Evaluation and Management of Gallstone-Related Diseases in Non-Pregnant Adults

**Patient Population:** Adult patients with suspected or confirmed biliary colic, acute cholecystitis, choledocholithiasis, cholangitis, or mild gallstone pancreatitis. Pregnant patients and patients with a history of gastric bypass surgery or biliary surgery are excluded from this guideline, and subspecialty consultation is appropriate in those cases. This document does not provide detailed recommendations for the general care of patients with acute pancreatitis.

**Objectives:** To create an evidence-based standard for the management of gallstone-related diseases that provides prompt and appropriate service to patients, reduces unnecessary diagnostic tests, and improves patient outcomes.

**Key Points**

**Clinical Presentation**

Patients presenting with upper abdominal pain or jaundice should be evaluated for gallstone-related disease.

**Diagnosis**

The evaluation for gallstone-related disease is summarized in Table 1. The evaluation routinely includes:

1. Complete physical exam
2. Laboratory evaluation – CBC, comprehensive metabolic panel, amylase/lipase
3. Imaging – Right upper quadrant (RUQ) ultrasound

In the vast majority of patients with acute cholecystitis, the diagnosis can be made based upon the history, physical findings, laboratory tests, and ultrasound (see Table 3 for the ultrasound findings that are suggestive of acute cholecystitis.) In cases where the diagnosis of cholecystitis remains uncertain after this evaluation, additional imaging modalities may be necessary.

**Treatment**

The treatment of gallstone-related diseases is summarized in Figure 1.

**Biliary Colic**

1. Minimally symptomatic or with symptoms that resolve: Provide reassurance, education on avoidance of triggers (e.g. dietary fat). Provide direct referral to elective surgery (at University of Michigan, Priority Gallbladder Clinic for surgery within 2 weeks, See Appendix A). [II-C*].

**Acute Cholecystitis**

1. Admit to Surgery
2. Initiate IV antibiotics (see Table 2)
3. Perform laparoscopic cholecystectomy within 24-48 hours [I-A].
   - In patients without gallstones who have RUQ and/or epigastric pain and a HIDA scan showing delayed gallbladder filling or lack of gallbladder emptying, cholecystectomy should be recommended/I-A].

**Choledocholithiasis**

1. Evaluate for evidence of cholangitis. If suspected, treat as cholangitis (below).
2. If no evidence of cholangitis, admit to surgery and prepare for cholecystectomy.
3. Estimate the likelihood of choledocholithiasis (see Table 4)
   a. For low likelihood, no additional evaluation is needed, and routine IOC is not recommended [III-B]
   b. For intermediate risk, recommended approach is a one-stage procedure with laparoscopic cholecystectomy with intraoperative cholangiography (IOC) within 48 hours of admission (preferably within 24 hours)[I-A]. Alternate approaches might
include preoperative imaging with EUS or MRCP, especially if IOC will not be performed.

i. If IOC demonstrates a retained CBD stone:
   1. Perform procedure to remove CBD stones during the same operation [I-A], or
   2. Obtain gastroenterology consult within 24 hours after surgery for ERCP.

c. For high risk patients, or those with documented choledocholithiasis, preoperative ERCP is often performed to clear the duct.

Cholangitis
1. Admit to Medicine service.
2. Initiate IV antibiotics, NPO (see Table 2).
3. Obtain Gastroenterology consult.
4. Classify severity of acute cholangitis (see Tables 6).
   a. If mild cholangitis with adequate response to medical therapy: ERCP within 72 hours.
   b. If moderate-severe and not responsive to medical therapy: ERCP within 24 hours.
5. Consult surgery for laparoscopic cholecystectomy during same admission, after cholangitis resolves.

Gallstone Pancreatitis
1. Evaluate for evidence of cholangitis. If suspected, treat as cholangitis (above).
2. Classify severity of gallstone pancreatitis (see Table 7).

Mild gallstone pancreatitis:
   a. Admit to surgery service.
   b. Perform laparoscopic cholecystectomy with IOC within 48 hours (preferably 24 hours) [I-B].
   c. IF IOC demonstrates a retained CBD stone:
      1. Surgical removal of CBD gallstone [I-A], or
      2. Gastroenterology consult for ERCP within 24 hours of surgery

Moderate to severe gallstone pancreatitis:
   a. Admit to medicine.
   b. Consider gastroenterology consultation.
   c. Delay cholecystectomy until pancreatitis resolves.

3. For detailed management of acute pancreatitis, see other resources (University of Michigan resources include: http://www.med.umich.edu/i/intmed/gi/rizk/pancmap/index.html)

* Strength of recommendation:
  I = generally should be performed; II = may be reasonable to perform; III = generally should not be performed.
Levels of evidence reflect the best available literature in support of an intervention or test:
  A=randomized controlled trials; B=controlled trials, no randomization; C=observational trials; D=opinion of expert panel.

CBD: common bile duct; ERCP: endoscopic retrograde cholangiopancreatography; HIDA: hepatobiliary iminodiacetic acid, used in cholescintigraphy; IOC: intraoperative cholangiogram; RUQ: right upper quadrant
### Table 1. Clinical Features of Gallstone-Related Diseases

<table>
<thead>
<tr>
<th>Gallstone-Related Diseases*</th>
<th>Clinical Features (note: upper abdominal pain, nausea, and vomiting (N/V) are common to all of these disorders)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biliary Colic</td>
<td>H&amp;P: Severe, episodic, epigastric or RUQ pain; may be nocturnal, occasionally postprandial. +/− RUQ tenderness. Labs: no leukocytosis; total bilirubin, amylase/lipase are normal. Imaging: RUQ ultrasound indicating cholelithiasis without findings of cholecystitis (see Table 3).</td>
</tr>
</tbody>
</table>
| Acute Cholecystitis         | H&P: +/− fever; symptoms persist or worsening; + RUQ tenderness. Labs: leukocytosis is common. Total bilirubin is usually normal or mildly elevated (<2.0 mg/dL) unless there is concomitant choledocholithiasis. Amylase and lipase are usually normal unless there is concomitant pancreatitis. Imaging:  
  • RUQ ultrasound: Table 3. Note: The diagnosis of cholecystitis is NOT made based on ultrasound findings alone. Rather, the diagnosis is made based on the clinical findings above, in combination with consistent ultrasound findings.  
  • HIDA (indicated if RUQ ultrasound is inconclusive, or contradicts the clinical impression): demonstrates lack of gallbladder filling. |
| Choledocholithiasis         | H&P: biliary pain, jaundice, no fever. Labs: elevated bilirubin (total bilirubin often >2.0 mg/dL). Amylase/lipase are usually normal, unless there is concomitant pancreatitis. Imaging: RUQ ultrasound shows CBD dilation (> 7 mm).** |
| Cholangitis                 | H&P: jaundice, + fever. RUQ tenderness. Labs: Elevated bilirubin (total bilirubin >2.0 mg/dL), leukocytosis. Amylase/lipase are usually normal or mildly elevated, unless there is concomitant pancreatitis. Imaging: RUQ ultrasound: CBD dilation (> 7 mm).** |
| Gallstone Pancreatitis      | H&P: +/- jaundice, +/- fever. Epigastric tenderness. Labs: normal or elevated bilirubin, elevated amylase and/or lipase to typically 3x upper limit of normal. Elevated ALT>150 suggests a biliary cause of the pancreatitis, based on meta-analysis (American J Gastro; 89: 1893). Imaging: RUQ ultrasound: cholelithiasis and biliary dilation variably present. Note: RUQ ultrasound is often limited for the evaluation of the pancreatic parenchyma. Absence of other common causes of pancreatitis: ethanol abuse, hyperglycemia, hypertriglyceridemia, hypercalcemia, or medications known to cause pancreatitis. For classification of pancreatitis severity, see Table 7. |

* These diseases are not mutually exclusive and often present together. For example, patients with choledocholithiasis often present with gallstone pancreatitis.  
** Post-cholecystectomy patients may have CBD dilation in the absence of biliary pathology  

CBD: common bile duct; RUQ: Right upper quadrant
**Figure 1: Treatments for Gallstone-Related Diseases**

Note: These conditions are not mutually exclusive. For example, patients with cholecystitis can also have CBD stones or cholangitis.

*For University of Michigan, consult [http://www.med.umich.edu/i/intmed/gi/rizk/pancmap](http://www.med.umich.edu/i/intmed/gi/rizk/pancmap)*

**Active and/or unstable medical conditions may include but are not limited to:** ongoing cardiac ischemia, acute heart failure exacerbation, unstable glycemic control/DKA, flare of chronic respiratory condition (e.g. COPD/asthma), secondary severe infection, acute anuric/oliguric renal failure, active GI bleeding, acute neurological injury (e.g. CVA or intracranial bleed).

AST: Aspartate Aminotransferase/ Aspartate Transaminase; BUN: Blood Urea Nitrogen; CXR: chest radiograph; EKG: electrocardiogram; ERCP: Endoscopic Retrograde Cholangiopancreatography; HR: heart rate; IOC = intraoperative cholangiogram; NPO: Nils per os; WBC: White blood cell count.
Table 2. Antibiotic Guidelines for Treatment of Cholecystitis and Cholangitis in Adults

<table>
<thead>
<tr>
<th>Clinical Setting</th>
<th>Empiric Therapy</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Community Acquired</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild-Moderate Severity</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
| - Enteric gram-negative bacilli (E.coli, Klebsiella spp) | Ceftriaxone 2 gm IV daily +/- metronidazole 500 mg po/IV q 8 hrs | 4-7 days | Empiric coverage of Enterococcus and Candida is not recommended with community-acquired infection.  
Ampicillin/sulbactam is not recommended for use because of high rates of resistance among community-acquired E.coli.  
Duration of therapy may need to be extended with inadequate source control or persistent clinical symptoms.  |
| - Anaerobes (Bacteroides, Clostridium) in patients with biliary-enteric anastomosis | Alternative Therapies:  
If cephalosporin allergy without anaphylaxis, angioedema, or urticaria, use pipercillin/tazobactam* 4.5 gm IV q 8 hours |          |                                                                          |
| - Enterococcus coverage is not necessary | If anaphylactic PCN/cephalosporin allergy, use ciprofloxacin* 400 mg IV q 12 hours or 750 mg po q 12 hours +/- metronidazole 500 mg po/IV q 8 hrs |          |                                                                          |
|                                      | *Adjust dose based on renal function                                             |          |                                                                          |
| **Community Acquired**               |                                                                                 |          |                                                                          |
| High Risk or Severe                  |                                                                                 |          |                                                                          |
| - Enteric gram-negative bacilli (E.coli, klebsiella spp) | Piperocillin/tazobactam* 4.5 gm IV q 8 hours | 4-7 days | High risk individuals include patients with advanced age, prior antibiotics, immunocompromised, severe physiologic disturbance, or organ dysfunction, and following bilo-enteric anastomosis.  
Duration of therapy may need to be extended with inadequate source control or persistent clinical symptoms.  |
| - Anaerobes (Bacteroides, clostridium) in patients with biliary-enteric anastomosis | Alternative Therapies:  
If PCN allergy without anaphylaxis, angioedema, or urticaria, use Cefepime* 1 gm IV q 8 hours +/- Metronidazole 500 mg po/IV q 8 hrs |          |                                                                          |
| - Enterococci                        | If anaphylactic PCN/cephalosporin allergy, use ciprofloxacin* 400 mg IV q 12 hours or 750 mg po q 12 hours +/- metronidazole 500 mg po/IV q 8 hrs |          |                                                                          |
|                                      | For enterococcus coverage in critically ill patients with either non-life-threatening PCN allergy or anaphylactic PCN/cephalosporin allergy, consider the addition of vancomycin |          |                                                                          |
|                                      | *Adjust dose based on renal function                                             |          |                                                                          |
| **Health-Care Associated**           |                                                                                 |          |                                                                          |
| - Gram-negative bacilli (E.coli, klebsiella, Pseudomonas, enterobacter spp) | Piperocillin/tazobactam* 4.5 gm IV q 8 hours | 4-7 days | Health-Care Associated: includes patients with at least 1 of the following health care risk factors: (1) presence of an invasive device at time of admission, (2) history of MRSA infection or colonization, (3) history of surgery, hospitalization, dialysis or residence in a long term care facility in the previous 12 months preceding culture, (4) positive cultures from a normally sterile site >48 hrs after admission.  
Duration of therapy may need to be extended with inadequate source control or persistent clinical symptoms.  |
| - Anaerobes                          | Alternative Therapies:  
If PCN allergy without anaphylaxis, angioedema, or urticaria, cefepime* 1 gm IV q 8 hours + metronidazole 500 mg po/IV q 8 hrs |          |                                                                          |
| - Enterococci                        | For enterococcus coverage in critically ill patients with non-life-threatening PCN allergy, consider the addition of vancomycin.  
For anaphylactic PCN/cephalosporin allergy, vancomycin* + aztreonam* 2gm IV q 8 hrs + metronidazole 500 mg po/IV q 8 hrs |          |                                                                          |
|                                      | *Adjust dose based on renal function                                             |          |                                                                          |

*Adjust dose based on renal function

# This table was taken directly from the University of Michigan Intra-abdominal Infection Antimicrobial Use Guideline, available at: http://ummcpharmweb.med.umich.edu/i/GuidelinesForms/AntimicrobialUseGuidelines/tabid/303/Default.aspx
Table 3: Sonographic Findings of Acute Cholecystitis

The presence of gallstones is sensitive for the detection of acute cholecystitis but there are many false positives.

The following signs are rarely present, but when present are highly predictive for acute cholecystitis:
- Focal pericholecystic fluid localized between the gallbladder and liver (indicating gallbladder perforation)
- Sloughed mucosa (gangrenous cholecystitis)
- Air in gallbladder wall

The following findings may be present in acute cholecystitis, but are neither sensitive nor specific for acute cholecystitis:
- Gallbladder distention (width > 4 cm)
- Gallbladder wall thickening (nl < 3 mm)
- Common duct dilation (diameter > 5 mm) *
- Generalized pericholecystic fluid
- Sonographic Murphy’s sign **

* Post-cholecystectomy patients and older individuals may have CBD dilation in the absence of biliary pathology
** Highly operator dependent and thus not generally applicable

Table 4: Risk Stratification for the Probability of Choledocholithiasis (Common Bile Duct Stones)

<table>
<thead>
<tr>
<th>Clinical Predictors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Strong</td>
</tr>
<tr>
<td>CBD stone on radiological imaging</td>
</tr>
<tr>
<td>Clinical indication of ascending cholangitis</td>
</tr>
<tr>
<td>Total bilirubin &gt; 4 mg/dL</td>
</tr>
<tr>
<td>Strong</td>
</tr>
<tr>
<td>Dilated CBD on radiological imaging (see Table 1)</td>
</tr>
<tr>
<td>Bilirubin 1.8 – 4 mg/dL</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Abnormal liver function test other than bilirubin</td>
</tr>
<tr>
<td>Age &gt; 55 yo</td>
</tr>
<tr>
<td>Clinical gallstone pancreatitis</td>
</tr>
</tbody>
</table>

Risk stratification

- **High**: Presence of **any** “Very Strong” predictor
- **Intermediate**: Presence of both “Strong” predictors
- **Low**: No predictors present
- Intermediate: All other patients that are not “low” or “high” risk patients *

EUS: endoscopic ultrasound; MRCP: magnetic resonance cholangiopancreatography

Table 5: Diagnosis of Cholangitis: Tokyo Guidelines 2013

<table>
<thead>
<tr>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Systemic Inflammation</td>
</tr>
<tr>
<td>• Fever and/or shaking chills</td>
</tr>
<tr>
<td>• Laboratory data: evidence of inflammatory response (WBC, CRP, etc.)</td>
</tr>
<tr>
<td>B. Cholestasis</td>
</tr>
<tr>
<td>• Jaundice (Total bilirubin ≥2 mg/dL)</td>
</tr>
<tr>
<td>• Laboratory data: abnormal liver function tests (ALP, GGT, AST and ALT)</td>
</tr>
<tr>
<td>C. Imaging</td>
</tr>
<tr>
<td>• Biliary Dilatation</td>
</tr>
<tr>
<td>• Evidence of the etiology on imaging (striction, stone, stent, etc.)</td>
</tr>
<tr>
<td>• Clinical gallstone pancreatitis</td>
</tr>
</tbody>
</table>

**Diagnosis**

<table>
<thead>
<tr>
<th>Diagnosis of Cholangitis</th>
<th>Suspected: If presence of one item in A + one item in either B or C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Definite: If presence of one item in A, one item in B and one item in C</td>
</tr>
</tbody>
</table>

ALP: Alkaline Phosphatase; ALT: Alanine Transaminase; GGT: Gamma-Glutamyl Transferase.
Table 6: Assessment of Acute Cholangitis Severity: Tokyo Guidelines 2013 criteria

<table>
<thead>
<tr>
<th>Severity of Acute Cholangitis</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild</strong> (Grade I)</td>
<td>Does not meet the criteria of “Severe” or “Moderate” acute cholangitis at time of initial diagnosis</td>
</tr>
<tr>
<td><strong>Moderate</strong> (Grade II)</td>
<td>Acute cholangitis associated with any two of the following conditions:</td>
</tr>
<tr>
<td></td>
<td>- Abnormal WBC (&gt;12,000, &lt;4000/mm³)</td>
</tr>
<tr>
<td></td>
<td>- High fever (≥39°C)</td>
</tr>
<tr>
<td></td>
<td>- Age ≥ 75 years old</td>
</tr>
<tr>
<td></td>
<td>- Hyperbilirubinemia (total bilirubin ≥ 5mg/dL)</td>
</tr>
<tr>
<td></td>
<td>- Hypoalbuminemia (&lt;lower limit of normal x 0.7)</td>
</tr>
<tr>
<td><strong>Severe</strong> (Grade III)</td>
<td>Acute cholangitis associated with the onset of dysfunction in at least one of the following organs/systems:</td>
</tr>
<tr>
<td></td>
<td>- Cardiovascular dysfunction (Hypotension requiring pressors)</td>
</tr>
<tr>
<td></td>
<td>- Neurological dysfunction (Disturbance of consciousness)</td>
</tr>
<tr>
<td></td>
<td>- Respiratory dysfunction (PaO2/FiO2 ratio &lt;300)</td>
</tr>
<tr>
<td></td>
<td>- Renal dysfunction (Oliguria, serum creatinine &gt;2mg/dL)</td>
</tr>
<tr>
<td></td>
<td>- Hepatic dysfunction (Elevated PT/INR &gt;1.5)</td>
</tr>
<tr>
<td></td>
<td>- Hematological dysfunction (Platelet count &lt; 100,000/mm³)</td>
</tr>
</tbody>
</table>

Assessment of Urgency of Draining

- **Urgent** biliary drainage (<24 hours) is indicated when
  1. Obstructive biliary stones are associated with severe or moderate acute cholangitis OR
  2. Mild acute cholangitis is not responding to IV antibiotics and fluid resuscitation.
- **Early** (but not urgent) ERCP (<72 hours) is recommended for patient with mild acute cholangitis who respond to medical therapy

PT/INR: Prothrombin Time and International Normalized Ratio

Table 7: Classification of Gallstone Pancreatitis: Ranson and BISAP Criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Ranson Criteria</th>
<th>BISAP Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &gt;55 years</td>
<td>BUN &gt;25 mg/dl</td>
</tr>
<tr>
<td></td>
<td>Glucose &gt;200 mg/dL</td>
<td>Impaired mental status (any):</td>
</tr>
<tr>
<td></td>
<td>LDH &gt;350 mg/dL</td>
<td>- disorientation, lethargy, coma, somnolence, stupor</td>
</tr>
<tr>
<td></td>
<td>AST &gt;250 units/L</td>
<td>SIRS*</td>
</tr>
<tr>
<td></td>
<td>WBC &gt;16 K/mm³</td>
<td>Age &gt;60 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pleural Effusion</td>
</tr>
<tr>
<td>Severity Classification</td>
<td>Mild Gallstone Pancreatitis</td>
<td>Moderate to Severe Gallstone Pancreatitis</td>
</tr>
<tr>
<td></td>
<td>a. Clinical stability with admission to non-monitored bed</td>
<td>a. ≥ 4 Ranson criteria on admission, or ≥ 3 BISAP criteria within first 24 hours of admission</td>
</tr>
<tr>
<td></td>
<td>- No significant hypovolemia</td>
<td>- 4 Ranson criteria or &lt; 3 BISAP Criteria on admission</td>
</tr>
<tr>
<td></td>
<td>- BUN &lt;15</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- HR &lt;110 bpm</td>
<td></td>
</tr>
<tr>
<td></td>
<td>b. &lt; 4</td>
<td></td>
</tr>
</tbody>
</table>


*SIRS criteria = two or more of these: T > 38°C OR < 36°C; HR > 90; RR > 20 OR Pa CO2 < 32 mmHg; WBC > 12,000 OR < 4,000 OR > 10% bands
Clinical Problem and Management Issues

Gallbladder disease is common, with over 700,000 cases annually of gallstones alone in the US, and 10-15% incidence in white adults in developed countries. Risk factors for gallstones include female gender, increasing age, obesity, metabolic syndrome, and rapid weight loss.1

Gallstone-related disease is a common reason for hospitalization. Its management is uniquely multidisciplinary, involving emergency medicine, internal medicine, gastroenterology, radiology, and general surgery. Quality of care can be compromised by delays in treatment. Unnecessary testing can cause delays, and also can incur costs, increase length of stay, and may not change the care plan.

This clinical practice guideline is intended to enhance consistency in patient management, facilitate interdisciplinary consensus, increase efficiency of patient care, and improve clinical outcomes. This guideline is not comprehensive, but can guide the care of the majority of patients with gallstone-related disease.

Diagnosis

The evaluation of patients’ biliary-type pain should attempt to determine if the patient has any of the following: cholelithiasis, cholecystitis, choledocholithiasis, cholangitis, or gallstone pancreatitis. The diagnosis of gallstone-related conditions is based on the history and physical exam findings, in combination with imaging and laboratory testing, as summarized in Table 1. The conditions are not mutually exclusive and a given patient may suffer from a combination of any of the following: cholecystitis, choledocholithiasis, cholangitis, and pancreatitis.2

History, Physical Exam, Signs and Symptoms

History and symptoms. History should focus on the onset, pattern, and quality of the pain as well as anything that worsens or relieves it. The provider should take into consideration the presence of anorexia, nausea, or vomiting. Fever can be variably present. The term “colic” may be a misnomer as patients with all of these entities, except perhaps cholelithiasis alone, typically have constant pain that may get better or worse, but rarely goes away completely.

Physical exam and signs. No single finding or combination of physical findings establishes or excludes the diagnosis of RUQ pathology with sufficient certainty to avoid additional testing when clinical suspicion exists for its presence. The physical exam can include: fever, abdominal guarding, rebound, or right upper quadrant: mass, tenderness, Murphy’s sign, Boas’ sign, or Collins’ sign (all defined below), jaundice (bilirubin >2.5 mg/dl before scleral icterus is typically seen, > 5.0 before cutaneous manifestations are seen), but none are pathognomonic. Laboratory evaluation discussed below may further delineate which disease may be present.

Clinical gestalt based on history and physical exam can raise pretest probability from 5% to 60% in patients who present to the emergency department with abdominal pain. Elderly patients may not exhibit classic signs and symptoms of cholecystitis, and require a high index of suspicion to avoid missing the diagnosis.3

Murphy’s sign. The examiner hooks his/her fingers under the right costal margin and asks the patient to deeply inhale. A positive test is noted if the patient stops inhaling suddenly due to pain of the gallbladder meeting the examiner’s fingers.2

Sonographic Murphy’s sign. Performed like the Murphy’s sign above, this test makes use of the ultrasound probe to meet the gallbladder instead of the examiner’s fingers. This test may be more sensitive when performed by a radiologist (compared to the radiology technician) and is a physical finding associated with gallbladder disease, specifically cholecystitis, although it is not specific.

Boas’ sign. This sign is said to be present when hyperesthesia exists in the right upper quadrant or right infrascapular region.

Collins’ sign. This sign is said to be present when the patient points to the right scapular tip with a fist and thumb pointing upwards to describe the pain.

Imaging

In patients with suspected gallstone-related disease, the recommended initial imaging test is ultrasonography4,5. When the clinical presentation, lab tests, physical exam and ultrasound are consistent with diagnosis of acute cholecystitis, no additional imaging is required.

If the initial sonogram is inconclusive or is discordant with the clinical evaluation, cholestintigraphy may be indicated. Computed tomography (CT) and magnetic resonance imaging (MRI) may provide additional diagnostic value, but are not recommended as initial imaging tests for gallstone-related diseases. CT or MRI should be considered adjunctive radiographic modalities for diagnosis acute cholecystitis.6 If ultrasound confirms the diagnosis, there is no need to obtain these studies. Doing so may delay definitive care, which may complicate the course of the disease, in addition to incurring additional costs. In patients identified as having an intermediate risk of choledocholithiasis, MRCP or EUS could be used to confirm the presence of CBD stones.
The characteristics of the imaging modalities are explained below.

**Right upper quadrant ultrasound.** Ultrasonography of the gallbladder detects gallstones with >95% sensitivity and specificity, confirms no ionizing radiation and is noninvasive, readily available and relatively inexpensive. 2 The liver, biliary system, and pancreas are also imaged to assess for secondary signs of gallstone-related disease suggestive of acute cholecystitis and/or biliary obstruction. The sonographic findings suggestive of acute cholecystitis are shown in Table 3. None of the findings alone or in combination are pathognomonic for cholecystitis. Conversely, the absence of the described findings does not rule out cholecystitis.

**Cholescintigraphy.** Cholescintigraphy should be considered when the initial sonogram is inconclusive or is discordant with the clinical evaluation, if additional information supporting or refuting the diagnosis of acute cholecystitis would alter the clinical approach. Also known as HIDA (hepatobiliary iminodiacetic analog) scanning, cholescintigraphy provides imaging-based information on gallbladder function. It is superior to ultrasonography for the diagnosis of acute cholecystitis, with sensitivity of 96% and specificity of 83-100%. 3 In acute cholecystitis, a “positive” HIDA scan equates to the absence of gallbladder filling, which implies cystic duct obstruction.

There are two major technical considerations when ordering cholescintigraphy. First, the patient should fast for a minimum of 4 hours prior to imaging. Second, since opiate analgesics promote gallbladder filling, these substances should be avoided when possible prior to imaging to avoid reduced specificity of the test. Patients who have prolonged fasting or who have received opiates prior to imaging can be studied after pre-treatment with a synthetic cholecystokinin analog to promote gallbladder emptying which reduces the likelihood of a false positive.

**Computed tomography (CT).** The use of CT is generally reserved for use when other intra-abdominal processes are suspected. The evidence is scarce for the use of CT in the initial evaluation for gallstone-related diseases 5 and is not recommended as the primary modality to assess for acute cholecystitis.

CT detection of gallstones is poor when compared to ultrasound, as more than 60% of gallstones are not radiopaque and therefore difficult to detect or undetectable.

**Magnetic resonance imaging (MRI) and magnetic resonance cholangiopancreatography (MRCP).** MRI may be a useful alternative test for acute cholecystitis for patients in whom the US is technically degraded. Magnetic resonance imaging has become faster, more widely available and less expensive. With MRI, the summary estimate of sensitivity for acute cholecystitis is 85% with a specificity of 81%, with no significant difference between MRI and US. 6

MRCP is a noninvasive method for detecting common bile duct stones with a negative predictive value of 100%. 7 In the context of gallstone pancreatitis, MRCP may be inadequately sensitive to exclude choledocholithiasis, with a sensitivity of 62% and specificity of 98%. 10

**Laboratory Evaluation**

All patients presenting with suspected gallstone-related disease should be evaluated with laboratory testing, including a complete blood count, comprehensive metabolic panel, amylase, and lipase.

The typical historical, lab and imaging findings for each gallstone-related clinical condition are shown in Table 1.

**Biliary Colic.** The white blood count, serum bilirubin, amylase, and lipase are all within a normal range.

**Acute Cholecystitis.** A leukocytosis with a left shift is typically present. Bilirubin, alkaline phosphatase, amylase, and lipase are typically NOT increased, and their elevation should provoke consideration for complicating conditions such as cholangitis or choledocholithiasis. With severe/complicated acute cholecystitis, mild elevation in bilirubin and alkaline phosphatase are possible due to inflammation of the liver bed, gall bladder perforation and compression of the bile duct, etc.

**Choledocholithiasis.** Aseptic common bile duct obstruction typically manifests with biliary pain, elevated liver enzymes (Table 1), normal amylase and lipase and normal white blood cell count.

**Cholangitis.** As an infectious complication of biliary obstruction, cholangitis typically manifests with a leukocytosis with a left shift, elevated bilirubin>2.0 and normal amylase and lipase.

**Gallstone pancreatitis.** Amylase and lipase are typically elevated to 3 times above the upper limit of normal. An elevated ALT > 150 suggests that the pancreatitis may be of biliary origin (see also Table 1). Bilirubin and white blood count may or may not be in a normal range depending on the location and overall burden of obstructing stones and the presence of septic complications, respectively. Note that LDH, BUN and bicarbonate should be measured prior to admission if a diagnosis of gallstone pancreatitis is formulated in order to calculate Ranson criteria for survival, which will guide disposition. A CRP level drawn 24-48 hours after admission greater than 170 mg/L has been shown to predict a 7-fold increase in hospital mortality in such patients.
Treatment

The treatment of gallstone-related diseases depends on the accurate diagnosis of the underlying condition. Often, these disorders coexist, and treatment will need to be directed at multiple conditions simultaneously. The treatment of these conditions is summarized in Figure 1.

Biliary Colic

For summary recommendations, see Key Points on page 1.

Discussion. Patients who are found to have cholelithiasis and yet do not have a history of true biliary-type pain should not undergo surgery. Approximately 20% of these initially asymptomatic patients will eventually develop symptoms and warrant referral for outpatient surgical consultation. (See Appendix A for Gallbladder Priority Clinic information.)

Patients with moderate to severe biliary colic should have surgical consultation. While the majority of patients with moderate to severe biliary colic will have resolution of symptoms, most will still eventually undergo cholecystectomy. It is thus reasonable to offer laparoscopic cholecystectomy during the same visit, though timing of surgery should be dictated by the patient’s preference and availability of surgical resources.

Acute Cholecystitis

For summary recommendations, see Key Points on page 1.

Discussion. Patients with acute cholecystitis should undergo laparoscopic cholecystectomy within 24-48 hours. Compared to delayed cholecystectomy, early laparoscopic cholecystectomy is associated with decreased length of stay and no difference in complications or conversion to open cholecystectomy. Patients who are poor surgical candidates due to acute medical illness may be candidates for percutaneous cholecystostomy or gallbladder stent placement as a bridge to cholecystectomy (see Figure 1 for algorithm exceptions.)

Typically, antibiotics include Ceftriaxone 2 mg IV daily +/- metronidazole 500 mg po/IV q 8 hours, except for cases of severe infection, hospital acquired infection, or penicillin allergy (Table 2).

In patients without gallstones who have biliary-type pain and a positive HIDA scan, non-urgent cholecystectomy is recommended. These patients are more likely to experience symptom relief following cholecystectomy than those treated medically.

Choledocholithiasis

For summary recommendations, see Key Points on page 1.

Discussion. Patients with choledocholithiasis should be treated for that disorder, as outlined below. The discussion of choledocholithiasis in the setting of biliary pancreatitis is also discussed further below. Patients may be risk stratified for the likelihood of choledocholithiasis based upon clinical predictors (see Table 4).

For patients undergoing cholecystectomy with a low risk for choledocholithiasis (Table 4), routine IOC is not indicated. No adequately powered studies exist to detect a decrease in CBD injury risk with routine IOC. Routine IOC may be associated with increased operative times and increased perioperative complication rates.

For patients identified as having an intermediate risk of choledocholithiasis (Table 4), it is reasonable to proceed with a cholecystectomy with an intraoperative cholangiogram. Less than 1 in 4 of these patients would be expected to have a ductal stone. If the intraoperative cholangiogram reveals evidence of choledocholithiasis, stone extraction can occur via intraoperative duct exploration, or via postoperative ERCP. In some cases (e.g., if an IOC will not be performed), preoperative imaging with EUS or MRCP might be appropriate to further evaluate the presence of CBD stones.

Patients with high risk predictors for choledocholithiasis (Table 4) are usually treated with preoperative ERCP to clear the duct. However, if expertise is available to remove the CBD stones intra-operatively (surgical CBD exploration, or intra-operative ERCP), a one stage procedure is also a reasonable option.

Patients with proven choledocholithiasis are usually treated with preoperative ERCP, as above. For those patients who undergo ERCP as primary management for choledocholithiasis, cholecystectomy is still required during the same admission (within 72 hours). Delay is associated with an increased risk of biliary events (approximately 36% within 2-6 weeks).

Even in patients with choledocholithiasis, comparison of one-stage (laparoscopic common bile duct (CBD) exploration or intraoperative ERCP) versus two-stage management (ERCP pre- or post-operatively) demonstrates no difference in ductal cleanup rates, morbidity, mortality, or need for additional procedures. One-stage management, however, requires fewer procedures and lower cost. In addition, the risks of ERCP should be considered, including post-procedure pancreatitis (risk factors include young age and female gender). Recommendation for pre-operative ERCP should be tailored to the individual patient, recognizing the risk of post-ERCP pancreatitis that may delay cholecystectomy.

Cholangitis

For summary recommendations, see Key Points on page 2.

Discussion. Choledocholithiasis is the leading etiology of acute cholangitis. Diagnostic criteria of Charcot’s triad (fever, abdominal pain and jaundice) has favorable specificity, but low sensitivity for the diagnosis of
cholangitis. Therefore the presence of Charcot’s triad supports the diagnosis of acute cholangitis; however, lack of this finding does not exclude the diagnosis. International guidelines for the diagnosis of acute cholangitis are summarized in Table 5. Clinical suspicion remains critical in the diagnosis of this disorder.

Although the majority of patients respond to antibiotic therapy, clearing the bile duct is necessary to treat the underlying obstruction. Patients without clinical and laboratory response to medical therapy are at risk for progression to sepsis with or without organ dysfunction. These patients require further management including intensive care, organ-supportive care, and urgent biliary drainage in addition to antibiotics. International guidelines have graded severity of acute cholangitis as mild, moderate, or severe (Table 6). The severity assessment criteria are critical for determining the treatment strategy for acute cholangitis. Severe cholangitis includes the presence of organ dysfunction. Moderate acute cholangitis imparts the risk of increased severity without early biliary drainage. Mild acute cholangitis defines a patient population without hypotension or organ dysfunction who respond to medical therapy and require early ERCP (<72 hours).

Patients admitted with a working diagnosis of cholangitis should be maintained on NPO status, goal directed fluid resuscitation should be performed, and broad-spectrum antibiotics should be started pending further evaluation with ERCP based on clinical response.

Goal directed fluid resuscitation should be administered with crystalloids (0.9% NS or LR) to goal HR<100, SBP>90 and UOP>0.5ml/kg/hr. Fluid boluses should be administered to accomplish these goals and then IV fluids should be administered at a rate of 3cc/kg/hr (stipulating cardiac function that can safely tolerate this infusion rate). Patients that require intense resuscitation should preferably be managed in an intensive care environment.

Broad spectrum antibiotics should be administered as outlined in Table 2. (Typically, Ceftriaxone 2 mg IV daily +/- metronidazole 500 mg po/IV q 8 hours, except for cases of severe infection, hospital acquired infection, or penicillin allergy.)

Gallstone Pancreatitis

For summary recommendations, see Key Points on page 2.

Discussion. Patients with predicted mild (Ranson criteria 3 or less) gallstone pancreatitis without cholangitis should undergo laparoscopic cholecystectomy with IOC within 48 hours. Early cholecystectomy within this group reduces the length of the hospital stay, and has not been shown to increase complications compared to delaying cholecystectomy until resolution of abdominal pain or normalization of laboratory values. Routine use of preoperative ERCP is not recommended for patients with mild gallstone pancreatitis. Approximately 25% of these patients have CBD stones, and selective postoperative ERCP is associated with shorter hospital stay and no increase in combined treatment failure rate when compared with routine preoperative ERCP. IOC should be performed in this group of patients to identify CBD stones. In patients with CBD stones, laparoscopic CBD exploration, intraoperative ERCP, and post-operative ERCP are appropriate options.

In patients with cholangitis and/or increasing bilirubin, preoperative ERCP should be considered. These patients have a higher risk of persistent choledocholithiasis and may more urgently require biliary decompression via ERCP. Those with mild gallstone pancreatitis that undergo ERCP, however, should still undergo cholecystectomy during the index admission. Delay of cholecystectomy in this group of patients is associated with a 14% risk of recurrent biliary events. Endoscopic sphincterotomy during ERCP reduces the risk of recurrent pancreatitis but not other biliary events.

This guideline is not intended to provide detailed treatment recommendations for acute pancreatitis. (For University of Michigan, more detailed recommendations can be found at: http://www.med.umich.edu/i/intmed/gi/rizk/pancmap/index.html)

Strategy for Literature Search

The literature search for this guideline was conducted in Medline prospectively using major key words: biliary colic, cholecystitis, cholangitis, choledocholithiasis, gallstone pancreatitis. The search was limited to human adults population, and published in the English language between January 2009 and June 2013.

Additional key words included: clinical protocols, physician practice patterns, algorithms, consensus development conferences, practice guidelines, guidelines, outcomes and process assessment (health care); clinical trials, controlled clinical trials, multicenter studies, randomized controlled trials, cohort studies, meta-analysis or meta-analysis; diagnosis, diagnostic use, sensitivity and specificity, false negative reactions, false positive reactions, likelihood functions, sensitivity, specificity; predictive value therapy, drug therapy, antibiotics, ultrasound, HIDA, CT, MRCP, choangiopancreatography, endoscopic ultrasound, cholangiography, cholangiogram, percutaneous cholecystostomy tube (PCT), biliary drainage tube, endoscopic retrograde, IOC.

The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent clinical trials known to expert members of the panel. The search was a single cycle. Conclusions were based on prospective randomized clinical trials if available, to the
exclusion of other data; if randomized controlled trials were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size.

Within the Cochrane Database of Systematic Reviews, 18 reviews were found using the strategy in the search strategies document.

**Related National Guidelines**

The literature search revealed 10 established national guidelines specifically addressing Gallstone-Related Diseases.

**Related National Performance Measures**

At this time no major national programs have clinical performance measures related to gallstone related diseases. These programs include: Centers for Medicare & Medicaid Services (Physician Quality Reporting Measures for Group Practice Reporting option, Clinical Quality Measures for financial incentive for Meaningful Use of certified Electronic Health Record technology), National Committee for Quality Assurance: Healthcare Effectiveness Data and Information Set, and programs in our region (Blue Cross Blue Shield of Michigan: Physician Group Incentive Program clinical performance measures, Blue Care Network: clinical performance measures).

**Disclosures**

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

No team members reported conflicts of interest.

**Review and Endorsement**

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Health System to which the content is most relevant: Emergency Medicine, Family Medicine, General Medicine, Infectious Disease, Gastroenterology, and Radiology. Medication recommendations were reviewed by the Pharmacy and Therapeutics Committee. The final version was endorsed by the Clinical Practice Committee of the University of Michigan Faculty Group Practice and the Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers.
Appendix A:

Referral to the University of Michigan Health System’s Priority Patient Gallbladder Clinic

The University of Michigan Health System has established a clinic with the purpose of accommodating gallbladder patients’ surgeries within two weeks. Text from the promotional materials (below) lists criteria for referral, as well as specific information regarding the process of referral.

The Priority Patient Gallbladder Clinic is prioritizing gallbladder patients to guarantee surgery within two weeks.

Consider directing patients to the U-M Priority Patient Gall Bladder Clinic if they meet the following:

- BMI<40
- Are able to climb a flight of stairs or walk a city block without stopping or shortness of breath
- Are not currently taking blood thinners or Suboxone
- Do not have an implanted cardiac device
- Do not have any significant cardiac disease
- Have not had a seizure in the past 6 months
- Have not had a stroke or TIA in the past six months
- Do not have severe pulmonary disease
- Are not pregnant
- Have not been admitted to the hospital in the PAST year for cardiac or breathing issues

For a consult or referral call: 734-936-5738* or M-LINE (800-962-3555)

* The department will also continue to see patients who do not meet these criteria within two weeks in the General Surgery Clinic.
References