local inflammation and systemic septic response and to prevent intrahepatic and pericholecystic abscess formation. The antimicrobial agents that are appropriate for treating acute cholecystitis are the same whether or not a cholecystectomy is planned as discussed above. (See 'Antibiotics' above.)

While antibiotics are generally stopped the day after surgery in patients who undergo cholecystectomy (ie, source control) unless there is ongoing sepsis, the optimal duration of antimicrobial therapy for those managed nonoperatively is not known and requires clinical judgment. For patients who improve, we typically treat until the signs and symptoms of acute cholecystitis have resolved. Intravenous antibiotics can be converted to oral formulation (eg, amoxicillin-clavulanate, cephalexin plus metronidazole, or fluoroquinolone plus metronidazole) when the patient can tolerate an oral diet [14]. Patients who do not respond to antibiotic therapy and supportive care for one to three days require additional interventions such as gallbladder drainage or surgery. (See 'Gallbladder drainage' below.)

Gallbladder drainage — Some form of gallbladder drainage is required as the initial treatment, in conjunction with antibiotics, for patients who are septic or critically ill [14,78-81]. Gallbladder drainage is also suggested for patients managed nonoperatively who show disease progression or no appreciable clinical improvement after one to three days of nonoperative management with antibiotics [82].

Gallbladder drainage decompresses infected bile or pus from the gallbladder and allows both local inflammation and systemic illness to resolve before gallbladder removal can be accomplished at a lower risk to the patient at a later time. Gallbladder drainage can be accomplished via percutaneous or endoscopic methods. Percutaneous transhepatic drainage is generally preferred due to its ease, safety, and reduced costs, but endoscopic drainage methods may be employed when the requisite expertise is available [26].

Percutaneous drainage has been compared with endoscopic drainage in multiple observational studies [83] and meta-analyses [84,85]. In general, percutaneous drainage has the highest technical success rate. However, in some studies, the clinical success rate of endoscopic ultrasound-guided transmural drainage can be higher, and the complication and reintervention rates lower, than those of percutaneous drainage, due to the widespread use of lumen-apposing metal stents with flare ends that are more secure than double pigtail catheters [85]. Transpapillary drainage generally has the lowest success rate due to technical difficulties in cannulating the cystic duct. The safety profiles differ between the different drainage methods: significant risk of perforation and bleeding can be expected with transmural endoscopic drainage, and acute pancreatitis risk is significantly higher with transpapillary drainage, while percutaneous drainage is associated with significantly higher chances of disease recurrence and percutaneous drainage catheter dislodgement [85]. The overall rate of complications, however, varies between studies.

Percutaneous — Percutaneous cholecystostomy is an option for patients with acute cholecystitis who have all of the following [75]:

- Contraindications to general anesthesia and/or high surgical risk

- No coagulopathy or bleeding disorders
- Late presentation (>72 hours after onset of symptoms)
- Failure of medical (antibiotic) therapy

The optimal timing for percutaneous cholecystostomy is debated. However, one retrospective study showed that early placement (<24 hours from symptom onset) was associated with a lower procedure-related bleeding rate (0 versus 5 percent) and a shorter hospital stay (15 versus 21 days) compared with late placement (>24 hours from symptom onset) [86].

The timing of percutaneous cholecystostomy likely depends on its clinical indication. We suggest urgent percutaneous cholecystostomy tube placement in high-surgical-risk septic or critically ill patients with acute cholecystitis. For others who are being managed nonsurgically for ACC but are not critically ill, we place a cholecystostomy tube if the patient does not demonstrate clinical improvement after one to three days of antibiotic therapy. In most published studies, patients who respond to antibiotics do so within three days [82,87]. This practice also takes into consideration the fact that as a radiologic procedure, percutaneous cholecystostomy may not be readily available at nights and on weekends in all facilities.

Percutaneous cholecystostomy resolves acute cholecystitis in approximately 85 percent of patients [77] as indicated by resolution of fever, abdominal pain, and inflammatory markers. The technical success rates range from 82 to 100 percent in various series [78-81,88]. Minor complications include bleeding, catheter blockage and dislodgement (10 to 15 percent), and failure to resolve the acute cholecystitis (10 percent) [79,81,89]. In one study, major bleeding complications occurred rarely (0.4 percent) and were no different between patients with and without coagulopathy [89]. Failure is usually related to ineffective drainage due to thick sludge or pus. We generally irrigate the gallbladder contents manually with normal saline through the catheter. If irrigation is ineffective, the percutaneous pigtail catheter can be replaced over a wire with a larger one to achieve more effective irrigation.

Although percutaneous cholecystostomy is the most widely used and studied method of nonsurgical gallbladder drainage, there is no high-quality evidence supporting its use as a definitive therapy for ACC [90], nor has any study demonstrated its superiority over either antibiotic treatment or early cholecystectomy [82,91,92]. As an example, in a trial of 123 high-risk patients with acute cholecystitis who underwent percutaneous cholecystostomy or antibiotic therapy, a similar percentage of patients in each group had resolution of their symptoms (86 versus 87 percent). All successfully treated patients showed clinical improvement within the first three days [82]. In the CHOCOLATE trial cited above, high-risk patients who underwent early cholecystectomy had better outcomes than those who underwent percutaneous drainage [41]. (See 'Risk stratification' above.)

In some retrospective and database studies, higher or lower mortality and morbidity rates have been associated with percutaneous cholecystostomy treatment of acute cholecystitis compared with cholecystectomy [93-96]. This difference is likely due to patient selection bias as patients who underwent percutaneous cholecystostomy were usually older and had a higher American Society of Anesthesiologists (ASA) classification, more comorbidities, longer hospital stay, more complications, and more readmissions. In two studies of medicare provider claims, percutaneous cholecystostomy has increased from 0.3 percent (1994) to 2.9 percent (2009) to 6.1 percent (2018) of all gallbladder procedures [97,98].

Endoscopic — Endoscopic gallbladder drainage can be performed in patients with acute cholecystitis in whom percutaneous approaches are contraindicated or are not anatomically feasible (ie, advanced liver disease, ascites, or coagulopathy) [75,99,100]. Two different techniques, transpapillary drainage and transmural drainage, are available, depending on local expertise [75].

Transpapillary drainage — Transpapillary drainage utilizes endoscopic retrograde cholangiography (ERCP) techniques and equipment to place a drainage catheter into the gallbladder via the cystic duct. The other end of the catheter is either brought out through the nose (nasobiliary drain) or left to drain internally into the duodenum. The technical and clinical success rate of the two techniques are comparable [101,102].

When technically successful (in approximately 76 to 94 percent of patients), transpapillary drainage resolves acute cholecystitis in 80 to 90 percent of patients, including those with advanced liver cirrhosis [103-105]. However, this technique can be technically challenging because the cystic duct is often narrow and tortuous. In addition, this procedure has all the inherent and occasionally serious complications associated with ERCP (eg, postsphincterotomy bleeding). (See "Overview of endoscopic retrograde cholangiopancreatography (ERCP) in adults".)

Transmural drainage — Transmural drainage utilizes endoscopic ultrasound guidance to access the inflamed gallbladder with a needle puncture, followed by dilation and stent placement over a guidewire. The introduction of self-expandable, covered, lumen-apposing metal stents allows large-caliber (10 to 15 mm) direct endoscopic access to the gallbladder for decompression and stone removal [106]. The transmural drainage technique is technically successful in most cases (97 percent) and resolves acute cholecystitis in over 95 percent of patients [107,108].

In a 2020 randomized trial of 80 patients with very high risk for cholecystectomy, endoscopic ultrasound-guided and percutaneous gallbladder drain resulted in similar technical (97 versus

100 percent) and clinical success rates (92 versus 92 percent) and mortality (7.7 versus 10 percent) [109]. Compared with percutaneous drainage, endoscopic ultrasound-guided drainage was associated with reduced one-year adverse events (26 versus 78 percent), 30 day adverse events (13 versus 48 percent), reinterventions after 30 days (2.6 versus 30 percent), number of unplanned readmissions (15 versus 50 percent), recurrent cholecystitis (3 versus 20 percent), and postprocedural pain scores and analgesic requirements.

Endoscopic transmural drainage is used as a bridge to definitive gallbladder surgery. However, the adhesion created between the gallbladder and duodenum/stomach may interfere with future cholecystectomy surgery.

Subsequent care following drainage — For patients who undergo gallbladder drainage, subsequent care depends on whether their clinical symptoms resolve after the procedure (algorithm 2).

Effective drainage — The risk of recurrent biliary disease following percutaneous gallbladder drainage is between 19 to 41 percent [110-112]. In one study, 14, 19, and 29 percent of patients who were treated nonoperatively for ACC developed gallstone-related events at six weeks, 12 weeks, and one year, including biliary colic (70 percent), biliary obstruction (24 percent), and pancreatitis (6 percent) [113]. About half of the patients who did not undergo cholecystectomy after percutaneous gallbladder drainage were readmitted within one year, and 1 percent died while in the hospital [113].

As such, once cholecystitis resolves with nonoperative treatment, we suggest reassessing the patient's risk for surgery and offering cholecystectomy to reasonable surgical candidates. Percutaneous stone extraction or medical management is appropriate for those who continue to be poor or nonsurgical candidates.

Surgical candidates — In the context of ACC, gallbladder drainage is generally accepted as a bridge to definitive therapy, which remains cholecystectomy [114]. The risk for surgery should be reconsidered once cholecystitis resolves in patients treated nonoperatively with antibiotics and possibly gallbladder drainage. Patients who have become reasonable candidates for surgery should undergo elective cholecystectomy. Laparoscopic cholecystectomy is preferred in those who require surgery.

The timing of cholecystectomy after gallbladder drainage is dictated by a number of clinical and nonclinical factors, ranging from immediately after clinical improvement to after eight weeks. In a small randomized trial involving 61 patients with acute cholecystitis treated initially with percutaneous cholecystostomy, all patients achieved symptomatic relief within 24 hours [91]. Both early and delayed laparoscopic cholecystectomy were feasible in the majority of patients

(94 percent early versus 87 percent delayed); the average length of stay and cost were lower with early cholecystectomy.

Nonsurgical candidates — Although percutaneous cholecystostomy is often performed as a bridge to surgery, 43 to 94 percent of patients did not undergo cholecystectomy after gallbladder drainage in published series, most often due to ongoing contraindications to surgery [114-116]. Patients who stabilize but continue to be high risk for surgery can be considered for percutaneous gallstone extraction with or without mechanical lithotripsy [117]. Alternatively, medical management with interval cholecystectomy only for recurrent acute cholecystitis may be appropriate [31]. (See "Overview of nonsurgical management of gallbladder stones".)

Tube management — For potential surgical candidates, we prefer to keep the percutaneous cholecystostomy tube in situ until the patient undergoes cholecystectomy. In patients with calculous cholecystitis, the risk of recurrent symptoms can be as high as 20 percent within one year [86]. Maintaining adequate gallbladder drainage minimizes the risk of recurrent cholecystitis, which could further delay or complicate gallbladder surgery.

We perform a tube study to assess the patency of the cystic duct. If the cystic duct is patent, we cap the percutaneous cholecystostomy tube, which is more convenient for the patient than gravity drainage and also preserves the bile acid pool. The bile acid pool can be depleted by long-standing cholecystostomy tube drainage, which can lead to intrahepatic cholestasis and a rise in liver function tests.

The management of the percutaneous cholecystostomy tube in patients who will not undergo definitive gallbladder surgery is highly variable and not evidence based. In a systematic review of 50 studies, the timing of tube removal ranged from 2 to 193 days, with no correlation between tube duration and clinical outcomes [118].

Where available, percutaneous gallstone extraction with or without mechanical lithotripsy is performed via the cholecystostomy tube. The ritual just before tube removal is also highly variable: while some authors cap the tube for a few days before removal, others allow several weeks of tube drainage with the patient on oral bile acid supplement (to prevent depletion) before removal. Most would perform a tube study to ensure cystic duct patency before removing the tube.

A common cause of catheter failure relates to its internal pigtail tugging on the gallbladder wall in cases when the catheter is sutured or fixed with tape or a clamp to the skin very close to the percutaneous entry hole. This prevents the catheter from moving in and out as the gallbladder and liver move up and down with respiration. We do not suture but tape the percutaneous catheter to the skin, leaving a loop of catheter between the tape and the percutaneous entry hole. This allows the catheter to move in and out of the abdominal wall during respiration or if the patient were to stand up when the gallbladder and the liver will move down to some extent due to gravity.

Ineffective drainage — In the published literature, patients typically demonstrate clinical improvement within one to three days after a gallbladder drainage procedure, regardless of the approach (percutaneous or endoscopic) [82]. Therefore, patients who have not responded in three days after gallbladder drainage likely have progressed to gangrene of the gallbladder, in which case emergency cholecystectomy is mandatory regardless of the surgical risk. (See 'Indications for emergency cholecystectomy' above.)

ASSOCIATED COMMON BILE DUCT STONE

Five to 15 percent of patients who present with acute calculous cholecystitis (ACC) have associated common bile duct (CBD) stones. Hence, patients should undergo standard preoperative laboratory and imaging tests and/or intraoperative cholangiography to diagnose CBD stones; those who are diagnosed with CBD stones should be treated accordingly with endoscopic or surgical common duct exploration. Diagnosis and treatment of CBD stones are discussed in other topics. (See "Choledocholithiasis: Clinical manifestations, diagnosis, and management" and "Surgical common bile duct exploration".)

An uncommon condition that could occur in the context of acute cholecystitis and mimic CBD stones is Mirizzi syndrome, which occurs in 1 percent of patients with cholelithiasis. Mirizzi syndrome is discussed in a dedicated topic. (See "Mirizzi syndrome".)

MORBIDITY AND MORTALITY

The overall mortality of a single episode of acute cholecystitis is approximately 3 percent. However, the risk in a given patient depends upon the patient's health and surgical risk [79]. Mortality is less than 1 percent in young, otherwise healthy patients but approaches 10 percent in high-risk patients or those with complications. Perioperative morbidity and mortality associated with specific treatments are reviewed elsewhere. (See "Laparoscopic cholecystectomy", section on 'Postoperative complications' and "Open cholecystectomy", section on 'Complications of cholecystectomy'.)

Several studies identified older age as a risk factor for adverse outcomes with cholecystectomy:

- In a database study of low-risk (American Society of Anesthesiologists [ASA] I or II) patients with acute calculous cholecystitis (ACC), the 30 day mortality rate increased with age: 4.5 percent for those 80 years and older, 0.5 percent for those 65 to 79 years, and 0.2 percent for those 50 to 64 years [119].

- A 2020 systematic review and meta-analysis of 19 retrospective studies reported higher overall and major complication rates in all age cutoffs [120]. This study reported a sevenfold increase in perioperative mortality, which increased to tenfold in patients ≥80 years.

A study of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database evaluated outcomes following treatment of acute cholecystitis in 5460 patients with and without diabetes [121]. Mortality among 770 patients with diabetes was significantly higher than in the 4690 patients without diabetes (4.4 versus 1.4 percent). The risk for complications, including cardiovascular events and renal failure, was also significantly increased.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Gallbladder surgery" and "Society guideline links: Cholecystitis and other gallbladder disorders".)

SUMMARY AND RECOMMENDATIONS

- **Definition** – Acute cholecystitis refers to a syndrome of right upper quadrant pain, fever, and leukocytosis associated with gallbladder inflammation, which is usually related to gallstone disease (ie, acute calculous cholecystitis [ACC]). Once a patient is diagnosed with ACC, definitive therapy aimed at eliminating the gallstones is required, or else the likelihood of recurrent symptoms or complications is high. (See 'Introduction' above.)

- **Initial care** – Patients with ACC should be admitted to the hospital. Initial supportive care includes intravenous fluid therapy, correction of electrolyte disorders, and control of pain. Adequate pain control can usually be achieved with nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids. (See 'Supportive care' above.)

    - **Antibiotics** – Acute cholecystitis is primarily an inflammatory process, but secondary infection of the gallbladder can occur as a result of cystic duct obstruction and bile stasis.

- For patients with complicated ACC, broad-spectrum antibiotics are required.

- For patients with uncomplicated ACC, we also suggest empiric antibiotic therapy (**Grade 2B**).

Once started, antibiotics should generally be continued until either 24 hours after the gallbladder is removed or the cholecystitis has resolved clinically. (See 'Antibiotics' above.)

- **Definitive care** – The choice and timing of intervention for ACC (cholecystectomy, gallbladder drainage) depend upon the severity of symptoms and the patient's overall risk of surgery (algorithm 2):

  - **Indications for emergency cholecystectomy** – Regardless of surgical risk, patients require urgent cholecystectomy if they have (see 'Indications for emergency cholecystectomy' above):

    - Suspicion of complicated acute cholecystitis such as gallbladder gangrene/necrosis or gallbladder perforation, or emphysematous cholecystitis.

    - Progressive symptoms and signs such as high fever, hemodynamic instability, or intractable pain in spite of adequate antimicrobial therapy and gallbladder drainage.

  - **Good surgical candidates** – For good surgical candidates with ACC but without indications for emergency cholecystectomy, we recommend cholecystectomy during the initial hospitalization rather than nonoperative management (**Grade 1B**). Surgery should be performed as early as possible, preferably within three days of symptom onset. Cholecystectomy performed earlier rather than later in the hospitalization has been associated with reduced perioperative morbidity and mortality. (See 'Good surgical candidates' above.)

  - **Poor surgical candidates** – For poor surgical candidates with ACC but without indications for emergency cholecystectomy, we suggest initial nonoperative management rather than cholecystectomy (**Grade 2C**). These include patients who are in septic shock or have cardiopulmonary contraindications to anesthesia.

    Nonoperative treatment consists of antibiotics (for all patients) and gallbladder drainage (for all septic or critically ill patients and noncritical patients who fail to respond after one to three days of antibiotic therapy). Drainage options include percutaneous cholecystostomy and endoscopic transpapillary or transmural drainage. (See 'Poor surgical candidates' above.)

Once cholecystitis resolves with nonoperative treatment, we suggest reassessing the patient's risk for surgery and offering reasonable surgical candidates cholecystectomy (**Grade 2C**). Without definitive treatment for gallstones, the risk for recurrent symptoms is high.

Patients who continue to be high risk for surgery can be considered for percutaneous gallstone extraction with or without mechanical lithotripsy or simply observed and undergo interval cholecystectomy only for recurrent acute cholecystitis. (See 'Subsequent care following drainage' above.)

- **Surgical approaches** – For surgical treatment of patients with ACC, we recommend laparoscopic cholecystectomy over open cholecystectomy (**Grade 1A**). Laparoscopic cholecystectomy should be attempted unless there is an absolute anesthetic contraindication to laparoscopic surgery or a lack of requisite surgical expertise. (See 'Surgical approach' above.)

- **Associated common bile duct stones** – All patients should undergo standard preoperative laboratory and imaging tests and/or intraoperative cholangiography to look for concomitant common bile duct stones; those who are diagnosed with common bile duct stones should be treated accordingly with endoscopic removal or surgical common duct exploration. (See 'Associated common bile duct stone' above and "Surgical common bile duct exploration".)

- **Outcomes** – Mortality associated with a single episode of acute cholecystitis depends upon the patient's health and surgical risk. Overall mortality is approximately 3 percent but is less than 1 percent in young, otherwise healthy patients and approaches 10 percent in high-risk patients or those with complications. (See 'Morbidity and mortality' above.)

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Topic 3684 Version 53.0

GRAPHICS

Empiric antibiotic regimens for low-risk community-acquired intra-abdominal infections in adults

	Dose
Single-agent regimen	
Piperacillin-tazobactam*	3.375 g IV every 6 hours
Combination regimen with metronidazole*	
One of the following:	
Cefazolin	1 to 2 g IV every 8 hours
or	
Cefuroxime	1.5 g IV every 8 hours
or	
Ceftriaxone	2 g IV once daily
or	
Cefotaxime	2 g IV every 8 hours
or	
Ciprofloxacin	400 mg IV every 12 hours or 500 mg PO every 12 hours
or	
Levofloxacin	750 mg IV or PO once daily
Plus:	
Metronidazole¶	500 mg IV or PO every 8 hours

For empiric therapy of low-risk community-acquired intra-abdominal infections, we cover streptococci, Enterobacteriaceae, and anaerobes. Low-risk community-acquired intra-abdominal infections are those that are of mild to moderate severity (including perforated appendix or appendiceal abscess) in the absence of risk factors for antibiotic resistance or treatment failure. Such risk factors include recent travel to areas of the world with high rates of antibiotics-resistant organisms, known colonization with such organisms, advanced age, immunocompromising conditions, or other major medical comorbidities. Refer to other UpToDate content on the antimicrobial treatment of intra-abdominal infections for further discussion of these risk factors.

The antibiotic doses listed are for adult patients with normal renal function. The duration of antibiotic therapy depends on the specific infection and whether the presumptive source of infection has been controlled; refer to other UpToDate content for details.

IV: intravenously; PO: orally.

* When piperacillin-tazobactam or one of the combination regimens in the table cannot be used, ertapenem (1 g IV once daily) is a reasonable alternative.

¶ For most uncomplicated biliary infections of mild to moderate severity, the addition of metronidazole is not necessary.

Graphic 106948 Version 13.0

Empiric antibiotic regimens for high-risk community-acquired intra-abdominal infections in adults

	Dose
Single-agent regimen	
Imipenem-cilastatin	500 mg IV every 6 hours
Meropenem	1 g IV every 8 hours
Doripenem	500 mg IV every 8 hours
Piperacillin-tazobactam	4.5 g IV every 6 hours
Combination regimen with metronidazole	
ONE of the following:	
Cefepime	2 g IV every 8 hours
OR	
Ceftazidime	2 g IV every 8 hours
PLUS:	
Metronidazole	500 mg IV or orally every 8 hours

High-risk community-acquired intra-abdominal infections are those that are severe or in patients at high risk for adverse outcomes or antimicrobial resistance. These include patients with recent travel to areas of the world with high rates of antibiotics-resistant organisms, known colonization with such organisms, advanced age, immunocompromising conditions, or other major medical comorbidities. Refer to the UpToDate topic on the antimicrobial treatment of intra-abdominal infections for further discussion of these risk factors.

For empiric therapy of high-risk community-acquired intra-abdominal infections, we cover streptococci, Enterobacteriaceae resistant to third-generation cephalosporins, *Pseudomonas aeruginosa*, and anaerobes. Empiric antifungal therapy is usually not warranted but is reasonable for critically ill patients with an upper gastrointestinal source.

Local rates of resistance should inform antibiotic selection (ie, agents for which there is >10% resistance among Enterobacteriaceae should be avoided). If the patient is at risk for infection with an extended-spectrum beta-lactamase (ESBL)-producing organism (eg, known colonization or prior infection with an ESBL-producing organism), a carbapenem should be chosen. When beta-lactams or carbapenems are chosen for patients who are critically ill or are at high risk of infection with drug-resistant pathogens, we favor a prolonged infusion dosing strategy. Refer to other UpToDate content on prolonged infusions of beta-lactam antibiotics.

The combination of vancomycin, aztreonam, and metronidazole is an alternative for those who cannot use other beta-lactams or carbapenems (eg, because of severe reactions).

The antibiotic doses listed are for adult patients with normal renal function. The duration of antibiotic therapy depends on the specific infection and whether the presumptive source of infection has been controlled; refer to other UpToDate content for details.

IV: intravenous.

Graphic 106949 Version 12.0

Empiric antibiotic regimens for health care-associated intra-abdominal infections in adults

	Dose
Single-agent regimen	
Imipenem-cilastatin	500 mg IV every 6 hours
Meropenem	1 g IV every 8 hours
Doripenem	500 mg IV every 8 hours
Piperacillin-tazobactam	4.5 g IV every 6 hours
Combination regimen	
ONE of the following:	
Cefepime	2 g IV every 8 hours
OR	
Ceftazidime	2 g IV every 8 hours
PLUS:	
Metronidazole	500 mg IV or orally every 8 hours
PLUS ONE of the following (in some cases*):	
Ampicillin	2 g IV every 4 hours
OR	
Vancomycin	15 to 20 mg/kg IV every 8 to 12 hours

For empiric therapy of health care-associated intra-abdominal infections, we cover streptococci, enterococci, Enterobacteriaceae that are resistant to third-generation cephalosporins and fluoroquinolones, *Pseudomonas aeruginosa*, and anaerobes. We include coverage against methicillin-resistant *Staphylococcus aureus* (MRSA) with vancomycin in those who are known to be colonized, those with prior treatment failure, and those with significant prior antibiotic exposure. Empiric antifungal coverage is appropriate for patients at risk for infection with *Candida* spp, including those with upper gastrointestinal perforations, recurrent bowel perforations, surgically treated pancreatitis, heavy colonization with *Candida* spp, and/or yeast identified on Gram stain of samples from infected peritoneal fluid or tissue. Refer to other UpToDate content on treatment of invasive candidiasis.

If the patient is at risk for infection with an extended-spectrum beta-lactamase (ESBL)-producing organism (eg, known colonization or prior infection with an ESBL-producing organism), a carbapenem should be chosen. For patients who are known to be colonized with highly resistant gram-negative bacteria, the addition of an aminoglycoside, polymyxin, or novel beta-lactam combination (ceftolozane-tazobactam or ceftazidime-avibactam) to an empiric regimen may be warranted. In such cases, consultation with an expert in infectious diseases is advised.

When beta-lactams or carbapenems are chosen for patients who are critically ill or are at high risk of infection with drug-resistant pathogens, we favor a prolonged infusion dosing strategy. Refer to other UpToDate content on prolonged infusions of beta-lactam antibiotics.

The combination of vancomycin, aztreonam, and metronidazole is an alternative for those who cannot use other beta-lactams or carbapenems (eg, because of severe reactions).

The antibiotic doses listed are for adult patients with normal kidney function. The duration of antibiotic therapy depends on the specific infection and whether the presumptive source of infection has been controlled; refer to other UpToDate content for details.

IV: intravenous.

* We add ampicillin or vancomycin to a cephalosporin-based regimen to provide enterococcal coverage, particularly in those with postoperative infection, prior use of antibiotics that select for *Enterococcus*, immunocompromising condition, valvular heart disease, or prosthetic intravascular materials. Coverage against vancomycin-resistant enterococci (VRE) is generally not recommended, although it is reasonable in patients who have a history of VRE colonization or in liver transplant recipients who have an infection of hepatobiliary source.

Graphic 106950 Version 12.0

Antimicrobial recommendations for acute biliary infections

Severity	Community-acquired biliary infections			ass
	Grade I	Grade II	Grade III*	
Antimicrobial agents	**Cholangitis and cholecystitis**	**Cholangitis and cholecystitis**	**Cholangitis and cholecystitis**	**c**
Penicillin-based therapy	Ampicillin/sulbactam¶ is not recommended if >20% resistance rate	Piperacillin/tazobactam	Piperacillin/tazobactam	Pipe
Cephalosporin-based therapy	Cefazolin,Δ or cefotiam,Δ or cefuroxime,Δ or ceftriaxone, or cefotaxime ± metronidazole◇	Ceftriaxone, or cefotaxime, or cefepime, or cefozopran, or ceftazidime ± metronidazole◇	Cefepime, or ceftazidime, or cefozopran ± metronidazole◇	Cefe or ce or ce metr
	Cefmetazole,Δ cefoxitin,Δ flomoxef,Δ cefoperazone/sulbactam	Cefoperazone/sulbactam		
Carbapenem-based therapy	Ertapenem	Ertapenem	Imipenem/cilastatin, meropenem, doripenem, ertapenem	Imip merc dori
Monobactam-based therapy	–	–	Aztreonam ± metronidazole◇	Aztre metr
Fluoroquinolone-based therapy§	Ciprofloxacin, levofloxacin, pazufloxacin ± metronidazole◇	Ciprofloxacin, levofloxacin, pazufloxacin ± metronidazole◇	–	–
	Moxifloxacin	Moxifloxacin		

* Vancomycin is recommended to cover *Enterococcus* spp for grade III community-acquired acute cholangitis and cholecystitis and health-care-associated acute biliary infections. Linezolid or daptomycin is recommended if vancomycin-resistant *Enterococcus* (VRE) is known to be colonizing the patient, if previous treatment included vancomycin, and/or if the organism is common in the community.

¶ Ampicillin/sulbactam has little activity left against *Escherichia coli*. It has been removed from the North American guidelines[1,2].

Δ Local antimicrobial susceptibility patterns (antibiogram) should be considered for use.

◇ Antianaerobic therapy, including use of metronidazole, tinidazole, or clindamycin, is warranted if a biliary-enteric anastomosis is present. The carbapenems, piperacillin/tazobactam, ampicillin/sulbactam, cefmetazole, cefoxitin, flomoxef, and cefoperazone/sulbactam have sufficient antianaerobic activity for this situation.

§ Fluoroquinolone use is recommended if the susceptibility of cultured isolates is known or for patients with beta-lactam allergies. Many extended-spectrum beta-lactamase (ESBL)-producing gram-negative isolates are fluoroquinolone resistant.

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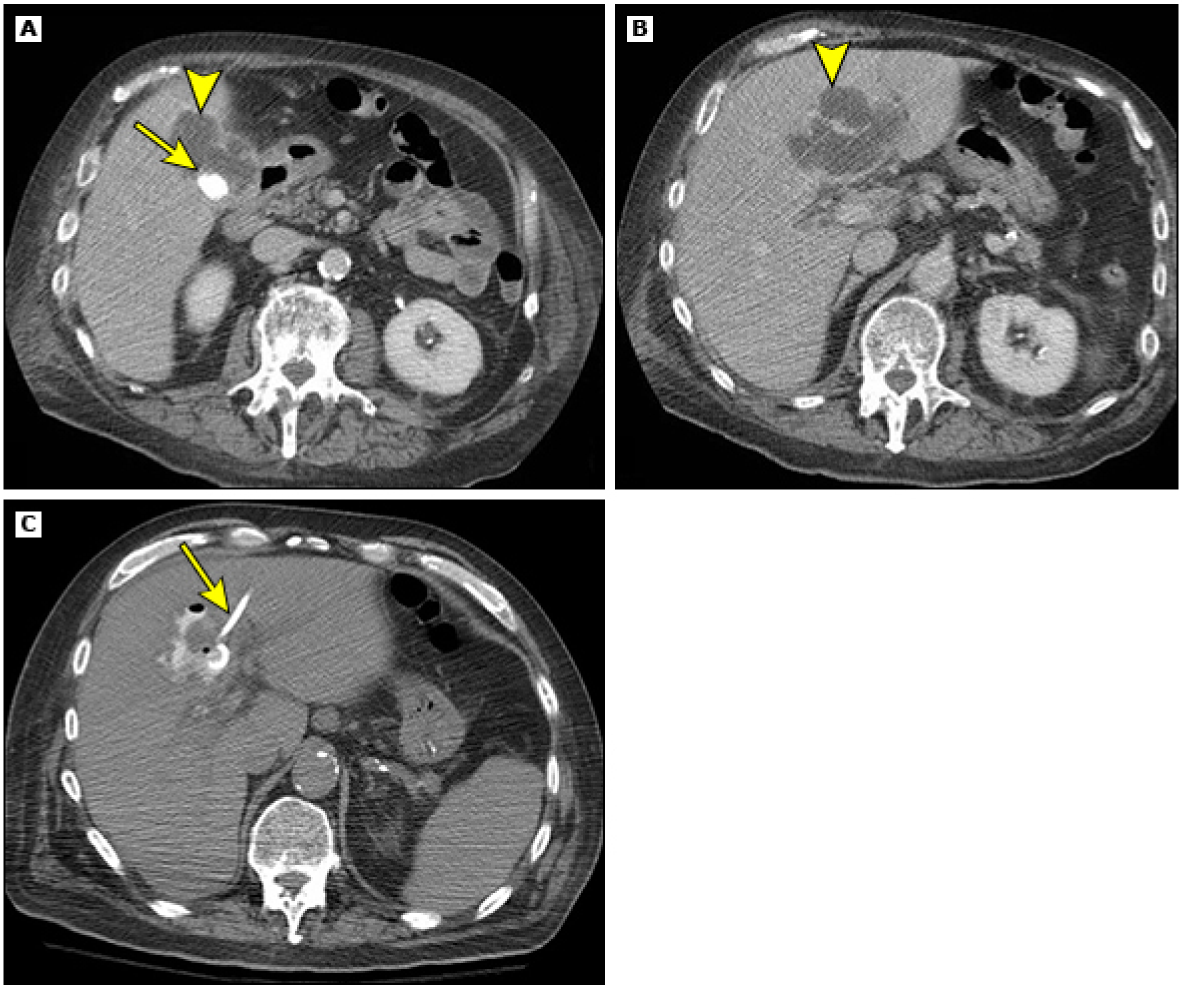
1. *Mazuski JE, Tessier JM, May AK, et al. The Surgical Infection Society Revised Guidelines on the Management of Intra-Abdominal Infection. Surg Infect (Larchmt) 2017; 18:1.*
2. *Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: Guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. Clin Infect Dis 2010; 50:133.*

From: Gomi H, Solomkin JS, Schlossberg D, et al. Tokyo Guidelines 2018: Antimicrobial therapy for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci 2018; 25(1):3-16. https://onlinelibrary.wiley.com/doi/abs/10.1002/jhbp.518.

Graphic 117719 Version 2.0

Liver abscess complicating acute cholecystitis



Computed tomographic (CT) scan in a patient with acute cholecystitis complicated by perforation and liver abscess formation.

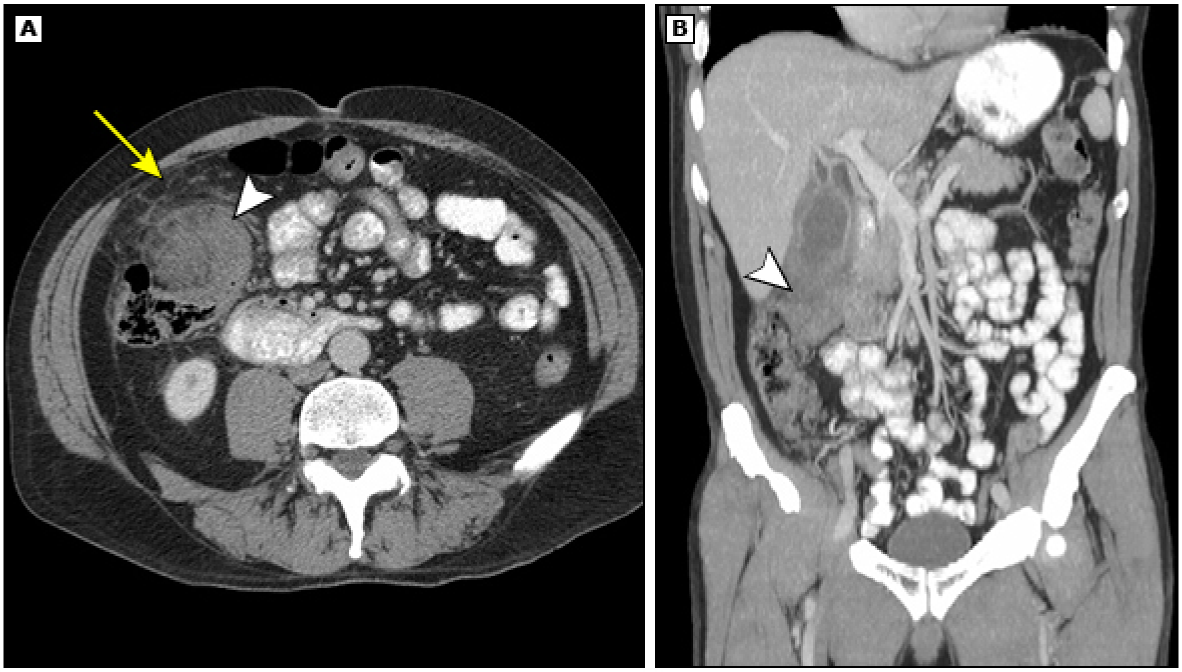
(A) The CT scan shows a gallstone (arrow) surrounded by an irregular accumulation of fluid with a hyperemic rim (arrowhead).

(B) The fluid can be seen extending from the gallbladder fossa into the liver parenchyma (arrowhead).

(C) Percutaneous aspiration of pus confirmed the presence of an abscess, and a drain was placed (arrow). Following drainage of the abscess, a small amount of contrast was injected into the decompressed cavity.

Graphic 86867 Version 2.0

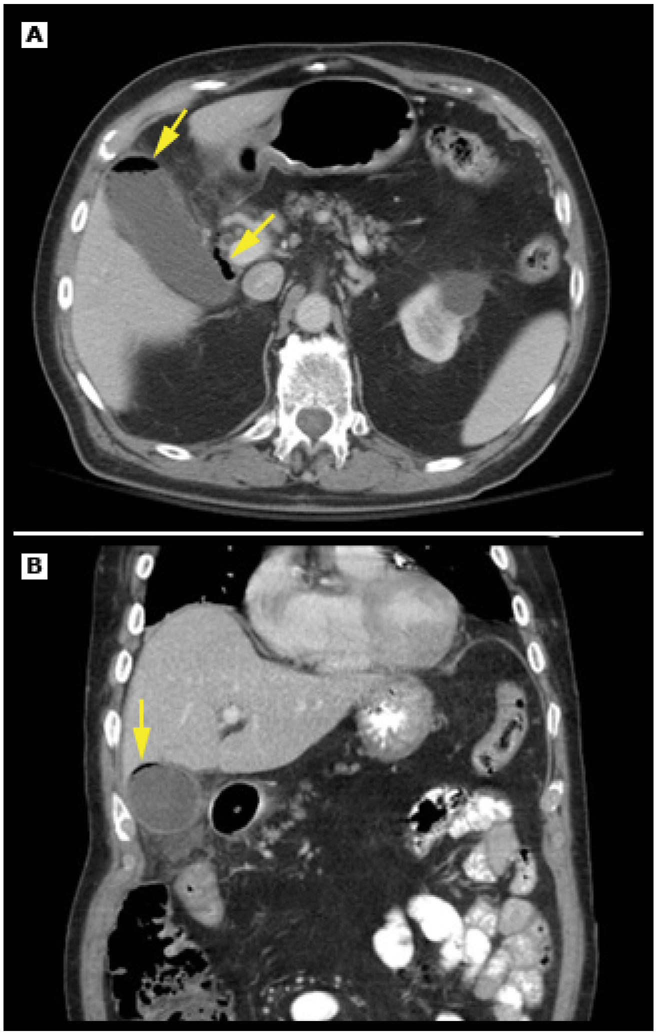
Contained gallbladder perforation in a patient with acute cholecystitis



Computed tomographic (CT) scan showing a sealed perforation of the gallbladder. Transverse (A) and reformatted coronal projections (B) of the CT scan demonstrate a focal accumulation of fluid near the fundus of the gallbladder (white arrowhead) with significant induration in the pericholecystic fat (yellow arrow). At surgery a necrotic and perforated gallbladder was identified.

Graphic 86865 Version 1.0

Emphysematous cholecystitis seen on computed tomographic scan



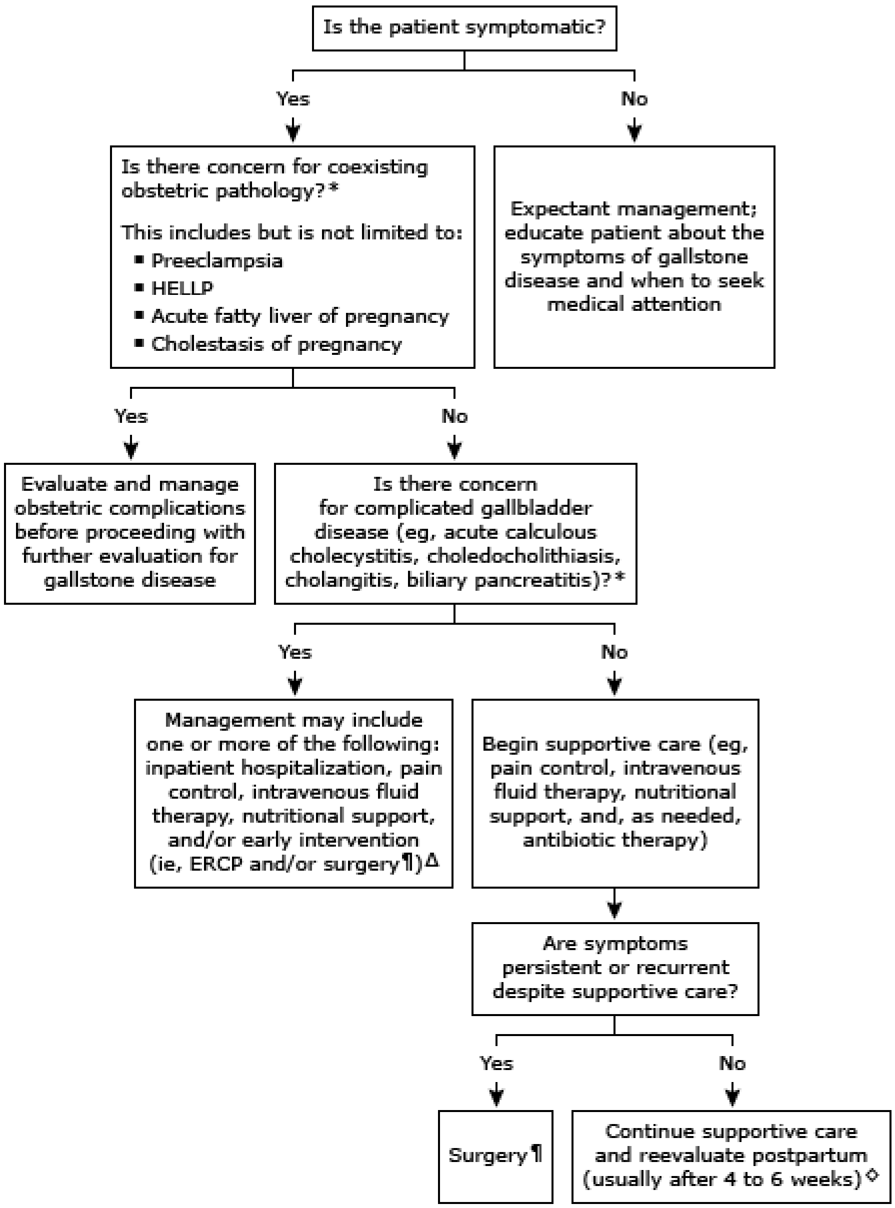
(A) An axial image of a contrast enhanced computed tomographic (CT) scan demonstrating air within the gallbladder lumen (arrows).

(B) A coronal reformat of a contrast enhanced CT demonstrating air within the wall of the gallbladder (arrow).

Courtesy of J Pierre Sasson, MD.

Graphic 56763 Version 3.0

Pregnant patient with imaging demonstrating gallstones



HELLP: Hemolysis, Elevated Liver enzymes, Low Platelet count; ERCP: endoscopic retrograde cholangiopancreatography; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CBC: complete blood count.

* Laboratory evaluation is usually normal in patients with uncomplicated gallstone disease; abnormal laboratory tests suggest the development of complicated gallstone disease or other pregnancy- or non-pregnancy-related conditions. We perform the following baseline evaluation:

- AST/ALT, total bilirubin, alkaline phosphatase (to evaluate for complicated gallstone disease, HELLP, and preeclampsia)
- Serum amylase and lipase (to evaluate for pancreatitis)

- CBC (to evaluate for infection, HELLP, and preeclampsia)
- Urine protein (to evaluate for preeclampsia)

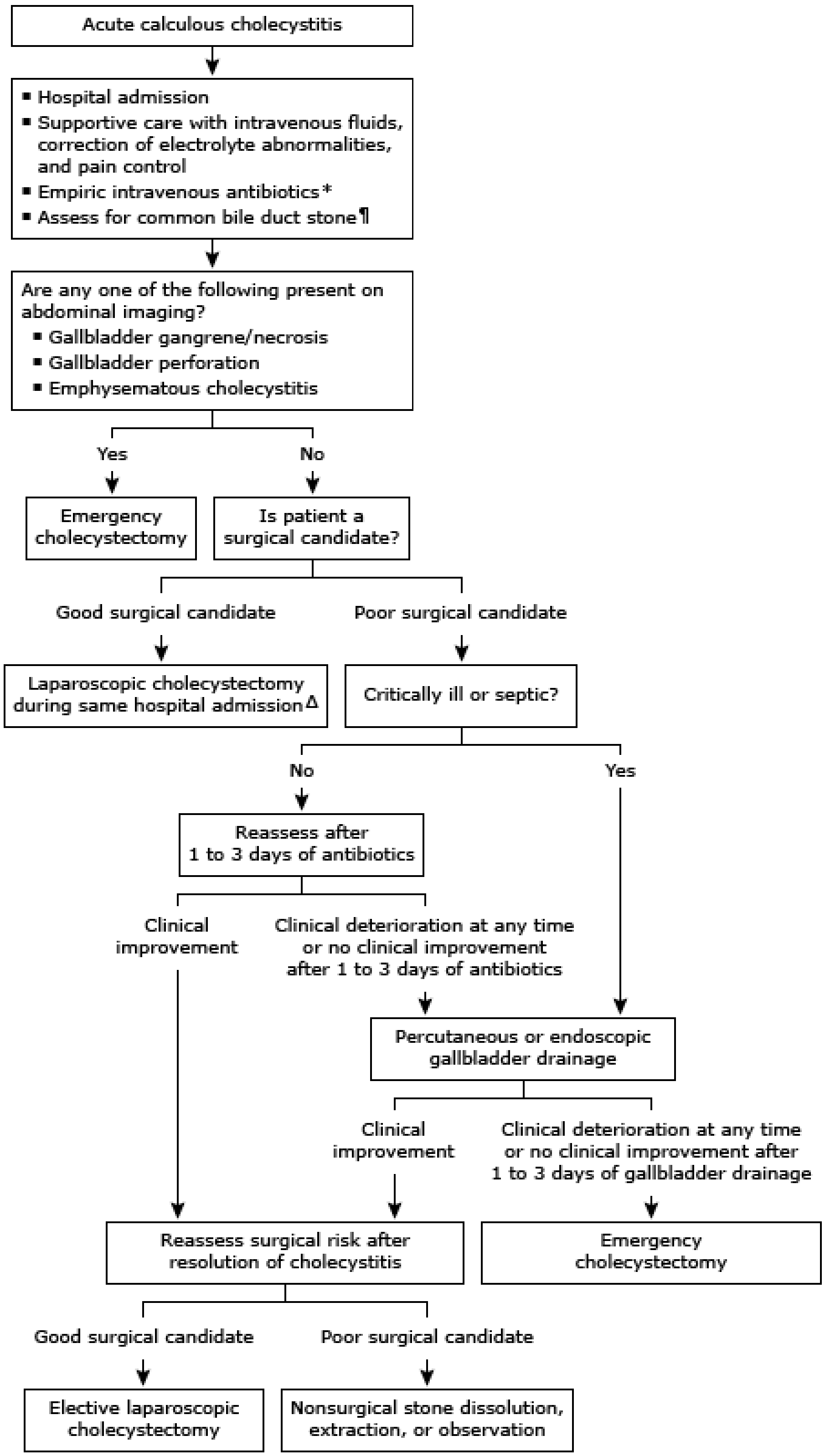
¶ Laparoscopic cholecystectomy is the preferred technique for removal of the gallbladder in pregnant patients and can be performed during any trimester.

Δ An alternative approach for those near term is to delay cholecystectomy until the postpartum period as long as the presenting symptoms have been adequately addressed by nonsurgical methods (eg, supportive treatment for gallstone pancreatitis, ERCP for choledocholithiasis or cholangitis).

◇ Some of our contributors do not delay surgery until the postpartum period and rather offer cholecystectomy to all patients with biliary colic (even if only a single episode).

Graphic 131757 Version 1.0

Treatment of acute calculous cholecystitis



* We suggest empiric antibiotic therapy to all patients with acute calculous cholecystitis. Refer to UpToDate topic for selection, dosing, and duration information on antibiotics.

¶ Refer to related UpToDate topics for information on diagnosis and treatment of common bile duct stone.

Δ Laparoscopic cholecystectomy should be performed as early as possible during the same admission, preferably within 3 days of symptom onset.

Graphic 64526 Version 5.0

Contributor Disclosures

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