DISCLAIMER: These guidelines were prepared by the Department of Surgical Education, Orlando Regional Medical Center. They are intended to serve as a general statement regarding appropriate patient care practices based upon the available medical literature and clinical expertise at the time of development. They should not be considered to be accepted protocol or policy, nor are intended to replace clinical judgment or dictate care of individual patients.

ACUTE CHOLECYSTITIS

SUMMARY

Acute cholecystitis is one of the most common conditions that requires acute care or general surgery consultation. The preponderance of evidence strongly advocates removal of the gallbladder within the first hospitalization and preferably in less than 72 hours after onset of symptoms. Early operation leads to fewer complications, decreased length of stay, fewer readmissions, and decreased overall cost.

RECOMMENDATIONS

- **Level 1**
  - **Early laparoscopic cholecystectomy within 24-72 hours of symptom onset reduces hospital length of stay, readmission rate, and overall cost.**
- **Level 2**
  - **Acute complications of acute cholecystitis such as choledocholithiasis, cholangitis, or gallstone pancreatitis should be treated with cholecystectomy on the same admission.**
  - **Perioperative antibiotics should be discontinued within 24 hours in patients with mild / uncomplicated acute cholecystitis.**
  - **Antibiotics should be discontinued within four days in patients with moderate acute cholecystitis and no septic complications (i.e. organ dysfunction).**
- **Level 3**
  - **Laparoscopic cholecystectomy for acute cholecystectomy can be safely performed regardless of age.**
  - **For mild to moderate acute cholecystitis, perioperative cefazolin, cefoxitin, or ceftriaxone are appropriate surgical prophylaxis.**
  - **For acute cholecystitis associated with severe physiologic disturbance (APACHE II score >15), advanced age, or immunocompromised state, perioperative piperacillin-tazobactam or cefepime plus metronidazole are appropriate surgical prophylaxis.**
  - **If clinical signs of infection persist, antibiotics may be continued for up to seven days at the surgeon's discretion.**
  - **Cholecystostomy tubes may be used as a temporizing measure in unstable patients with acute cholecystitis and multisystem organ failure, significant cardiovascular disease, or those who cannot otherwise safely undergo cholecystectomy.**
  - **Acute acalculus cholecystitis may be definitively treated with a cholecystostomy tube.**
  - **Cholecystostomy tube placement for calculus cholecystitis should be followed by cholecystectomy as definitive treatment.**
  - **Acute cholecystitis patients should be admitted to a surgical service.**
  - **MRI is an alternative imaging for pregnant patients with right upper quadrant pain.**
  - **Laparoscopic cholecystectomy should be performed in the second trimester when possible.**

EVIDENCE DEFINITIONS

- **Class I:** Prospective randomized controlled trial.
- **Class II:** Prospective clinical study or retrospective analysis of reliable data. Includes observational, cohort, prevalence, or case control studies.
- **Class III:** Retrospective study. Includes database or registry reviews, large series of case reports, expert opinion.
- **Technology assessment:** A technology study which does not lend itself to classification in the above-mentioned format. Devices are evaluated in terms of their accuracy, reliability, therapeutic potential, or cost effectiveness.

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Convincingly justifiable based on available scientific information alone. Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

INTRODUCTION

The first recorded laparoscopic cholecystectomy was performed in Germany on September 12, 1985. Since that time, the procedure has been modified and perfected such that it is now the standard of practice for removal of pathological gallbladder disease. There has been much debate over the last several years regarding the appropriate timing for cholecystectomy in the acute setting. Early proponents recommended "cooling down" the gallbladder with antibiotics and performing the procedure in a delayed fashion 6 to 8 weeks later. Current evidence, however, suggests that early cholecystectomy is more appropriate.

LITERATURE REVIEW

Early Versus Delayed Laparoscopic Cholecystectomy

Multiple prospective randomized trials and meta-analyses have compared early versus delayed cholecystectomy to evaluate which has a lower complication rate and better patient outcome (1-7). The original definition of early cholecystectomy was a procedure performed within 96 hours of the onset of symptoms. Current studies have narrowed that window down to 24 to 72 hours from the onset of symptoms. Late or delayed cholecystectomy was described as occurring at a later time after the original admission when the inflammation had resolved. The usual time frame was 6 to 8 weeks from the initial presentation. It was believed that by delaying surgery, the operation would be easier and there would be fewer complications such as injury to the common bile duct. The delayed operation strategy was also believed to decrease the need for conversion to open cholecystectomy. Current data, however, does not support these beliefs. In fact, prospective data demonstrates that there is no difference in conversion from laparoscopic to open surgery, or injury rate to biliary structures. The true advantage of proceeding with an early laparoscopic cholecystectomy is that patients have an average of four fewer hospital days reducing the overall cost of the disease process. Additionally, there is up to a 67% readmission rate for recurrent acute cholecystitis that is prevented by proceeding with cholecystectomy during the initial admission. A retrospective review of 967 patients showed that patients admitted to a surgical service were five times more likely to have their gallbladder removed on the initial presentation of cholecystitis (8).

Several review series, in addition to the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES), recommend that patients have removal of their gallbladder on the initial admission if they present with an acute complication of cholelithiasis (2). In the case of gallstone pancreatitis, up to 50% of people will have a second attack within 3 months. Thus, once they have clinical resolution of symptoms and a decreasing trend in laboratory values, gallstone pancreatitis patients and those with choledocholithiasis should undergo laparoscopic cholecystectomy (9,10).

There is some debate on the best approach to the elderly patient with acute cholecystitis. The paucity of data, which is all retrospective, shows that laparoscopic cholecystectomy can be performed safely in patients over the age of 74 (11,12). These older patients have the same rate of operative complications as younger patients, but will have a slightly higher rate of post-operative complications. This is attributed to the number of comorbidities that may be present. Patient selection will help to lower potential complication rates.

Treatment of Acute Cholecystitis with Antibiotics

Patients with acute cholecystitis should have antimicrobial therapy initiated (13). Antibiotics with good activity against microorganisms in the *Enterobacteriaceae* family should be utilized (14). For mild to moderate community acquired cholecystitis, appropriate antibiotics include cefazolin, cefoxitin, or ceftriaxone. For community acquired acute cholecystitis associated with severe physiologic disturbance (APACHE II score >15), advanced age, or immunocompromised state, the choice of antibiotics include piperacillin-tazobactam or cefepime plus metronidazole (13).

Although there is little debate on the initiation of antibiotics in acute cholecystitis, the duration of therapy is more controversial. It is generally accepted that antibiotics should be discontinued within 24 hours post-operatively in patients undergoing cholecystectomy for acute cholecystitis that have no evidence of infection outside the wall of the gallbladder or experience intra-operative contamination, as reflected in the Infectious Diseases Society of America guidelines (13). Treatment duration after undergoing

cholecystectomy is less defined in patients that have high risk of septic complications and/or evidence of infection outside the gallbladder wall. Existing guidelines suggest a generic treatment duration of 4 to 7 days, along with clinical signs of infectious resolution (13,15). The risks of longer treatment duration include microbial resistance, adverse events associated with the antibiotic(s), and cost; however, inadequate treatment duration could result in a higher incidence of surgical site infections (SSI). A few trials evaluating treatment duration and incidence of SSIs have been recently published and are reviewed below.

Rodriguez-Sanjuan et al. published an observational study in 2013 evaluating the frequency and risk of SSI in patients undergoing early cholecystectomy receiving antibiotic courses of different treatment durations (16). The study included patients with a diagnosis of acute cholecystitis with grade II (moderate) severity according to the Tokyo classification, which includes patients with one of the following conditions: white blood cell count (>18,000/mm^3), palpable tender mass in right upper quadrant, complaint duration >72 hours, or marked local inflammation (gangrenous cholecystitis, pericholecystic abscess, hepatic abscess, biliary peritonitis, emphysematous cholecystitis). They excluded patients with biliary leak or evidence of SSI prior to withdrawal of antibiotics. Patients were classified into three groups according to treatment duration: group 1 (0-4 days, n=45, 15.7%), group 2 (5-7 days, n=75, 26.1%) and group 3 (>7days, n=167, 58.2%). Results showed no statistically significant differences in the incidence of SSI between the groups: group 1 (2.2%) vs group 2 (10.7%) vs group 3 (9%) (p=0.24). In addition, multivariate risk analysis did not demonstrate a difference in risk of SSI among the groups. (Class II)

In 2014, Regimbeau et al. published a prospective, multi-centered, randomized, non-inferiority trial evaluating the incidence of post-operative infection within 4 weeks (17). The study included 414 total patients with grade I (mild) or grade II (moderate) acute cholecystitis that were randomized to a non-treatment group (no antibiotics after surgery) or a treatment group (received 5 days of antibiotics post-operatively). In the intention-to-treat analysis, the post-operative infection rates were 17% in the non-treatment group compared to 15% in the treatment group (absolute difference 1.93%; 95% CI, -8.98%-5.12%; p=0.007). Similar results were found in the per-protocol analysis. Authors concluded that patients with mild to moderate acute cholecystitis receiving no antibiotics after cholecystectomy did not result in a higher incidence of post-operative infections. (Class I)

Increasing evidence suggests that patients with mild to moderate acute cholecystitis with no septic complications (i.e., organ dysfunction) require a treatment duration of no more than four days without an increase in risk of SSI. However, in patients that do not experience resolution in clinical signs of infection, treatment should be extended to seven days or perhaps longer.

Cholecystostomy Tubes

In the event that the patient is too ill to undergo a laparoscopic or open cholecystectomy, and there is evidence of biliary obstruction of the gallbladder, a percutaneous cholecystomy tube may be placed (18-22). This tube is used for acute decompression of the gallbladder so that it does not progress to gangrene and perforation. Mortality rates can exceed 10% if this happens. The pathophysiology must be delineated between acalculous and calculous cholecystitis. The latter is a result of biliary stasis from critical illness, whereas calculous cholecystitis is a result of true luminal obstruction.

The use of cholecystostomy tubes has been controversial and recommendations regarding when they should be implemented and appropriate patient stratification is ambiguous. According to Cherng et al., patients with mean age of 71 years who had ≥ 1 comorbidity seemed to benefit from temporizing cholecystostomy tube placement (23). The benefit in temporizing these patients resulted in decreased conversion to open cholecystectomy and its associated morbidity and mortality (24). Cholecystostomy tubes should be used as a temporizing measure, placed either percutaneously or laparoscopically, to avoid open cholecystectomy and to allow for definitive laparoscopic cholecystectomy in a delayed fashion. The timing of placement is an alternative decision to operation. Patients that are critically ill and are high risk for operation will benefit the most from percutaneous drainage.

There is no prospective data to support when to remove the cholecystostomy tube. However, Level III evidence suggests 4-6 weeks is the appropriate time frame. In regard to need for delayed laparoscopic

cholecystectomy, there is a 2.7% recurrence rate with acalculous cholecystitis versus a 23% recurrence rate for calculous cholecystitis in one retrospective review (25). This leans for removal of the gallbladder for calculous cholecystitis after tube placement. However, it may not be necessary for removal of the gallbladder with acalculous cholecystitis after percutaneous cholecystomy tube removal (14). There is no published data to support or refute the use of cholecystostomy tube cholangiography to guide tube removal.

Acute Cholecystitis in Pregnancy

Acute cholecystitis is one of the most common non-obstetric abdominal emergencies during pregnancy. Date et al. performed a thorough review of all studies comparing non-operative treatment and cholecystectomy (26). Approximately one out of four of the patients treated non-operatively failed this treatment and progressed to cholecystectomy during pregnancy. There was no significant difference in preterm delivery rates whether the patient underwent surgery or not. Gallstone pancreatitis is associated with a higher rate of fetal mortality, and the trend in the data suggests intervention with cholecystectomy in these patients. The laparoscopic technique is safe in all three trimesters for the mother, but attempts should be made to pursue operative intervention during the second trimester as it has a lower incidence of preterm labor. (27)

Magnetic Resonance Imaging (MRI) during pregnancy

Many patients and physicians justly try to limit ionizing radiation to the pelvis and abdomen in pregnant patients. For this reason, MRI and ultrasound are commonly used to assess for acute cholecystitis in the pregnant patient with right upper quadrant or epigastric pain. The American College of Radiology does endorse the use of MRI during all trimesters; however, the use of gadolinium as a contrast agent is a Category C FDA drug with regard to pregnancy. MRI can also delineate between acute appendicitis and acute cholecystitis.

MRI imaging and interpretation often is more time consuming outside tertiary or quaternary medical facilities. Thus, a computed tomography (CT) scan should be used to diagnose suspected acute cholecystitis in the pregnant patient rather than to delay treatment. Lead shielding and lower radiation doses are strategies to reduce ionizing radiation exposure to the fetus.

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