Aetiology, diagnosis and management for ischaemic cholecystitis: current perspectives

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ABSTRACT

In the absence of gallstones or any other form of mechanical obstruction, hypoperfusion to the gallbladder can lead to inflammation, ischaemia and perforation. This constellation of findings has historically been simply referred to as ‘acalculous cholecystitis’. However, this term makes no distinction between inflammation due to critical illness and poor perfusion, or what we will refer to as ischaemic cholecystitis, versus other non-obstructive aetiologies. Ischaemic cholecystitis presents diagnostic as well as treatment challenges that are unique to patients in the critical care setting. More importantly, the morbidity and mortality of this proposed subcategory of acute gallbladder inflammation is much higher compared with other forms of acute cholecystitis. In the present manuscript, we introduce the concept of ischaemic cholecystitis and the importance of differentiating this clinical diagnosis from other forms of acalculous cholecystitis. Additionally, we elaborate on the most recent diagnostic modalities and treatment options specific to this vulnerable patient population.

INTRODUCTION

Cholecystitis broadly describes inflammation of the gallbladder tissue and cystic duct. Most frequently this inflammation occurs from an obstructive process involving the cystic duct; this could be secondary to cholelithiasis or external compression. Cholecystitis may also result when inflammation of the gallbladder occurs in the absence of gallstones or another form of external compression, and instead emanates from a systemic process. Specifically, we propose to refer to this non-obstructive cause of cholecystitis as ‘ischaemic cholecystitis’, with emphasis on the unique clinical setting, diagnosis, management and prognosis for this patient population.

Obstructive cholecystitis

Traditionally, the distinction between the various forms of cholecystitis is primarily based on diagnostic imaging identifying gallstones (or external compression in rare circumstances). However, the absence of gallstones on diagnostic imaging does not equate to a diagnosis of non-obstructive cholecystitis for all circumstances. The rate of false-negative sonographic findings when assessing for gallstones is approximately 1%–4%. For instance, small gallstones (<4 mm) or gallstones in the presence of bile sludge or polyps were described in the setting of false-negative sonographic findings. Moreover, for select cases of gas-containing gallstones, the only evidence of their existence on diagnostic imaging is the visible pocket of air making diagnosis challenging. For our institutional practice, we have had approximately 2% of patients present with a classical clinical history consistent with acute obstructive cholecystitis and negative sonographic evidence of gallstones. Despite this initial clinical presentation, gallstones were identified in the operating room or on final pathological examination. Thus, to accurately define non-obstructive or acalculous cholecystitis, a pathological diagnosis excluding gallstones is optimal. Furthermore, clinical history consistent with biliary colic cannot be overlooked in the setting of negative diagnostic imaging.

Non-obstructive cholecystitis

Non-obstructive cholecystitis is an uncommon cause of cholecystitis and accounts for <10% of all diagnoses of cholecystitis in adults. In contrast to the diagnosis of obstructive cholecystitis, which is commonly reliant on patient history and imaging findings, the diagnosis of non-obstructive cholecystitis is dependent on the clinical setting (table 1).

Pathophysiology: hypoperfusion

While the pathophysiology of non-obstructive cholecystitis is not fully understood, it is separate from that of a mechanical obstruction of the cystic duct. In the setting of the typical patient who is critically ill with a hypovolemic state (eg, prolonged absence of oral nutrition, systemic hypotension, decreased cardiac output), the pathophysiology is suspected to originate from poor perfusion to gallbladder
This is evidenced by a study comparing the vasculature in gallbladder specimens post-cholecystectomy, containing stones versus those that did not. Notably, the gallbladder microangiography in the setting of stones showed dilated arterioles with regular filling patterns whereas the microangiography for gallbladder specimens without stones were noted to have irregular vascular filling with areas of poor perfusion. The associated inflammatory response produces mucosal oedema which is accompanied by decreased gallbladder contractility. Bile stasis, increased bile viscosity and increased intraluminal pressure ensue. Biliary stasis along with continued hypoperfusion cause ischaemia and concomitant bacterial colonisation, which leads to cholecystitis. Cholecystitis will likely cause fever and leukocytosis; however, because critically ill patients have multiple medical problems, gallbladder pathology as the cause of fever and leukocytosis might not be the first source clinicians focus on. Furthermore, in the setting of a critically ill patient where there is an absence of patient-derived complaints and a diminished response to physical examination that would reliably identify right upper quadrant tenderness, a diagnosis of cholecystitis may go undetected. If identification of cholecystitis remains unidentified, necrosis and gallbladder wall perforation may develop.

Gallbladder ischaemia as an aetiology for non-obstructive cholecystitis derives from the association that patients with this diagnosis present in the setting of critical illness from sepsis, cardiogenic or hypovolemic shock, trauma, large surface area burns (>30%) or after major surgeries such as exploratory laparotomies. Furthermore, the cystic artery is a terminal artery with limited collateral blood flow and thus highly susceptible to ischaemia.

Pathophysiology: non-obstructive, non-ischaemic cholecystitis

Non-obstructive cholecystitis has been diagnosed in select cases that are not consistent with hypoperfusion or ischaemia but similarly do not appear to be related to a mechanical obstruction. These include non-obstructive cholecystitis in the setting of (1) prolonged fasting states or those receiving total parenteral nutrition (TPN), (2) biliary vasculitis for individuals with autoimmune conditions (eg, systemic lupus erythematosus, Kawasaki disease), (3) infectious processes for immunocompromised individuals (eg, AIDS) or (4) symptomatic gallbladder calcifications commonly known as ‘porcelain gallbladder’. These patients have been classically diagnosed with acalculous cholecystitis; however, they clinically behave differently and have a substantially better prognosis than patients diagnosed with acalculous cholecystitis in the intensive care unit (ICU) setting (ischaemic cholecystitis). For these rare clinical scenarios such as biliary vasculitis or gallbladder specimens containing opportunistic microorganisms, patients present in a non-critical care setting where patient history and symptomatology are instrumental in narrowing a diagnosis to pathology within the hepatobiliary tree. Furthermore, the appropriate treatment modalities align with those for a patient who presents with obstructive cholecystitis from gallstones. This argument further validates the need to distinguish ischaemic cholecystitis from these other clinical scenarios of non-obstructive cholecystitis described above. Because other causes of acalculous cholecystitis outside of the ICU setting are uncommon, for all practical purposes it is best for a clinician to focus on obstructive cholecystitis and ischaemic cholecystitis.

Ischaemic cholecystitis

While cholecystitis in the absence of gallstones may result from a variety of pathophysiological processes, the most consequential form for clinical practice is the one that occurs from gallbladder ischaemia in the setting of a critically ill patient with other comorbidities (eg, systemic hypoperfusion, polytrauma). These patients have a substantially worse prognosis than obstructive cholecystitis and mortality has ranged as high as 50%. Thus, it is important that this patient population be labelled differently from other less consequential non-obstructive processes such as biliary stasis or autoimmune conditions or from those whose stones are simply not visualised by imaging on initial presentation. To eliminate ambiguity, the most appropriate term for this patient population is ‘ischaemic cholecystitis’. Thus, a patient who walks into the emergency room whose stones are not visualised by diagnostic imaging, will not carry a diagnosis of ischaemic cholecystitis.
Distinguishing ischaemic cholecystitis from other forms of acalculous cholecystitis is important because it affects patients in critically ill states or patients who suffer from chronic conditions. Ultimately, introducing the concept of ischaemic cholecystitis can be beneficial because it reshapes the framework in which obstructive and non-obstructive biliary pathology can be assessed, treated and followed. Ischaemic cholecystitis will be the focus for the discussion below as the patient cohort afflicted by this condition is unique, have obscure clinical presentations, require ancillary diagnostic modalities along with a high degree of suspicion and typically necessitate different therapeutic interventions compared with patients with obstructive cholecystitis from gallstones.

**CLINICAL PRESENTATION**

Consistent with the pathophysiology of ischaemic cholecystitis, the cohort affected by this condition are patients who are critically ill, admitted to the ICU and suffering from low-flow states (eg, sepsis, multiorgan failure, polytrauma, low cardiac output, large surface area burns). Fever and leukocytosis are common signs for patients admitted to the ICU and may be reflective of a variety of underlying pathologies that prompt clinicians to entertain a wide differential diagnosis. The absence of a reliable physical examination for this cohort does not exclude its pivotal necessity as patients may have infectious processes (eg, soft tissue infections, peri-anal abscesses) that can be identified during examination and subsequently addressed. However, physical examination is unlikely to direct clinicians towards a diagnosis of ischaemic cholecystitis. Thus, after common sources of infection have been addressed (eg, pulmonary, urinary, indwelling venous catheters), clinicians should rapidly entertain the possibility of intra-abdominal processes such as ischaemic cholecystitis. When considering intra-abdominal pathology, clinicians may obtain additional laboratory studies such as liver function tests or inflammatory markers; however, aberrations of these values are common for patients admitted to the ICU with sepsis and are frequently non-diagnostic for ischaemic cholecystitis.

While any patient admitted to the ICU with unexplained fever and leukocytosis should prompt consideration of ischaemic cholecystitis as the underlying cause, certain patient factors make the diagnosis more likely. For example, the development of ischaemic cholecystitis for critically ill polytrauma patients has been well established. In one of the earliest reports linking major trauma to ‘acalculous cholecystitis’, Lindberg *et al* reported that out of 2412 patients admitted to US Air Force Hospital, Clark Air Base, in the Philippines during the Vietnam War, 12 developed signs and symptoms of acute cholecystitis within 10–35 days after their injury.11 For all 12 patients, surgical findings confirmed acute cholecystitis without gallstones. All 12 patients described in this series had significant extremity trauma (eg, fracture or amputation), 7 had injuries to major blood vessels and 8 suffered abdominal trauma requiring laparotomy prior to their diagnosis of cholecystitis.11 Another series reported 5 out of 1386 patients admitted after experiencing major trauma developed ‘acalculous cholecystitis’ ranging from 9 to 58 days after admission.30 A case series presented by Orlando *et al* describes 11 cases consistent with ischaemic cholecystitis diagnosed in the ICU from 1980 to 1982.18 For 9 out of 11 patients with available pathological review, 4 were admitted to the ICU after major abdominal surgery; 3 after cardiovascular operations and 2 after major trauma. Authors argue that hypotension was likely central in the formation of gallbladder ischaemia and subsequent inflammation in these patients.18 More recently, Franch-Llasat *et al* reported 3 cases of ‘acalculous cholecystitis’ diagnosed in patients who were admitted to the ICU for acute respiratory distress syndrome secondary to COVID-19 infection.21 Of note, all three patients were diagnosed with ‘acalculous cholecystitis’ after being discharged from the ICU (2, 12 and 20 days after discharge), highlighting that there may be a delay in the manifestation of ischaemic cholecystitis after a critical illness.

Previous series have failed to identify specific risk factors that predispose patients to a diagnosis of ischaemic cholecystitis.20 Instead, preceding patient-related factors such as hypotension, thermal injury, sepsis, mechanical ventilatory support, opioid use, male sex, blood transfusions, prolonged fasting and TPN administration have been described as characteristics present among those who were ultimately diagnosed with ischaemic cholecystitis.2 19 20 22 While non-specific, the presence of one or multiple of these factors in a patient admitted to the ICU with unexplained fever and leukocytosis should raise suspicion for ischaemic cholecystitis as a potential culprit and prompt further investigation and diagnostic imaging to ascertain if this pathology is present.

**DIAGNOSTIC MODALITIES**

**Ultrasoundography**

Ultrasoundography is an effective and accurate imaging modality that can be used as the initial option to assess ischaemic cholecystitis. Sonography is a non-invasive modality and easily transportable diagnostic tool, and ultrasonographic evaluation of the gallbladder is accurate in determining gallbladder wall thickness.23 Its practicality is especially useful in the evaluation of patients in the ICU, for whom transport to a CT scanner may be challenging. Ultrasound findings that are predictive of ischaemic cholecystitis have been categorised into major and minor criteria (table 2).2 23 24 Diagnosis is typically made in the presence of two major criteria or one major and two minor criteria.2 There are some limitations to ultrasonography as a diagnostic tool for ischaemic cholecystitis. Ultrasound technology is user dependent. Sonography might also be of limited diagnostic yield in patients with severe obesity. Additionally, ultrasound evaluation may be non-specific in the critical care setting because
gallbladder abnormalities (eg, gallbladder sludge, gallbladder distention, wall thickening) have been frequently found in this patient population; even in patients who are not suspected of having ischaemic cholecystitis. Thus, for critically ill patients with clinical concern for potential ischaemic cholecystitis, ultrasound assessment is a good first test to perform. The results may unequivocally confirm your suspicion (ie, presence of intramural gas indicating gangrenous cholecystitis) and lead clinicians to discuss subsequent management strategies. For ambiguous ultrasound findings (eg, significantly distended gallbladder seen without other findings), additional diagnostic modalities may be required to confirm or exclude a diagnosis of ischaemic cholecystitis.

**Computed tomography**

The ubiquitous use of cross-sectional imaging in today’s medical landscape, especially for the population susceptible to ischaemic cholecystitis, lends itself to being a form of diagnostic imaging for this pathology. Because acalculous cholecystitis is frequently encountered in the critical care setting, patients will often undergo CT as part of the workup for any deterioration in clinical status as it allows for visualisation of the entire abdomen and pelvis. CT can also supplement ultrasonography in cases where ultrasound evaluation is difficult to obtain, such as in patients with morbid obesity or in the presence of a significant amount of abdominal intestinal gas. Gangrenous cholecystitis and emphysematous cholecystitis have unique findings on dynamic CT that may not always be as evident with ultrasonographic evaluation. These findings include: irregular gallbladder wall thickening, poor contrast enhancement of gallbladder wall, increased fat density of fatty tissue surrounding the gallbladder, gas within the gallbladder lumen or wall, membranous structures within the gallbladder lumen and abscess surrounding the gallbladder. One of the major limitations of CT is that it requires transportation of the patient to the scanner. This may be difficult for patients who are in the ICU. While CT may not be the initial radiographic test to obtain, it is an imaging modality that can be important in the critical care setting.

**Hepatobiliary iminodiacetic acid cholescintigraphy**

Hepatobiliary iminodiacetic acid (HIDA) cholecintigraphy is considered the gold standard for diagnosing cholecystitis and it is pivotal in providing a definitive diagnosis for patients with ischaemic cholecystitis prior to proceeding with treatment or intervention. However, HIDA is not typically the first diagnostic imaging test to obtain when the diagnosis of ischaemic cholecystitis is suspected; the initial imaging test continues to be ultrasonography. HIDA involves intravenous injection of technetium-99m labelled HIDA, which becomes integrated into bilirubin metabolism and subsequently excreted into the biliary tree making it useful in visualising hepatobiliary anatomy via scintigraphy. Adjuncts may be given, such as morphine (ie, promotes sphincter of Oddi constriction and thus bile preferentially travels to the gallbladder vs the duodenum), fatty meals (stimulates gallbladder emptying/contraction), cholecystokinin (stimulates gallbladder emptying) or time (periods of latency if slow transit is present) to assist the performance of a HIDA scan by encouraging biliary tree function. When there is an obstruction and/or dysfunction of this process, a HIDA image is considered positive. When there is increased bile viscosity, decreased smooth muscle contractility and increased intraluminal pressure, as is the case in ischaemic cholecystitis, radiotracer entrance and thus visualisation of the gallbladder is not achieved, thereby yielding a positive examination.

The major disadvantage to HIDA cholescintigraphy is that its performance is challenging in critical care settings. HIDA imaging is a dynamic process—there are repetitive periods of latency while awaiting action of administered pharmacologics and may also require patient mobilisation into supine, decubitus and upright positions. Of note, false positive rates of up to 40% have been reported when performed for non-selective patients with critical illness; this supports the notion that in order
to maximise HIDA’s utility as a diagnostic tool it must be performed in the right clinical setting. One series investigated the diagnostic accuracy of ultrasonography followed by morphine cholescintigraphy in the setting of critically ill patients (n=28) with concern for ‘acalculous cholecystitis’ or unexplained sepsis. This study reported a morphine cholescintigraphy specificity of 100% for this cohort. Recognising feasibility, costs and setting, the authors recommended sonography as a screening modality supplemented by cholescintigraphy for patients with suspected ischaemic cholecystitis. In cases where there is disagreement between these two modalities, specifically when sonography is positive and cholescintigraphy is negative, clinicians must rely on other clinical data and/or repeat imaging at intervals.

BEST MANAGEMENT PRACTICES

Antibiotic treatment

According to the most recent iteration of the Tokyo Guidelines, antibiotic use for patients with acute cholecystitis is important for three primary reasons: to mitigate systemic septic response and local inflammation, to prevent surgical site infections and to prevent intrahepatic abscess formation. The most common Gram-negative bacteria found in acute biliary tract infections include *Escherichia coli*, *Klebsiella* and *Pseudomonas*, whereas the most common Gram-positive organisms are *Enterococcus* and *Streptococcus*. While local antimicrobial susceptibility data play a role in antibiotic choice, recommendations from the most recent version of the Tokyo Guidelines incorporate a grade system that accounts for infection severity and whether infection is hospital versus community acquired (table 3). Grades I, II and III acute cholecystitis are defined as mild, moderate and severe cholecystitis, respectively. Typical prophylactic antibiotic regimens for patients with acute cholecystitis (calculous, acalculous or ischaemic) or acute cholangitis are either piperacillin or cephalosporin based and are represented in table 3. Additional antimicrobial agents including carbapenems, monobactams, fluoroquinolones and vancomycin may be necessary depending on the clinical setting, patient allergies, local antimicrobial resistance patterns and patient colonisation. Recommendations regarding duration of antibiotic therapy are also based on grade severity. If bacteraemia with Gram-positive cocci is encountered during the clinical course, antibiotic treatment duration of minimum of 14 days is recommended. This extended course differs from that of Gram-negative bacteria, as Gram-positive microorganisms (eg, *Enterococcus* and *Streptococcus*) are associated with infective endocarditis. The typical patient scenario for a diagnosis of ischaemic cholecystitis is consistent with grade III severity and hence, we advocate for following this broad regimen.

Non-surgical interventions

After initiating resuscitation and antibiotic administration, source control of the ischaemic gallbladder tissue is paramount. For this cohort, source control most commonly comes in the form of temporary gallbladder drainage. Gallbladder drainage procedures represent a quick and minimally invasive alternative to cholecystectomy for critically ill patients. These approaches have been shown to be an effective method of decompressing the gallbladder and thereby reducing inflammation and minimising bacterial overgrowth. Multiple studies have demonstrated the outcome benefits of drainage procedures versus immediate cholecystectomy for critically ill patients, including decreased morbidity, fewer ICU admissions, decreased hospital length of stay and lower patient costs. There are currently two primary drainage procedures employed for patients diagnosed with ischaemic cholecystitis and deemed to be poor surgical candidates: percutaneous transhepatic gallbladder drainage (PTGD) and endoscopic drainage, which can be done via a transpapillary or transmural approach.

### Table 3 Antibiotic grade system

<table>
<thead>
<tr>
<th>Grade</th>
<th>Clinical setting</th>
<th>Antibiotic regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Otherwise, healthy patient, no end-organ dysfunction</td>
<td>Ampicillin-sulbactam* or Cefazolin+metronidazole</td>
<td>Discontinue 24 hours post-cholecystectomy</td>
</tr>
<tr>
<td></td>
<td>Leukocytosis &gt;18,000/mm³, palpable right upper quadrant mass, symptom duration &gt;72 hours, marked inflammatory changes (abscess or emphysematous changes)</td>
<td>Piperacillin/Tazobactam or Ceftriaxone+metronidazole</td>
<td>Discontinue 24 hours post-cholecystectomy</td>
</tr>
<tr>
<td>II</td>
<td>End-organ dysfunction present (eg, hypotension, decreased mentation, renal dysfunction)</td>
<td>Piperacillin/Tazobactam† or Cefepime+metronidazole†</td>
<td>Continue for 4–7 days after source control†</td>
</tr>
</tbody>
</table>

Adapted from Tokyo Guidelines. *For grade I, ampicillin-sulbactam therapy should not be used if local resistance rate is >20%.
†Also serves as antibiotic treatment for hospital-acquired biliary tract infections.
‡Recommendations for Gram-positive bacteraemia may extend up to a 14-day course.
Percutaneous transhepatic gallbladder drainage

Recent guidelines regarding the management of acute cholecystitis recommend PTGD as the first alternative to surgical intervention for surgically high-risk patients.\(^{32}\) This intervention is overall less invasive, technically less demanding (technical success rate of 95%) and associated with fewer adverse events when compared with laparoscopic or open cholecystectomy in this setting.\(^{32,33}\) Nonetheless, complications from PTGD occur at a non-negligible rate (approximately 14%) and include bleeding, biliary peritonitis, pneumothorax and accidental catheter dislodgement.\(^{33}\) Given that PTGD is not a definitive management strategy, the potential for recurrence exists. For all-comers with cholecystitis, the rate of recurrence after catheter removal has been estimated to be as high as 33%.\(^{33,34}\) To our knowledge, only a handful of retrospective studies and case series have reported cholecystitis recurrence rates for patients who had PTGD for ‘acalculous cholecystitis’ specifically (table 4).\(^{35-41}\) For these patients, reported recurrence rates were low and ranged from 0% to 17%.\(^{35-42}\) Ultimately, PTGD may be viewed as an effective and safe initial intervention to achieve source control for critically ill patients diagnosed with ischaemic cholecystitis. While its role as a definitive treatment is still debated, the use of PTGD as a temporising procedure before definitive cholecystectomy is well established.

Table 4 Summary of published studies reporting outcomes for various treatments for acute cholecystitis, focusing primarily on acalculous forms of this disease

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial treatment modality</th>
<th>N</th>
<th>Mortality (%)</th>
<th>Recurrence rate (%)*</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shirai et al(^{42})</td>
<td>PC</td>
<td>15</td>
<td>0</td>
<td>0 (0/13)</td>
<td>PC is safe, effective and usually definitive for AAC.</td>
</tr>
<tr>
<td>Sugiyama et al(^{35})</td>
<td>PC</td>
<td>13</td>
<td>8</td>
<td>0 (0/12)</td>
<td>PC is a safe and effective treatment for cholecystitis in elderly patients with high-risk comorbidities.</td>
</tr>
<tr>
<td>Chung et al(^{36})</td>
<td>PC</td>
<td>57</td>
<td>21</td>
<td>7 (2/28)</td>
<td>PC is an effective alternative option for patients with AAC who are deemed unfit for surgery.</td>
</tr>
<tr>
<td>Simorov et al(^{31})</td>
<td>OC</td>
<td>199</td>
<td>2†</td>
<td>–</td>
<td>PC yields superior outcomes for critically ill patients with AAC.</td>
</tr>
<tr>
<td></td>
<td>LC</td>
<td>822</td>
<td>.</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PC</td>
<td>704</td>
<td>3</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Kirkegård et al(^{37})</td>
<td>PC</td>
<td>56</td>
<td>11</td>
<td>17 (8/46)</td>
<td>PC is definitive treatment option for AAC.</td>
</tr>
<tr>
<td>Noh et al(^{40})</td>
<td>PC</td>
<td>271</td>
<td>35</td>
<td>2 (2/88)</td>
<td>PC can be a definitive treatment option for the majority of patients with AAC.</td>
</tr>
<tr>
<td>Abbas et al(^{45})</td>
<td>LC</td>
<td>3</td>
<td>30‡</td>
<td>6 (2/30)</td>
<td>It is safe to avoid an interval cholecystectomy for AAC.</td>
</tr>
<tr>
<td></td>
<td>PC</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abx only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ozyer(^{41})</td>
<td>PC</td>
<td>75</td>
<td>9</td>
<td>13 (6/47)</td>
<td>PC may be a definitive treatment option for AAC in the majority of high-risk patients.</td>
</tr>
<tr>
<td>Kim et al(^{32})</td>
<td>OC/LC</td>
<td>48</td>
<td>0</td>
<td>–</td>
<td>Non-surgical treatment of AAC was not inferior to surgical treatment.</td>
</tr>
<tr>
<td></td>
<td>PC</td>
<td>14</td>
<td>0</td>
<td>14 (2/14)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Abx only</td>
<td>27</td>
<td>0</td>
<td>7 (2/27)</td>
<td></td>
</tr>
<tr>
<td>Chen et al(^{38})</td>
<td>PC for AAC</td>
<td>84</td>
<td>45</td>
<td>8 (2/24)</td>
<td>Recurrent cholecystitis after PC is rare for patients with AAC and interval cholecystectomy may not be required.</td>
</tr>
<tr>
<td></td>
<td>PC for ACC</td>
<td>85</td>
<td>21</td>
<td>16 (5/31)</td>
<td></td>
</tr>
</tbody>
</table>

*Results represent known patients eligible for recurrence (ie, those that had not transitioned to another treatment modality or those known to be alive).†All patients began with LC with a 27% conversion rate to OC; LC patients had significantly lower mortality compared with OC patients.‡Study describes the majority of deaths occurred in the Abx-only group.

AAC, acute acalculous cholecystitis; Abx, antibiotics; ACC, acute calculous cholecystitis; LC, laparoscopic cholecystectomy; OC, open cholecystectomy; PC, percutaneous cholecystostomy.

Endoscopic drainage

Utilisation of endoscopic techniques to achieve gallbladder drainage for patients with ischaemic cholecystitis (or ‘acalculous cholecystitis’) is a more recently developed approach. Endoscopic transpapillary gallbladder drainage (ETGD) is one such example and this technique is performed via endoscopic retrograde cholangiopancreatography.\(^{42,43}\) Data from multiple studies (randomised
controlled trials, observational studies, systematic reviews, case studies) regarding management strategies for gallbladder drainage for patients with acute cholecystitis (from all aetiologies) have been summarised in the most recent version of the Tokyo Guidelines. The results have shown no statistically significant difference between ETGD and PTGD with regard to technical success rate, clinical success rate and frequency of adverse events.32 The major downside of ETGD is that it involves complex techniques and requires specialised equipment, both of which are only likely to be available at high-volume academic centres.33 These limitations are likely why ETGD approaches have not become as widely adopted as PTGD. Endoscopic ultrasound gallbladder drainage (EUS-GD) is a third option for minimally invasive alternatives to laparoscopic or open cholecystectomy for patients with acute cholecystitis. First introduced in 2007, this procedure can be performed under conscious sedation and consists of creating a cholecystoenterostomy or cholecystogastrostomy and placing either a self-expanding metal stent or a lumen apposing metal stent between the gallbladder and the bowel lumen.33 Pooled technical and clinical success rates for this technique, regardless of stent type, are >90% and adverse event rates are 9.9% and 12.3% for lumen apposing metal stents and self-expanding metal stents, respectively.33 When compared with PTGD and ETGD, EUS-GD has demonstrated equal, if not superior, results with regard to technical success, clinical success and adverse event rate.33 However, the clinical application of EUS-GD in the setting of ischaemic cholecystitis remains limited as this type of procedure is mainly performed at specialised centres with appropriately trained staff and access to equipment. Depictions of these minimally invasive techniques are represented in figure 1 and pooled outcomes are represented in table 5. It is important to acknowledge, however, that these results regarding the use of advanced endoscopic interventions include all-comers experiencing acute cholecystitis; nonetheless, these new strategies may be options for patients with ischaemic cholecystitis.

**Surgery**

Cholecystectomy is the definitive management for patients with cholecystitis. Cholecystectomy, whether open, laparoscopic, or robotic, is best deferred for a time when the patient’s operative risk is deemed appropriate and therefore tends to follow temporising gallbladder drainage procedures for patients with ischaemic cholecystitis.34 Some data suggest that interval cholecystectomy after minimally invasive interventions may not always be necessary for all instances of ischaemic cholecystitis. A retrospective analysis by Abbas et al demonstrated that treatment with antibiotics and/or cholecystostomy were a viable option as a definitive management strategy for 33 patients with ‘acalculous cholecystitis’ who were followed for a median of 18 months after their initial diagnosis.45 Of the 33 patients in this series, 2 developed recurrent ‘acalculous cholecystitis’. Similar results were reported from an institutional series assessing outcomes of surgical (n=48) vs non-surgical (n=41) management for 89 patients diagnosed with ‘acalculous cholecystitis’ from 2007 to 2014.31 Non-surgical patients were followed for

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**Management Strategies for Ischaemic Cholecystitis**

<table>
<thead>
<tr>
<th>Percutaneous transhepatic gallbladder drainage</th>
<th>Endoscopic retrograde cholangiopancreatography</th>
<th>Endoscopic ultrasound gallbladder drainage</th>
<th>Cholecystectomy</th>
</tr>
</thead>
</table>

- **Minimally invasive options for critically ill patients**
  - Most common initial intervention
  - Technical success rate of 95%
  - Adverse event rate ≤ 14%
  - Similar technical success rate to PTGD
  - Technically more complex
  - Requires specialized centers
  - Technical success rate > 90%
  - Technically more complex
  - Requires specialized centers
  - Rarely performed as initial management
  - Interval cholecystectomy after initial gallbladder drainage is case specific

**Figure 1** Management strategies for ischaemic cholecystitis. PTGD, percutaneous transhepatic gallbladder drainage.
a median of 5.7 years and there were 4 recurrences of cholecystitis. While surgical removal of the gallbladder has been the mainstay for all forms of cholecystitis, the patient population affected by ischaemic cholecystitis continue to be high-risk surgical candidates beyond their initial diagnosis. Therefore, the decision to pursue an interval cholecystectomy must balance patients’ perioperative risk and the time-related risk of recurrence, which may ultimately mean deferral of surgery indefinitely.

CONCLUSION
Gallbladder inflammation is a common pathology encountered by general surgeons and gastroenterologists; most commonly this occurs secondary to the presence of stones, however many other aetiologies have been described. Cholecystitis in the setting of critical illness in a patient with systemic signs of insufficient end-organ perfusion and no evidence of gallbladder stones is the most consequential and presents unique challenges to clinicians. For these reasons, we believe ischaemic cholecystitis is a more accurate term to describe this pathophysiology, convey clinical severity and adequately distinguish this entity from other forms of non-obstructive cholecystitis. Creating this distinction is an important step towards being able to guide clinical and surgical management. While many of the initial steps in management, including resuscitation and antibiotic treatment, remain the same for all forms of cholecystitis, knowing the underlying aetiology in combination with the patient’s clinical status direct the choice of intervention to address the acutely inflamed gallbladder—surgery, percutaneous drainage or endoscopic drainage. We hope that by introducing this new framework of thinking about gallbladder disease in the critically ill, clinicians will be able to recognise predisposing factors, take definitive steps towards diagnosis and ultimately provide the best treatment for this challenging clinical presentation.

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REFERENCES

Table 5 Results related to non-surgical interventions for acute cholecystitis

<table>
<thead>
<tr>
<th>Treatment modality</th>
<th>Technical success rate (%)</th>
<th>Adverse event rate (%)</th>
<th>Recurrence rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percutaneous transhepatic gallbladder drainage</td>
<td>≥95</td>
<td>≤14</td>
<td>≤33</td>
</tr>
<tr>
<td>Endoscopic transpapillary gallbladder drainage</td>
<td>≥78</td>
<td>≤17</td>
<td>≤7</td>
</tr>
<tr>
<td>Endoscopic ultrasound-guided gallbladder drainage</td>
<td>≥90</td>
<td>≤18</td>
<td>≤5</td>
</tr>
</tbody>
</table>

Results include a combination of all aetiologies of cholecystitis.


