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Management of acute cholecystitis and acute cholangitis in emergency setting

Review Article

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Abstract: Acute biliary infection (acute cholecystitis and acute cholangitis) is one of the common emergency conditions which carries significant morbidity and mortality. The risk factors are often associated with gallstones, biliary stasis and bile infection. Gram-negative bacteria are frequent isolates from bile and blood cultures in infectious cholangitis. Endotoxaemia from the gram-negative microbes results in circulatory shock and organ dysfunction. Therefore, prompt diagnosis with severity stratification and recognition of its potential rapid progression to life-threatening shock and multi-organ failure ensure execution of the three fundamental interventions in the initial management strategy, namely: resuscitation to support the organ, antimicrobial therapy and biliary decompression drainage to control the infection. This is the core principle in the management of severe acute cholangitis.

Keywords: *Acute cholangitis • Acute cholecystitis • Emergency • Management*

1. Acute cholecystitis and cholangitis

Acute cholecystitis is an acute inflammatory disease of the gallbladder commonly secondary to the presence of gallstones. 90-95% of acute cholecystitis is due to gallstones while 5-10% are secondary to acalculus cholecystitis [1-4]. Other rare causes include ischaemia, motility disorder, microbial infections.

Patients with symptomatic gallstones may progress to severe acute cholecystitis complicated by edematous cholecystitis, emphysematous cholecystitis, necrotizing cholecystitis and suppurative cholecystitis or gallbladder empyema [5,6]. The degree and duration of obstruction as well as the presence of infection determine the severity of the disease [7]. Co-morbidity and medications are the other factors. For instance, diabetic patients are at higher risk for acute gangrenous cholecystitis [8].

Acute cholangitis is an acute condition with inflammation and infection of the biliary tract. In 1877, Charcot first described the Charcot's triad – a clinical pattern with intermittent fever accompanied by chills and rigor, right upper abdominal pain and jaundice. About 50-70% of the patients with acute cholangitis present with Charcot's triad [9]. Later, in 1959, Reynolds and Dragan described a syndrome consisting of fever, jaundice, abdominal pain, mental confusion or lethargy and shock [10]. They called it Reynold's pentad with the underlying pathology of acute obstructive cholangitis. Longmire described these two conditions as acute suppurative cholangitis and acute obstructive suppurative cholangitis [11]. They are associated with increased morbidity and mortality [12]. On the other hand, Boey and Way analysed 99 cases of cholangitis and found that biliary

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suppuration did not correlate well with the clinical manifestation of severe cholangitis [13]. Moreover, acute cholangitis or infectious cholangitis can occur in the absence of biliary obstruction.

The common etiology for acute cholangitis includes choledocholithiasis, biliary strictures, hepatolithiasis (in East Asia), cholangiocarcinoma or pancreatic carcinoma, occluded endobiliary stent or biliary parasitic infestation [14,15]. Others include iatrogenic causes (Endoscopic Retrograde Cholangio- pancreatography [ERCP] or percutaneous transhepatic cholangiography) and primary sclerosing cholangitis.

The presentation of these two acute conditions varies from mild biliary colic to critically ill patients with septicaemic shock. This review will emphasize on the management of moderate and severe acute cholecystitis and severe acute cholangitis in an emergency setting, i.e. during the first 72 to 96 hours following admission to the hospital. Definitive management of the underlying pathology and surgical techniques are not within the scope of this review.

2. Clinical approach in emergency setting

The approach to acute cholecystitis and cholangitis follows the principles of first haemodynamics stabilization of patients, then establish the diagnosis and assess the severity of the condition prior to treatment planning. The algorithm consists of parallel tracks of both antimicrobial treatment arm and interventional arm for source control. The mainstay in the control of biliary infection centers on effective systemic antibiotics with biliary decompression and drainage. Sound clinical judgment in sequencing and timing of these therapeutic activities has significant impact on the clinical outcome.

3. Diagnosis of acute cholecystitis

3.1. Acute cholecystitis

Acute cholecystitis is diagnosed clinically in patients with acute onset of right upper abdominal pain associated with fever and nausea. Localized abdominal tenderness and rebound with positive Murphy's sign may be presence. Occasionally, the distended gallbladder is palpated. Patient with perforated gallbladder and bile peritonitis may have signs of peritonism.

In the process of diagnosing acute cholecystitis, the differential diagnoses to consider are perforated duodenal ulcer, acute pancreatitis, right pyelonephritis, liver abscess and hepatitis. It must be emphasized that elderly patients, patients with long-standing history of diabetes mellitus, steroid medication and immune-compromised patients may not have the full display of clinical symptoms and signs. In this group of patients, high index of clinical suspicion for acute cholecystitis is crucial.

When acute cholecystitis is complicated by empyema gallbladder, the clinical presentation may mimic acute cholangitis. Patient may appear toxic with clinical jaundice. White blood cells count and liver enzymes are elevated. Conversely, in a healthy and stoic individual with empyema gallbladder completely localized by omentum, the clinical signs may not be informative. The detection of gram-negative bacteria in blood culture should alert the clinician of the possibility of empyema gallbladder even when there are paucity of symptoms and signs for acute cholecystitis.

3.2. Acute cholangitis

A patient with acute cholangitis may deteriorate rapidly and progress to life- threatening critical condition [16]. This underscore the importance of early diagnosis based on initial clinical and laboratory assessment. The diagnosis is clear-cut when patients presents with Charot's triad and Reynold's pentad, however some patients may not manifest all the symptoms and signs [17]. Clinical acuity with high index of suspicion should be exercised for high risk patients.

The clinical strategy should be disease's severity based. It is also important to distinguish between acute cholangitis and acute cholecystitis. Occasionally, both conditions can co-exist in acute biliary infection. Acute pancreatitis may occur in the presence of acute cholangitis.

Clinicians must be aware of other conditions such as acute coronary syndrome and perforated duodenal ulcer which can mimic an acute biliary emergency.

4. Severity assessment and risk stratification

Severity assessment and grading not only guide the clinicians in the management of the patients, it also helps to allocate and prioritize scarce hospital resources. The risk assessment and stratification of acute biliary infection is based on Tokyo Guidelines 2013 (TG13) severity assessment criteria for acute cholangitis following the recent revision to the 2007 Tokyo Guidelines for the Management of Acute Cholangitis and Cholecystitis [18-20].

4.1. Acute cholecystitis

The acute management of acute cholecystitis is guided by the severity of the condition as the spectrum of clinical presentation may vary from a self-limiting infection to a potentially life-threatening fulminant disease. The concept of severity assessment in acute cholecystitis is based on the degree of inflammation and/or infection which may impact on organ dysfunction. The stratification guides the clinician in decision making.

The revised Tokyo Guidelines TG13, proposed three grades of severity in acute cholecystitis. In severe (Grade III) acute cholecystitis, one or more of the following features are detected indicating the presence of organ dysfunction

1. Cardiovascular system – hypotension requiring dopamine ≥5μg/kg per min or any dose of norepinephrine
2. Central nervous system – change in mental status or consciousness
3. Respiratory system – PaO_2/FiO_2 ratio <300
4. Renal system – oliguria, serum creatinine > 2 mg/dl
5. Liver – PT-INR > 1.5
6. Haematological system – platelets < 100,000/mm^3

In moderate (Grade II) patient, the acute cholecystitis is accompanied by any one of the following

1. Raised white blood cell count (>18,000/mm^3)
2. Palpable tender mass in the right upper abdominal quadrant
3. More than 72 hours from the onset
4. Marked local inflammation such as biliary peritonitis, pericholecystitic abscess, hepatic abscess, gangrenous cholecystitis, emphysematous cholecystitis

Mild (Grade I) acute cholecystitis is a category by exclusion when patient's condition does not satisfy Grade II and Grade III acute cholecystitis criteria. Those patients with no organ dysfunction have mild inflammation of the gallbladder and suitable for cholecystectomy because it will be safe and low risks fall under this category of Grade I acute cholecystitis.

Progression of severity may not be step-wise. When patient develops any organ or system dysfunction, the severity is upgraded from Grade I to Grade III.

4.2. Acute cholangitis

Severity of acute cholangitis is classified into mild, moderate and severe or Grade I, II and III respectively. The main criteria in the assessment of severity are the onset of organ dysfunction and the predicted risk of severity progression without prompt biliary intervention.

Organ dysfunction is a reliable predictor of poor outcome. Severe (Grade III) acute cholangitis is defined as acute cholangitis for the group of patients who is associated with the onset of organ and system dysfunction in at least one of the following

1. Cardiovascular system – hypotension requiring dopamine ≥5μg/kg per min or any dose of norepinephrine
2. Central nervous system – change in mental status or consciousness
3. Respiratory system – PaO_2/FiO_2 ratio <300
4. Renal system – serum creatinine > 2 mg/dl
5. Liver – PT-INR > 1.5
6. Haematological system – platelets < 100,000/mm^3

Moderate (Grade II) acute cholangitis is associated with any two of the following

1. Abnormal white blood cell count (>12,000/mm^3 or <4,000/mm^3)
2. High fever (≥39 degree Celsius)
3. Age (≥75 years old)
4. Hyperbilirubinaemia (total bilirubin ≥5 mg /dL)
5. Hypoalbuminaemia (STD x 0.7)

When a patient with acute cholangitis, in the absence of organ dysfunction, does not meet the Grade III and Grade II acute cholangitis criteria at the initial diagnosis, it is classified as mild Grade I acute cholangitis.

It is important to be aware that patient initially assessed as mild cholangitis may deteriorate to moderate and severe. The clinical condition can be very fluid and dynamic especially for elderly patients and immune-suppressed patients.

4.3. Special high risk groups

High index of suspicion is needed in the elderly, geriatrics and immune- compromised patients. Often these patients do not display clear and defined clinical symptoms and signs to guide the diagnosis. They are also more likely to deteriorate rapidly because of their limited physiological reserve [21].

5. Investigations

5.1. Laboratory tests

Full blood counts, procalcitonin and C-reactive protein (CRP) are useful index for inflammation and infection. Liver function tests helps to assess biliary stasis and obstruction. Elevated AST and ALT may suggest liver dysfunction and sepsis. Renal panel and coagulation profile assess the extent of organ dysfunction. When acute pancreatitis is suspected, serum amylase and lipase assay are relevant. Serum CA19-9 is less relevant at this juncture for the reason that the result can be spurious in the presence of hyperbilirubinaemia.

Although there is no Level 1 evidence to support blood and bile culture in patients with acute cholangitis, it is generally a good practice to obtain the culture prior to antimicrobial therapy.

5.2. Diagnostic imaging

Imaging is necessary to confirm the diagnosis and to exclude the differential diagnoses. In addition, imaging provides quantitative assessment of the bile duct, clarify the specific etiology for the biliary obstruction (calculus or tumour or stricture) and guide subsequent therapeutic interventions.

Erect abdominal roentgenography can be informative in patients with calcified gallstones and aerobilia. Occasionally, pneumoperitoneum suggesting a perforated viscus may be detected. In both, acute cholecystitis and acute cholangitis, the initial diagnostic imaging of choice is hepatobilairy ultrasonography, because it is non-invasive and cost-effective. The sonography findings supporting the diagnosis of acute cholecystitis are peri- cholecystic fluid with thickened gallbladder wall or enlarged gallbladder (long axis >8cm and short axis >4 cm), sonography Murphy's sign and striated lucent gallbladder wall [22].

Ultrasound has high sensitivity in detecting dilated bile duct but its sensitivity for diagnosing choledocholithisis is low. It is important to note that a normal size bile duct on ultrasonography does not rule out acute cholangitis because it takes time for the bile duct to dilate following migration of obstructing gallstones in the bile duct. In most tertiary institutions, magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasound (EUS), and ERCP are available to diagnose choledocholithiasis. All of them have comparable sensitivity and specificity [23]. MRCP is indicated when biliary calculus migration to common bile duct is suspected. MRCP imaging is not only radiation-free, it is also non-invasive. Therefore, it is preferred to ERCP when the probability of choledocholithiasis is assessed to be low [24]. With the advent of MRCP, the role of diagnostic ERCP for bile duct stone is fast disappearing. However, it still plays a crucial role in the diagnosis of ampullary pathology. ERCP is best utilized when the likelihood of common bile duct stone or the need for intervention is high, or when less risker alternatives are not available [25].

EUS also offers high sensitivity in the diagnosis of choledocholithiasis. As EUS requires a skilled endoscopist, this imaging service may not be available in some centers. CT scan is indicated in acute abdomen where abdominal ultrasonography may be technically difficult due to the pain. CT scan helps to exclude the differential diagnoses of acute pancreatitis, Mirizzi's syndrome, perforated viscus and acute pyelonephritis. Tc-HIDA scan is rarely used in emergency setting.

6. Management in emergency setting

6.1. General

The acute management requires hospital admission to co-ordinate haemodynamic monitoring, intravenous fluid hydration, antibiotics administration, pain relief, resting of digestive system.

Bowel rest and intravenous fluids resuscitation and hydration should be instructed upon admission. Intramuscular or intravenous analgesia as indicated. Central venous line and per-urethral bladder catherterization are indicated for grade III cholangitis to guide resuscitation and monitor the progress of the patient. Patients with grade II cholangitis with high risk of deterioration should be monitor closely in high dependency ward. Low fat diet is recommended when oral feeding commences.

6.2. Antimicrobials therapy

The principles and concepts in the choice of antimicrobial is based on the knowledge of the most likely offending micro-organism, the pharmacokinetics and pharmacodynamics, adverse effects of the drugs, local antimicrobial susceptibility data, the severity of the infection, history of antimicrobial medication and the host physiology. The availability and cost of the drugs may be factors for consideration in some institutions. Initial broad spectrum antimicrobial therapy is revised to a more targeted narrow spectrum therapy once the micro-organism culture and sensitivity testing results are available.

If clinical response to the first line initial broad spectrum antimicrobial therapy within the first 48 hours is poor, prompt revision to second line antimicrobial therapy is crucial. At this juncture, it is important to remember that patients who are unresponsive to antibiotics therapy may require urgent or early drainage (cholecystostomy) or cholecystectomy (gallstones).

It must be recognised that the recommended antimicrobial therapy protocol differs from institution to institution due to the differences in the local susceptibility of the micro-organisms and availability of the drugs. Institutions with antibiotics stewardship programme will provide a relevant guide to the choice of antimicrobial therapy.

6.2.1. Acute choelcystitis

In mild acute cholecystitis, mono-microbial gram-negative organism such as Escherichia coli is often the pathogen while in severe acute cholecystitis, poly-microbial gram-negative and anaerobes or multi-drugs resistant microganisms are present [26,27].

For mild (Grade I) acute cholecystitis, oral cephalosporins (Cefotiam), wide- spectrum penicillin/β-lactamase inhibitor (ampicillin/sulbactam) or oral fluoroquinolones (Levofloxacin or ciprofloxacin or Moxifloxacin) are recommended if indicated (Table 1). Cefazolin, Ceftriaxone, Cefoperazone and Ertapenem are the alternatives. The Tokyo Guidelines 2007 recommended wide-spectrum penicillin/β-lactamase inhibitor (piperacillin/tazobactam or ampicillin/sulbactam) or second generation cephalosporin (cefmetazole) as the first line antimicrobial therapy for moderate acute cholecystitis [28]. In the revised TG13 guidelines Ampicillin/sulbactam monotherapy is not recommended for Grade I acute cholecystitis because of its limited activity against *Escherichia coli* in the North America [29]. TG 13 guidelines recommeded Piperacillin/tazobactam for both hospital associated acute cholecystitis and community acquired Grade II acute cholecystitis [30].

The antimicrobials recommended for severe (Grade III) acute cholecystitis in TG13 guidelines are ceftazidime or cefepime or cefozopran with addition of or without metronidazole. The concern of ceftriaxone in association with biliary sludge is unproven scientifically and its clinical relevance remains unclear. The alternative antimicrobials are Piperacillin/tazobactam or carbapanem based therapy (Imipenem/cilastin, meropenam, doripenem or ertapenam) or Aztreonam with or without metronidazole. The antimicrobials for healthcare-associated acute biliary infections are the same as for Grade III disease.

The duration of antimicrobial therapy for grade II and III acute cholecytitis, 4-7 days are recommended unless there is Gram–positive bacteremia (e.g. *Enterococcus spp* and *Streptoccoccus spp*), two weeks antimicrobial therapy is advised to reduce the risk of infective endocarditis [29,30]. For grade I acute cholecytitis, antimicrobial therapy can be discontinued 24 hours following cholecystectomy. However, if there is evidence of perforation or emphysematous changes or necrosis of the gallbladder during cholecystectomy, 4-7 days of antimicrobials therapy is advocated.

Table 1. TG13 Antimicrobial Recommendation for Acute Cholecystitis [30]

	Community-acquired acute cholecystitis			*Healthcare-associated[e] acute cholangitis*
Severity	Grade I	Grade II	Grade III[e]	All severities
Antimicrobial agents				
Penicillin -based	Ampicillin/sulbacta m[b] not recommended	Piperacillin/tazobactam	Piperacillin/tazobactam	Piperacillin/tazobactam
Cephalosporin -based	Cefazolin,[a] or cefotiam,[a] or cefuroxime,[a] or ceftriaxone, or cefotaxime ± metronidazole[d] Cefmetazole,[a] cefoxitin,[a] flomoxef,[a] cefoperazone/ sulbactam	Ceftriaxone, or cefotaxime, or cefepime, or cefozopran, or ceftazidime ± metronidazole[d] Cefoperazone/sulbactam	Cefepime, or ceftazidime, or cefozopran ± metronidazole[d]	Cefepime, or ceftazidime, or cefozopran ± metronidazole[d]
Carbapenem-based	Ertapenem	Ertapenem	Imipenem/cilastatin, meropenem, doripenem, ertapenem	Imipenem/cilastatin, meropenem, doripenem, ertapenem
Monobactam-based	-	-	Aztreonam ± metronidazole	Aztreonam ± metronidazole
Fluorquinolon e-based[c]	Ciprofloxacin, or levofloxacin, or pazufloxacin ± metronidazoled Moxifloxacin	Ciprofloxacin, or levofloxacin, or pazufloxacin ± metronidazolec Moxifloxacin	-	-

[a] Local antimicrobial susceptibility patterns (antibiogram) should be considered for use.
[b] Ampicillin/sulbactam has little activity left against E. coli.
[c] Fluoroquinolone use is recommended if the susceptibility of cultured isolates is known or for patients with b-lactam allergies. Many ESBL-producing Gram-negative isolates are fluoroquinolone-resistant.
[d] Anti-anaerobic therapy, including use of metronidazole, tinidazole, or clindamycin, is warranted if a biliary-enteric anastomosis is present. The carbapenems, piperacillin/tazobactam, ampicillin/sulbactam, cefmetazole, cefoxitin, flomoxef, and cefoperazone/sulbactam have sufficient anti-anerobic activity for this situation.
[e] Vancomycin is recommended to cover Enterococcus spp. for grade III community-acquired acute cholangitis and cholecystitis, and healthcare-associated acute biliary infections. Linezolid or daptomycin is recommended if vancomycin-resistant Enterococcus (VRE) is known to be colonizing the patient, if previous treatment included vancomycin, and/or if the organism is common in the community.

6.2.2. Acute cholangitis

The most frequent pathogens are gastrointestinal flora. There are *Escherichia coli*, *Klebsiella species, Enterobacter species* and *Enterococcus species* [31-33]. Streptococococcus and Proteus are less frequent pathogen [34]. Polymicrobial with anaerobes such as Clostridium and Bacteriodes often occur in diabetes and immunocompromised patients. Empirical coverage for these organisms is advised. Resistant pathogens may be encountered in patients with health care-associated infections and empirical coverage should be adjusted accordingly. Once the bacteriology and sensitivity data are available, the most appropriate antibiotics must be selected.

The choice of antimicrobial agents is guided by severity of the infection. This practice is consistent with the Infectious Diseases Society of America (IDSA) guidelines for intra-abdominal infection [35] and Tokyo Guidelines 2013 (TG13). The antimicrobials recommendation by TG13 Tokyo Guidelines for acute biliary infection for acute cholangitis parellel that of antimicrobials for acute cholecystits (Table 2). For grade I acute cholangitis, the antimicrobials options are cephalosporin-based therapy, carbapenem-based therapy and fluoroquinolone-based therapy (Table 2). Likewise, Ampicillin/sulbactam monotherapy is not recommended for the same reason as acute cholecystitis as mentioned earlier. Coverage of anaerobic bacteria is generally not indicated in mild (Grade I) acute cholangitis unless an endobiliary stent or a biliary-enteric anastomosis is present.

For Grade II acute cholangitis, Piperacillin/tazobactam and third and fourth generations cephlosporin are recommended. The other choices include either fluroquinolone-based therapy (Ciprofloxacin, or levofloxacin, or pazufloxacin plus metronidazole, Moxifloxacin) or carbapenem based therapy (ertapenem). Comparing with Tokyo Guidelines 2007, monobactam-based is reserved for grade III acute cholangitis or healthcare assciated acute cholangitis in the new guideline [36]. Additional coverage for anaerobes with metronidazole is justified in moderate (grade II) acute cholangitis as majority of moderate acute cholangitis is pyogenic infection and polymicrobial cholangitis may be present [37]. Patients from institution suspected with hospital-acquired multi-drug resistant organisms, especially those with indwelling stents, bilio-enteric anastomosis

Table 2. Antimicrobial Recommendation for Acute Cholangitis from the TG13 [30]

	Community-acquired acute cholangitis			*Healthcaressociated[e] acute cholangitis*
Severity	Grade I	Grade II	Grade III[e]	All severities
Antimicrobial agents				
Penicillin-based	Ampicillin/sulbactam[b] not recommended	Piperacillin/tazobacta m	Piperacillin/tazobactam	Piperacillin/tazobactam
Cephalosporin-based	Cefazolin,[a] or cefotiam,[a] or cefuroxime,[a] or ceftriaxone, or cefotaxime ± metronidazole[d] Cefmetazole,[a] cefoxitin,[a] flomoxef,[a] cefoperazone/ sulbactam	Ceftriaxone, or cefotaxime, or cefepime, or cefozopran, or ceftazidime ± metronidazole[d] Cefoperazone/sulbactam	Cefepime, or ceftazidime, or cefozopran ± metronidazole[d]	Cefepime, or ceftazidime, or cefozopran ± metronidazole[d]
Carbapenem-based	Ertapenem	Ertapenem	Imipenem/cilastatin, meropenem, doripenem, ertapenem	Imipenem/cilastatin, meropenem, doripenem, ertapenem
Monobactam-based	-	-	Aztreonam ± metronidazole	Aztreonam ± metronidazole
Fluorquinolon e-based[c]	Ciprofloxacin, or levofloxacin, or pazufloxacin ± metronidazole[d] Moxifloxacin	Ciprofloxacin, or levofloxacin, or pazufloxacin ± metronidazole[c] Moxifloxacin	-	-

[a] *Local antimicrobial susceptibility patterns (antibiogram) should be considered for use.*
[b] *Ampicillin/sulbactam has little activity left against E. coli.*
[c] *Fluoroquinolone use is recommended if the susceptibility of cultured isolates is known or for patients with b-lactam allergies. Many ESBL-producing Gram-negative isolates are fluoroquinolone-resistant.*
[d] *Anti-anaerobic therapy, including use of metronidazole, tinidazole, or clindamycin, is warranted if a biliary-enteric anastomosis is present. The carbapenems, piperacillin/tazobactam, ampicillin/sulbactam, cefmetazole, cefoxitin, flomoxef, and cefoperazone/sulbactam have sufficient anti-anerobic activity for this situation.*
[e] *Vancomycin is recommended to cover Enterococcus spp. for grade III community-acquired acute cholangitis and cholecystitis, and healthcare-associated acute biliary infections. Linezolid or daptomycin is recommended if vancomycin-resistant Enterococcus (VRE) is known to be colonizing the patient, if previous treatment included vancomycin, and/or if the organism is common in the community.*

and malignancies, antibiotics should be selected accordingly.

For severe (Grade III) acute cholangitis, the antimicrobials options are Piperacillin/tazobactam or carbapanem based therapy (Imipenem/cilastin, meropenam, doripenem or ertapenam) or cepalosporin based therapy (ceftazidime or cefepime or cefozopran with or without metronidazole) or Monobactam based therapy (Aztreonam with or without metronidazole). Vancomycin may be added for hospital-associated MRSA biliary infections of any severity.

Infectious disease physician's input and the availability of institution antibiotic stewardship programme with local susceptibility pattern data will be invaluable in the decision making for antimicrobial agents against multi-drug resistant micro-organisms [38,39].

To achieve the best clinical outcome, the drug dosage must be titrated according to the renal and hepatic functions, particularly for patients with septicaemic shock. For instance, patient with liver impairment or failure, ceftriaxone must be titrated. The recommended duration of antimicrobial treatment is 4-7 days for acute cholangitis, however, if bacteraemia with Gram–positive bacteria e.g. *Enterococcus spp* and *Streptococcus spp*, two weeks antimicrobial therapy is advocated because of the risk of infective endocarditis [29,30].

7. Early biliary tract decompression and drainage for acute cholangitis

Older age, history of chronic smoking, prolonged prothrombin time, higher blood glucose level, and dilated common bile duct on ultrasonography are predictors for poor response to conservation management alone. Patients aged older than 75 years had a significantly higher chance of failure of conservative treatment than those aged 75 years or less [40]. This group of patients will benefit from urgent biliary drainage.

In the era of minimally invasive surgery, the indication for emergent open operation for acute cholangitis is rapidly disappearing. Emergency operation for severe cholangitis carries high mortality rate [41]. Retrospective and randomized controlled trial data have convincingly demonstrated the better outcome, in term of morbidity and mortality, of minimally invasive biliary drainage [42,43]. Biliary decompression and drainage is an effective intervention to control endotoxaemia in grade II and III acute cholangitis [44]. It also helps to improve the active transfer of antimicrobial drugs into the bile [45,46].

There are two minimally invasive options in draining the biliary system without resorting to open operation, that is endoscopically or transhepatic percutaneously [47,48]. The endoscopic route is the preferred choice with proven safety and efficacy record [49,50]. In a randomized study, comparing between endoscopic nasobiliary drainage with sphincterotomy to T-tube drainage under laparotomy, the hospital mortality was significantly lower, 10% and 32% respectively [51]. For grade III cholangitis, especially when the patient is critically ill, endoscopic biliary drainage with either nasobiliary stent (external drainage) or endobiliary stent (internal drainage) suffices [52,53]. In term of success rate, effectiveness and morbidity, randomised control trials data did not show a significant difference between naso-biliary and endobiliary stents [54]. However, endobiliary stent is more attractive because internal drainage has the advantage in preserving the enterohepatic circulation of the bile and therefore causes less electrolytes imbalance [55]. Furthermore, naso- biliary stent has a higher incidence of dislodge and patient's discomfort. Endoscopic sphincterotomy and one-stage endoscopic choledocholithotomy is not recommended, especially for critically ill patients because of higher risk of haemorrhage [56]. Other complications associated with sphincterotomy are acute pancreatitis and bowel perforation [57].

Recent innovation has added single- or double-balloon enteroscopy-assisted biliary drainage and endoscopic ultrasonography-guided biliary drainage to the endoscopic biliary drainage armamentarium [58,59]. In patients with altered surgical anatomy such as previous Roux-en-Y anastomosis, enteroscopy assisted biliary drainage can be useful [60]. Endoscopic ultrasonography guided biliary drainage provides a salvage therapy when standard endoscopic drainage failed [61]. It must be emphasized that these innovative techniques should be performed by skilled endoscopists in high volume centers. TG13 recommends that endoscopic biliary drainage should be the first choice for biliary decompression in patients with non-surgically altered anatomy and the choice for techniques in cannulation and drainage should be left to endoscopist's preference and comfort [62].

In patients who are not a candidate for endoscopic approach eg previous gastric or intestinal operation (eg Bilroth II subtotal gastrectomy and Roux-en-Y hepaticojejunostomy), or when endoscopic service is not available, percutaneous transhepatic approach is an alternative [63,64]. Improvement of clinical condition with fever resolution can be witnessed within 18-24 hours in majority of the patients following percutaneous transhepatic biliary drainage [44].

Percutaneous drainage of the bile duct is also recommended to bail patients out from sepsis when they are too unwell to tolerate prone position for endoscopic

biliary drainage. Serious complications associated with percutaneous transhepatic biliary drainage are haemorrhage, sepsis, abscess, peritonitis and pleural effusion [65]. Retrospective data on percutaneous drainage reported a morbidity rate of 7% and mortality rate of 5% in a cohort of 42 patients [66].

Open drainage under laparotomy is a last resort where minimally invasive procedures are either not available or contraindicated. As emergency open operation carries high risk of morbidity and mortality, the duration of the operation should be kept as brief as possible with the primary objective to decompress the biliary tract with a T-tube placement. Attempt to remove or clear the biliary calculi should be avoided during the operation [67].

The timing of biliary drainage depends on the severity of infection. Biliary drainage for grade III acute cholangitis is best performed as soon as possible when the patient is stabilized. Delay in biliary drainage for more than 72 hours is associated with poor outcome [68]. For grade II acute cholangitis, the procedure should be performed early within 12-24 hours following stabilizing the haemodynamics of the patients [52]. It must be emphasized here that patients with acute cholangitis may deteriorate rapidly and thereby losing the opportunity to intervene early. The patients who have delayed decompression following failed medical therapy are at high mortality risk [69].

8. Gallbladder drainage for acute cholecystitis

Unlike acute cholangitis, gallbladder drainage is generally not the first consideration and is seldom indicated. The mainstay of treatment for acute cholecystitis is early or emergency laparoscopic cholecystectomy. Unless patients do not respond to initial antibiotics therapy, and at the same time unfit for cholecystectomy, gallbladder drainage is indicated [70-72]. Acalculous cholecystitis in elderly high-risk patients with prohibitive co-morbidities are suitable indications for percutaneous gallbladder drainage [73]. In situation when the diagnosis of acalculous cholecystitis is uncertain, percutaneous cholecystotomy can be diagnostic with majority of the patients improved after the procedure.

The technical options for gallbladder drainage are percutaneous transhepatic gallbladder drainage (PTGBD), percutaneous gallbladder aspiration, endoscopic ultrasonography-guided gallbladder drainage (EUSGD) and endoscopic naso-cholecystic drainage [74,75]. Percutaneous transhepatic gallbladder drainage is performed under image guidance and this technique is generally less demanding than endoscopic naso-gallbladder drainage. Although EUSGD has been reported to be comparable to PTGBD in term of feasibility and efficacy, it is currently not recommended as a standard method of drainage [72,76].

9. Emergency cholecystectomy and cholecystostomy

Laparoscopic cholecystectomy is the operation of choice for mild acute cholecystitis. As to the question of timing of operation, early laparoscopic cholecystectomy is generally well accepted as safe and effective in centres with the expertise in minimally invasive surgery [77,78]. It is important to take note that early operation should be scheduled within 96 hours after the onset [79]. Early surgery has been shown to be advantages in terms of reduced hospital stays, absence from work, treatment cost, conversion rate and re-operation rate [80].

In moderate grade II cholecystitis, early cholecystectomy is advocated in experienced centers, however, consideration for subtotal cholecystectomy, cholecystostomy or open gallbladder drainage if severe local inflammation is discovered and cholecystectomy is judged hazardous or technically difficult during the operation. If this is suspected pre-operatively and cholecystectomy is predicted to be technically challenging, percutaneous gallbladder drainage and medical treatment first followed by delayed cholecystectomy is recommended [81].

Urgent laparoscopic cholecystectomy carries a higher risk of conversion. Conversion should not be viewed as failure of the operation but rather as a sound surgical judgment for patient safety reason. The duration of emergency laparoscopic cholecystectomy is an independent predictor for a higher incidence of postoperative complications. Comparing with laparoscopic cholecystectomies performed in less than an hour, the cumulative risk for perioperative complications is four folds higher for operations performed in more than two hours [82].

Emergency cholecystectomy for Grade III acute cholecystitis is best avoided as it carries significant morbidity and mortality. Delayed cholecystectomy following urgent management of organ dysfunction and possible gallbladder drainage is recommended [81].

10. Management of choledocholithiasis

Definitive management of choledocholithiasis is usually deferred till the resolution of acute cholangitis. The options of one-stage and two-stage laparoscopic choledocholithotomy depend on the availability of expertise in the institution [83]. In experienced hands, one-stage operation (laparoscopic cholecystectomy with either transcystic or transcholedochotomic choledocholithotomy) and two-stage operation (laparoscopic cholecystectomy with either pre- or postoperative ERCP common bile duct exploration) are safe and reliable in clearing common bile duct stones [84,85]. Detailed discussion on the definite surgery is not within the scope of this review.

11. Predictors of outcome

The outcome of acute cholecystitis and acute cholangitis correlates with the severity grading. Gigot selected seven predictors of mortality in acute cholangitis – acute renal failure, associated liver abscesses, high malignant biliary stricture, liver cirrhosis, age and female gender–from a statistical analysis of 140 parameters in 449 acute attacks [86]. In a recent study of 108 patients, total bilirubin, partial prothrombin time and associated liver abscess were identified as predictors of mortality for acute cholangitis [87]. Most of these predictors for mortality in acute cholangitis are the criteria for severe grade III acute cholangitis. Predictors of post-operative mortality following emergency biliary surgery for severe acute cholangitis are co-morbidity, pH<7.40, platelet count <150x10^9/mL, serum albumin <30 gm/L and total bilirubin ≥90 µmol/L [88]. These predictors are the function of surgical fitness and the degree of sepsis. By bailing the patient out of sepsis with medical and minimally invasive procedure in the emergency setting, it saves the patient from a high risk emergency operation and hence, converting it to an elective operation.

12. Conclusion

Acute biliary infection presents with varying severity and has a diverse etiology. As severe acute biliary infection is associated with grave prognosis and high mortality rate, co-ordinated and organized efforts to execute the clinical strategy in resuscitation, organ support, administration of systemic antimicrobials, early scheduling of biliary decompression and subsequent definitive management are key factors in achieving good clinical outcome. Better understanding and innovations in the application of intensive care, the appropriate antimicrobial treatment and prompt biliary decompression has contributed to the improved mortality and morbidity profiles of this disease in the last two decades.

Conflict of interest statement

Authors state no conflict of interest.

References

[1] Gouma DJ, Obertop H. Acute calculous cholecystitis. What is new in diagnosis and therapy? HPB

[2] Sharp KW. Acute Cholecystitis. Surg Clin North Am. 1988;68:269-279

[3] Williamson RC. Acalculous disease of the gallbladder. Gut. 1988;29:860-872

[4] Barie PS, Fischer E. Acute acalculous cholecystitis. J Am Coll Surg 1995;180:232-244

[5] Merriam LT, Kanaan SA, Dawes LG, Angelos P, Prystowsky JB, Rege RV, et al. Gangrenous cholecystitis: analysis of risk factors and experience with laparoscopic cholecystectomy. Surgery 1999;126:680-685

[6] Bedirli A, Sakrak O, Sozuer EM, Kerek M, Guler I. Factors effecting the complications in the natural history of acute cholecystitis. Hepatogastroenterology. 2001;48:1275-1278

[7] Kimura Y, Takada T, Kawarada Y, Nimura Y, Hirata K, Sekimoto M, et al. Definitions, pathophysiology and epidemiology of acute cholangitis and cholecystitis: Tokyo guidelines. 2007;14:15-26

[8] Fagan SP, Awad SS, Rahwan K, Hira K, Aoki N, Itani KM, et al. Prognostic factors for the development of gangrenous cholecystitis. Am J Surg. 2003;186(5):481-485

[9] Charcot M. De la fievre hepatique symptomatique. Comparaison avec la fievre uroseptique. Lecons sur les maladies du foie des voies biliares et des reins. Paris: Bourneville et Sevestre; 1877:176-85

[10] Reynolds BM, Dargan EL. Acute obstructive cholangitis. A distinct syndrome. Ann Surg 1959;150:299-303

[11] Longmire WP. Suppurative cholangitis. In: Hardy JD, editor. Critical surgical illness. New York: Saunders;1971;p397-424

[12] Andrew DJ, Johnson SE. Acute suppurative cholangitis, a medical and surgical emergency. A review of 10 years. Am J Gastroenterol 1970;54:141-54.
[13] Boey JH, Way LW. Acute Cholangitis. Ann Surg. 1980;191(3):264-270
[14] Fan ST, Lai ECS, Mok FPT, Choi TK, Wong J. Acute cholangitis secondary to hepatolithiasis. Arch Surg. 1991;126(8):1027-1031
[15] Lipsett PA, Pitt HA. Acute cholangitis. Surg Clin North Am. 1990;70:1297-312
[16] Welch JP, Donaldson GA. The urgency of diagnosis and surgical treatment of acute suppurative cholangitis. Am J Surg. 1976;131:527-532
[17] O'Connor MJ, Schwartz ML, McQuarrie DG, Sumer HW. Acute bacterial cholangitis: an analysis of clinical manifestation. Arch Surg 1982;117:427-441
[18] Kiriyama S, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Pitt HA, et al. TG13 guidelines for diagnosis and severity grading of acute cholangitis (with videos). J Hepatobiliary Pancreat Sci. 2013;20:24-34
[19] Yokoe M, Takada T, Strasberg SM, Solomkin JS, Mayumi T, Gomi H, et al. TG13 diagnotic criteria and severity grading of acute cholecystitis (with videos). J Hepatobiliary Pancreat Sci. 2013;20:35-46
[20] Takada T, Kawarada Y, Nimura Y, Yoshida M, Mayumi T, Sekimoto M, et al. Tokyo guidelines for management of acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Surg. 2007;14:1-126
[21] Sugiyama M, Atomi Y. Treatment of acute cholangitis due to choledocholithiasis in elderly and younger patients. Arch Surg. 1997;132:1129-1133
[22] Ralls PW, Hall J, Lapin SA, Quinn MF, Morris UL, Boswell W. Prospective evaluation of the sonographic Murphy sign in suspected acute cholecystitis. J Clin Ultrasound. 1982;10:113-115
[23] Stiris MG, Tennoe B, Aadland E, Lunde OC. MR Cholangiopancreaticography and endoscopic retrograde cholangiopancreaticography in patients with suspected common bile duct stones: a prospective blinded study. Acta Radiologica. 2000;41(3):269-272
[24] Kondo S, Isayama H, Akahane M, Toda N, Sasahira N, Nakai Y, et al. Detection of common bile duct stones: comparison between endoscopic ultrasonography, magnetic resonance cholangiography and helical-computed-tomographic cholangiography. Eur J Radiol. 2005;54(2):271-275
[25] NIH Consensus State Sci Statement. NIH state-of-the-science statement on endoscopic retrograde cholangiopancreatography (ERCP) for diagnosis and therapy. 2002 Jan 14-16;19(1):1-26
[26] Marne C, Pallares R, Martin R, Sitges-Serra a. Gangrenous cholecystitis and acute cholangitis associated with anaerobic bacteria in bile. Eur J Clin Microbiol. 1986;5:35-39
[27] Claesson B, Holmlund D, Matzsch T. Microflora of the gallbladder related to duration of acute cholecystitis. Surg gynecol Obstet 1986;162:531-535
[28] Yoshida M, Takada T, Kawarada Y, Tanaka A, Nimura Y, Gomi H, et al. Antimicrobial therapy for acute cholecystitis: Tokyo guidelines. J Hepatobiliary Pancreat Surg. 2007;14:83-90
[29] Solomkin JS, Mazuski JE, Bradley JS, Rodvold KA, Goldstein EJ, Baron EJ, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: Guidelines by the Surgical Infection Society and Infectious Diseases Society of America. Clin Infect Dis. 2010;50(2):133-164(CPG)
[30] Gomi H, Solomkin JS, Takada T, Strasberg SM, Pitt HA, Yoshida M, et al. TG13 antimicrobial therapy for acute cholangitis and cholecystitis. J Hepatobiliary Pancreat Sci. 2013;20:60-70
[31] Saharia PC, Cameron JL. Clinical management of acute cholangitis. Surg Gynecol Obstet. 1976 Mar;142(3):369-372
[32] Chang W, Lee K, Wang S, Chuang S, Kuo K, Chen J, et al. Bacteriology and antimicrobial susceptibility in biliary tract disease: an audit of 10-years' experience. Kaohsiung J Med Sci. 2002;18:221-228
[33] Maluenda F, Csendes A, Burdiles P, Diaz J. Bacteriological study of choledochal bile in patients with common bile duct stones, with or without, acute suppurative cholangitis. Hepatogastroenterology. 1989;36:132-135
[34] Csendes A, Mitru N, Maluenda F, Diaz J, Burdiles P, Csendes P, et al. Counts of bacteria and pyocites of choledochal bile in controls and patients with gallstoens or common bile duct stones with or without acute cholangitis. Hepatogastroenterology 1996;43:800-806
[35] Solomkin J, Mazuski J, Baron E, Sawyer R, Nathens A, DiPiro J, et al. Guidelines for the selection of anti-infective agents for complicated intra-abdominal infections. Clin Infect Dis 2003;37:997-1005
[36] Tanaka A, Takada T, Kawarada Y, Nimura Y, Yoshida M, Miura F, et al. Antimicrobial Therapy for Acute Cholangitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14:59-67
[37] Nielsen M, justesen T. Anaerobic and aerobic bacteriological studies in biliary tract disease. Scand J Gastroenterol. 1976;11:437-446

[38] Lesprit P, Brun-Buisson C. Hospital antibiotic stewardship. Curr Opin Infect Dis. 2008;21(4):344-349
[39] Owens RC Jr. Antimicrobial stewardship: concepts and strategies in the 21st century. Diagn Microbial Infect Dis. 2008 May;61(1):110-128
[40] Yeung YP, Yip AWC. Predictors for emergency biliary decompression in acute cholangitis. European Journal of Gastroenterology & Hepatology. 2006;18(7):727-731
[41] Thompson JE, Tompkins RK, Longmire WP. Factors in management of acute cholangitis. Ann Surg. 1982;195(2):137-145
[42] Leese T, Neoptolemos JP, Baker AR, Carr-Locke DL. Management of acute cholangitis and the impact of endoscopic sphincterotomy . Br J Surg 1986;73:988–992
[43] Gogel HK, Runyon BA, Volpicelli NA, Palmer RC. Acute suppurative obstructive cholangitis due to stones: treatment by urgent endoscopic sphincterotomy. Gastrointest Endose 1987;33:210–213
[44] Lau JY, chung SC, Leung JW, Ling TK, Yung MY, Li AK. Endoscopic drainage aborts endotoxaemia in acute cholangitis. Br J Surg. 1996;83:181-184
[45] Leung J, Chan R, Cheung S, Sung J, Chung S, French G. The effect of obstruction on biliary excretion of cefoperazone and ceftazidime. J Antimicrob Chemother. 1990;25:399-406
[46] Van den Hazel S, de vries X, Speelman P, Dankert J, Tytgat G, huuibregtse K, et al. Biliary excretion of ciprofloxacin and piperacillin in the obstructed biliary tract. Antimicrob Agents Chemother. 1996;40:2658-2660
[47] Sharma BC, Kumar r, Agarwal N, Sarin SK. Endoscopic biliary drainage by nasobiliary drain or by stent placement in patients with acute cholangitis. Endoscopy. 2005;37:439-443
[48] Chen MF, Jan YY, Lee TY. Percutaneous transhepatic biliary drainage for acute cholangitis. Int Surg. 1987;72:131-133
[49] Leung JW, Chung SC, Sung JJ, Banez VP, Li AK. Urgent endoscopic drainage for acute suppurative cholangitis. Lancet 1989;10:1307-1309
[50] Hui CK, Liu CL, Lai KC, Chan SC, Hu WHC, Wong WM, et al. Outcome of emergency ERCP for acute cholangitis in patients 90 years of age and older. Alimentary Pharmacology & Therapeutics. 2004 Jun;19(11):1153-1158
[51] Lai ECS, Mok FPT, Tan ESY, Lo CM, Fan ST, You KT, et al. Endoscopy Biliary Drainage for Severe Acute Cholangitis. N Engl J Med; 1992 June;326:1582-1586
[52] Lai EC, Paterson IA, Tam PC, Choi TK, Fan ST, Wong J. Severe acute cholangitis: the role of emergency nasobiliary drainage. Surgery. 1990 Mar;107(3):268-272
[53] Sharma BC, Agarwal DK, Baijal SS, Sraswat VA, Choudhuri G, Naik SR. Endoscopic management of acute calculous cholangitis. J Gastroenterology and Hepatology. 1997 Dec;12(12):874-876
[54] Lee DW, Chan AC, Lam YH, Ng EK, Lau JY, Law BK, et al. Biliary decompression by nasobiliary catheter or biliary stent in acute suppurative cholangitis: a prospective randomized trial. Gastrointest Endosc 2002;56:361-365
[55] Tsuyuguchi T, Takada T, Kawarada Y, Nimura Y, Wada K, Nagino M, et al. Techniques of biliary drainage for acute cholangitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14:35-45
[56] Nagino M, Takada T, Kawarada Y, Nimura Y, Yamashita Y, Tsuyuguchi T, et al. Methods and timing of biliary drainage for acute cholangitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14:68-77
[57] Freeman ML, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, et al. Complications of endoscopic biliary sphincterotomy. N Engl J Med. 1996;335:909-918
[58] Itoi T, Ishii K, Sofuni A, Itokawa F, Tsuchiya T, Kurihara T,et al. Single balloon enteroscopy- assisted ERCP in 206 patients with Billroth II gastrectomy or Roux-en-Y anastomosis (with video). Am J Gastroenterol. 2010;105:93-99
[59]]Kahaleh M, Hernandez AJ, Tokar J, Adams RB, Shami VM Yeaton P. Interventional EUS-guided cholangiography: evaluation of a technique in evolution. Gastrointest Endosc. 2006;64:52-59
[60] Saleem A, Baron TH, Gostout C, Topazian MD, Levy MJ, Petersen PT, et al. Endoscopic retrograde cholangiopancreatography using single-balloon enteroscope in patients with altered Roux-en-Y anatomy. Endoscopy. 2010;42:656-660
[61] Burmester E, Niehaus J, Leineweber T, Huetteroth T. EUS-cholangio-drainage of the bile: report of 4 cases. Gastrointest Endosc. 2003;57:246-251
[62] Itoi T, Tsuyuguchi T, Takada T, Strasberg SM, Pitt HA, Kim MH, et al. TG13 indications and techniques for biliary drainage in acute cholangitis (with videos) J Hepatobiliary Pancreat Sci. 2013;20:71-80
[63] Szabo S, Mendelson MH, Mitty HA, Bruckner HW, Hirschman SZ. Infections associated with transhepatic biliary drainage devices. Am J Med. 1987;82:921-926

[64] Audisio RA, Morosi C, Bozzetti F, Cozzi G, Bellomi M, Pisani P, et al. The outcome of cholangitis after percutaneous biliary drainage in neoplastic jaundicve. HPB Surg. 1993;6:287-293

[65] Burke DR, Lewis CA, cardella JF, Citron SJ, Drooz AT, Haskal ZJ, et al. Society of Interventional Radiology Standards of Practice Committee Quality improvement guidelines for percutaneous transhepatic cholangiography and biliary drainage. J Vasc Interv Radiol. 2003;14:243-246

[66] Pessa ME, Hawkins IF, VogelSB. The treatment of acute cholangitis: percutaneous transhepatic biliary drainage before definitive therapy. Ann Surg 1987;205:389-392

[67] Saltzstein EC, Peacock JB, Mercer LC. Early operation for acute biliary tract stone disease. Surgery 1983;94:704-708

[68] Khashab MA, Tariq A, Tariq U Kim K, Ponor L, Lennon AM, et al. Delayed and unsuccessful endoscopic retrograde cholangiopancreatography are associated with worse outcomes in patients with acute cholangitis. Clin Gastroenterol Hepatol 2012;10:1157-1161

[69] Gigot JF, Leese T, Dereme T, Coutinho J, Castaing D, Bismuth H. Acute cholangitis. Multivariate analysis of risk factors. Ann Surg. 1989 Apr;209(4):435-438

[70] Inui K, Nakazawa S, naito Y, Kimoto E, Yamao K. Nonsurgical treatment of cholecystolithiasis with percutaneous transhepatic cholecystoscopy. Am J Gastroenterol 1988;83:1124-1127

[71] Boland GW, Lee MJ, Mueller PR, Dawson SL, Gaa J, Lu DS, et al. Gallstones in critically ill patients with acute calculous cholecystitis treated by percutaneous cholecystotomy: nonsurgical therapeutic options. Am J Roentfgenol AR. 1994;162:1101-1103

[72] Tsuyuguchi T, Itoi T, Takada T, Strasberg SM, Pitt HA, Kim MH, et al. TG13 indications and techniques for gallbladder drainage in acute cholecystitis (with videos) J. Hepatobiliary Pancreat Sci. 2013;20:81-88

[73] Shirai Y, Tsukada K, Kawaguchi H, Ohtani T, Muto T, Hatakeyama K. Percutaneous transhepatic cholecystostomy for acute acalculous cholecystitis. Br J Surg. 1993;80:1440-1442

[74] Tsuyuguchi T, Takada T, Kawarada Y, Nimura Y, Wada K, Nagino M, et al. Techniques of biliary drainage for acute cholecystitis: Tokyo Guidelines. J Hepatobiliary Pancreat Surg. 2007;14:46-51

[75] Chopra S, Dodd GD, Mumbower AL, Chintapalli KN, Schwesinger WH, Sirinek KR. et al. Treatment of acute cholecystitis in non-critically ill patients at high surgical risk: comparison of clinical outcomes after gallbladder aspiration and after percutaneous cholecystotomy. Am J Roentgenol AJR 2001;176:1025-1031

[76] Itoi T, Itokawa F, Kurihara T. Enoscopic ultrasonography-guided gallbladder drainage: actual technical presentations and review of the literature (with videos) J Hepatobiliary Pancreat Sci. 2011;18:282-286

[77] Flowers JL, Bailey RW, Scovill WA, Zucker KA. The Baltimore experience with laporoscopic manangement of acute cholecystitis. Am J Surg 1991;161:388-392

[78] Zacks SL, Sandler RS, Rutledge R, Brown RS. A population-based cohort study comparing laparoscopic cholecystectomy and open cholecystectomy. Am J Gastroenterology 2002;97:334-340

[79] Araujo-Teixeria JP, Rocha-Reis J, Costa-Cabral A, Barros H, Saraiva AC, Araujo- Teixeira AM. Laparoscopic versus open cholecystectomy for cholecysytitis (200 cases) Comparison of results and predictive factors for conversion. Chirurgie 1999;124:529-535

[80] Banz V, Gsponer T, Candinas D, Güller U. Population-based analysis of 4113 patients with acute cholecystitis: defining the optimal time-point for laparoscopic cholecystectomy. Ann. Surg. 2011;254(6):964-970

[81] Yamashita Y, Takada T, Strasberg SM, Pitt HA, Gouma DJ, Garden OJ, et al. TG13 surgical management of acute cholecystitis. J Hepatobiliary Pancreat Sci. 2013;20:89-96

[82] Giger UF, Michel JM, Opitz I, Inderbitzin DT, Kcher T, Krähenbühl L, et al. Risk factors for perioperative complications in patients undergoing laparoscopic cholecystectomy: analysis of 22,953 consecutive cases from the Swiss Association of Laparoscopic and Thoracoscopic Surgery Database. J Am Coll Surg. 2006 nov;203(5):723-728

[83] Rhodes M, Sussman L, Cohen L, Lewis. Randomized trial of laparoscopic exploration of common bile duct versus postoperative endoscopic retrograde cholangiography for common bile duct stones. Lancet, 1998;351(9097):159-161

[84] Berthou JC, Drouard F, Charbonneau P, Moussalier K. Evaluation of laparoscopic manangment of common bile ducts in 220 patients. Surg Endosc. 1998;12(1):16-22

[85] Clayton ESJ, Connor S. Alexakis N. Leandros E. Meta-analysis of endoscopy and surgery versus surgery alone for common bile duct stones with the gallbladder in situ. Br J Surg. 2006;93(10):1185-1191

[86] Gigot J F, Leese T, Dereme T, Coutinho J, Castaing

D, Bismuth H. Acute cholangitis. Multivariate analysis of risk factors. Ann Surg. 1989;209(4):435-438
[87] Salek J. Livote E, Sideridis K, Bank S. Analysis of risk factors predictive of early mortality and urgent ERCP in acute cholangitis. J Clin Gastroenterol. 2009 Feb;43(2):171-175
[88] Lai ECS, Tam PC, Paterson IA, Ng MT, Fan ST, Choi TK, Wong J. Emergency surgery for severe acute cholangitis. The high-risk patients. Ann Surg. 1990;211(1)55-59