Acute cholangitis: current concepts

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Abstract

Background: Acute cholangitis, also known as ascending cholangitis, is a life threatening systemic condition which results from a biliary tree infection and obstruction. Severe acute cholangitis was reported to have a mortality rate between 11% and 27% in the 1990s. This article is a literature review about acute cholangitis. Its aim is to review the latest literature about acute cholangitis and to discuss its pathogenesis, clinical presentation, diagnosis, prognosis, risk factors and treatment.

Methods: Ovid Medline and PubMed database searches were performed for articles about acute cholangitis published in English from 1877 to 2016. The keyword search headings included "acute," "ascending", "cholangitis" and a combination of these were used. Only articles with full text descriptions were chosen for this literature review.

Results: Common causes of biliary tree obstruction include choledocholithiasis, benign and malignant biliary strictures. According to the Tokyo Guideline, clinical presentation, laboratory blood results and diagnostic imaging are important in the diagnosis of acute cholangitis. Treatments consist of intravenous fluids and antibiotics followed by biliary decompression and drainage. Available drainage options include endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), endoscopic ultrasound (EUS) and open surgical drainage.

Discussion: It is important to diagnose acute cholangitis as early as possible to initiate appropriate treatments to reduce mortality and morbidity.

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Introduction

Acute cholangitis is a potentially life threatening systemic condition characterised by an infection of the bile, which is normally sterile, and biliary obstruction. This condition was first described in 1877 by Charcot as having a triad of right upper abdominal pain, fever, and jaundice (Charcot's triad).[1] The diagnosis of acute cholangitis is made based on clinical presentation, laboratory results and diagnostic imaging. If acute cholangitis is not recognised early and treated appropriately, it can quickly develop into systemic inflammatory response syndrome (SIRS), sepsis and death. Acute cholangitis carried a mortality rate of more than 50%[2-3] in the 1970s and less than 7% in the 1980s.[4-5] Severe acute cholangitis had a mortality rate between 11% and 27% in the 1990s.[6-8] Early treatment with intravenous antibiotics and biliary decompression with drainage is fundamental in the management of acute cholangitis.

Materials and methods

Ovid Medline and PubMed database searches were performed for articles about acute cholangitis published in English from 1877 to 2016 (the condition was first described in 1877 by Charcot). The keyword search headings included "acute," "ascending", "cholangitis" and a combination of these were used. A list of articles was obtained and was examined to be carefully selected in this literature review. Only articles with full text descriptions were chosen. An organised discussion regarding pathogenesis, clinical presentation, diagnosis, prognosis, risk factors and treatment was then commenced.

Pathogenesis and Cause

Acute cholangitis results from both an obstruction of the biliary ducts and superposing bacterial infection. Causes of biliary obstructions are benign biliary strictures (post-surgical, acute and chronic pancreatitis, autoimmune cholangitis, primary sclerosing cholangitis, complicated stone or congenital anomalies), malignant biliary strictures (pancreatic cancer, gallbladder cancer, cholangiocarcinoma, small intestine malignancy or liver metastases), biliary stent obstruction, haemobilia or parasitic infections. The most common cause of biliary obstruction is choledocholithiasis[9]. Bile is sterile and bacterial infection of the bile results from ascending migration of pathogens or portal bacteraemia. The normal pressure at which hepatic bile is secreted is 12 – 15 cm H_2O and the normal extrahepatic bile duct pressure is 10 – 15 cm H_2O. Those pressures are regulated by the relaxation and contraction of the sphincter of Odi which maintain bile flow from the common bile duct to the duodenum and help in preserving the sterility of bile. If the pressure exceeds 30 cm H_2O, secretion of bile from the liver is inhibited.[9] Hepatic defence mechanisms are compromised when the choledochal pressure is more than 25 cm H_2O. Cholangiovenous reflux follows and pathogens have access to intrahepatic canicules, hepatic veins and lymphatics causing bacteraemia, systemic inflammatory response syndrome (SIRS) resulting in sepsis. Infection of the biliary tree without obstruction does not usually result in clinical acute cholangitis.[10] The most common organisms causing acute cholangitis are Escherichia Coli, Enterococcus species, Klebsiella species and Pseudomonas aeruginosa. [11-13] A few studies showed that Escherichia Coli is the main pathogen isolated in bile cultures from patients with acute cholangitis. [14-16] Weber et al found that Enterococcus species and Pseudomonas aeruginosa were most commonly isolated from bile cultures in patients with acute cholangitis with biliary stent endoprosthesis compared to acute cholangitis patients without biliary stent endoprosthesis.[11] Rerknimitr et al also found a higher incidence of Enterococcus species in

patients with acute cholangitis with biliary stent endoprosthesis.[12] Isolated Enterococcus species and Pseudomonas aeruginosa from bile cultures were shown to have a higher risk of bacteraemia.[11] Moreover, the presence of biliary stent endoprosthesis itself increases the risk of bacteraemia and polymicrobial infections.[12] Biliary stent endoprosthesis is sometimes inserted during endoscopic retrograde cholangiopancreatography (ERCP) after biliary drainage as part of the treatment of acute cholangitis. Because biliary stent endoprosthesis itself poses a risk for bacteraemia and polymicrobial infection, it is thus recommended to change or remove the endoprosthesis every 3 months.

Clinical Presentation

In 1877, Charcot first described acute cholangitis as having right upper abdominal pain, fever and jaundice (Charcot's triad).[1] In 1959, Reynolds and Dragan then proceeded to describe a more severe form of acute cholangitis that included Charcot's triad with altered metal state and septic shock (Reynold's pentad).[17] Prior to the introduction of the Tokyo Guidelines for the diagnosis and severity assessment of acute cholangitis in 2007, diagnosis of acute cholangitis were based on Charcot's triad and Reynold's pentad. However, it was not uncommon for Charcot's triad to be absent in patients with acute cholangitis and Reynold's pentad was even rarer. This is especially true in elderly patients with acute cholangitis and these results in delay in diagnosis and treatment. [18] Thompson et al found that the incidence of Charcot's triad was about 60% in 66 patients with acute cholangitis.[19] Gigot et al showed that Charcot's triad and Reynold's pentad were present in 72% (323 attacks) and 3.5% (15 attacks) respectively in a total of 449 acute cholangitis attacks.[20] Furthermore, Boey and Way consistently found that Charcot's triad and Reynold's pentad were observed in 69.7% (69 patients) and 5.1% (5 patients) in 99 acute cholangitis patients.[21] Amongst the 3 symptoms of

the Charcot's triad, abdominal pain and fever are the most common clinical features in acute cholangitis with an incidence of at least 80% whilst jaundice is about 60 – 70% [22-23]

Laboratory investigations

Blood tests that are useful in acute cholangitis are those suggesting inflammation (increased white blood cells and/or elevated C-reactive protein level) and evidence of biliary duct partial or complete obstruction (increased bilirubin, raised liver and biliary enzymes such as aspartate alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP] and ϒ-glutamyl transpeptidase [GGT]). Table S1 illustrates the positive rate of those blood tests in acute cholangitis as reported in the literature and has been submitted as a supporting information table (Table S1).

Diagnostic Imaging

Available imaging modalities that are useful in acute cholangitis are transabdominal ultrasound (US), endoscopic ultrasound (EUS), computed tomography with contrast (CT), magnetic resonance cholangiopancreatography (MRCP) and ERCP. Their role is to assess the presence or absence of an obstruction of the biliary tree, the cause of the obstruction such as gallstones and biliary strictures, and the level of the obstruction. US is readily available in all tertiary institutions. They are non-invasive and cheap. However it is operator dependent and thus the sensitivity for choledocholithiasis can vary from 25% to 63%. CT, on the other hand, has a higher sensitivity than US in locating the level of obstruction and underlying cause of the obstruction such as malignancy. Nevertheless, CT poses a radiation risk and use of contrast can cause acute kidney injury or allergies. In suspected malignancy, CT offers no

therapeutic capability and no tissue sampling. Akaike et al found that peribiliary oedema on CT can be a valuable sign to help in the diagnosis of acute cholangitis.[24] When the biliary tree is obstructed by a sludge or stone, the intraductal pressure increases and bacteria proliferate causing inflammation which spreads through the fibromuscular layer of the biliary tree and its surrounding fat tissues causing oedema. In acute cholangitis, the sensitivity and specificity of peribiliary oedema were 88.9% and 78.6% respectively.[24] Compared to its high sensitivity, the relatively low specificity of peribiliary oedema in detecting acute cholangitis shows that it is still important to correlate CT findings with clinical information. Arai et al reported a statistically significant increase in inhomogeneous enhancement frequency in the liver on CT in the acute cholangitis patient group (11 of 13 patients) compared to the control group without acute cholangitis (19 of 393 patients, $p < 0.001$).[25] MRCP has become more popular and widespread in recent years as it is non-invasive, has no radiation risk and is thus safe to be used in pregnancy. MRCP has a high sensitivity for biliary obstruction and bile duct stones of more than 6mm. However, MRCP offers only diagnostic and no therapeutic options. In addition, MRCP is not possible in patients who have severe claustrophobia and ferromagnetic implants. Eun et al described a statistically significant finding of transient periductal signal difference on MRCP in the acute cholangitis group (31 of 66 patients, 47%, $p < 0.05$) when compared to the non-acute cholangitis group (9 of 107 patients, 8.4%, $p < 0.05$) and an increased periductal signal intensity on T2-weighted images in the cholangitis group (26 of 66 patients, 39.4%, $p < 0.050$) compared to the non-cholangitis group (7 of 107 patients, 6.5%, $p < 0.050$).[26] EUS can be considered in rural places where MRCP is not available. In a systematic review, Ledro-Cano demonstrated no statistically significant differences in the accuracy, sensitivity and specificity in diagnosing choledocholithiasis between EUS and MRCP.[27] Prat et al showed that the sensitivity, specificity, positive predictive value and negative predictive value of EUS in detecting choledocholithiasis were

93%, 97%, 98% and 88% respectively.[28] But EUS is invasive, requires sedation and intravenous contrast and involves radiation exposure. ERCP can be both diagnostic and therapeutic especially in septic patients after normal working hours. Even though ERCP is not routinely thought as a diagnostic tool nowadays, it is particularly important in some places where there are no other modalities. ERCP has a sensitivity of 89%, specificity of 100%, positive predictive value of 100% and negative predictive value of 83% in identifying choledocholithiasis.[28] EUS is interestingly as sensitive as ERCP and EUS can potentially prevent unnecessary invasive common bile duct explorations.

Diagnostic Criteria for acute cholangitis

The Tokyo Guidelines for the diagnosis of acute cholangitis was introduced in 2007 at the Tokyo International Consensus Meeting due to a previous lack of internationally accepted criteria to diagnose acute cholangitis despite carrying a high morbidity and mortality rate. At the Tokyo Consensus Meeting, at least 90% of all participants agreed that the following 4 criteria were appropriate in the diagnosis of acute cholangitis; (1) history of biliary disease, (2) clinical presentation, (3) laboratory results suggesting inflammation and biliary obstruction and (4) diagnostic imaging findings indicating biliary dilatation or obstruction or evidence of an aetiology such as stricture, stent or stone.[22] These are summarised in Table S2 which has been submitted as a supporting information table (Table S2). Moreover, at least 70% of the participants at the Tokyo International Consensus Meeting decided that there was a need to categorise the severity of acute cholangitis into three grades to help in its management; mild (grade 1), moderate (grade 2) and severe (grade 3). [22] Two main criteria were used to assess the severity of acute cholangitis; 'response to the initial medical treatment" and "onset of organ dysfunction."[22] Initial medical treatments involve general

supportive treatment, intravenous fluid and intravenous antibiotics and should be started as soon as a diagnosis of acute cholangitis is suspected. Most cases respond well with initial medical treatment with improvement of clinical symptoms and laboratory results. But some patients do not respond to initial medical treatment and develop sepsis with or without organ dysfunction. Those patients require urgent biliary decompression and drainage, organ supportive care and intensive care together with medical treatments. Mild or grade 1 acute cholangitis is characterised as acute cholangitis which response to initial medical treatment. Moderate or grade 2 acute cholangitis is defined as acute cholangitis which does not respond to initial medical treatment but does not have organ dysfunction. Severe or grade 3 acute cholangitis is regarded as acute cholangitis which does not respond to initial medical treatment and is accompanied by organ failure; cardiovascular system (hypotension requiring dopamine e 5 μg/kg/min or any dose of dobutamine), central nervous system (altered mental state), respiratory system (PaO_2: FiO_2 ratio < 300), kidney (serum creatinine > 176 μmol/L), liver (PT-INR > 1.5) and haematological system (platelet < 100 x 10^9/L). [22] A summary of the severity of acute cholangitis is illustrated in Table S3 and has been submitted as a supporting information table (Table S3).

Prognostic Indicators and Risk Factors

Organ dysfunction is the most common predictor of a poor prognosis.[22] Confusion and shock are good clinical indicators of organ dysfunction.[29] Laboratory results in acute cholangitis suggesting organ dysfunction are serum creatinine (> 132 -> 176 μmol/L), low platelet count (<10 x 10^9/L <- 15 x 10^9/L), increased bilirubin (> 37.6 -> 171 μmol/L) and urea (> 7.4 -> 28 mmol/L). [22] Old age is also associated with significantly higher mortality and morbidity.[30] Rosing et al found that a total bilirubin of more than 171 μmol/L on admission has a 56%

sensitivity, 85% specificity, 21% positive predictive value and 96% negative predictive value for predicting death.[31] Moreover, white cell count on admission has a 50% sensitivity, 92% specificity, 63% positive predictive value and 88% negative predictive value for organ failure or death.[31] Agarwal et al showed that the rise in white cell count is less in elderly patients compared to younger patients with acute cholangitis.[32] The presence of Charcot's triad or Reynolds's pentad at presentation was not significantly associated with a higher mortality.[33] The timing of ERCP and biliary decompression is fundamental in acute cholangitis as delay can result in increased in mortality and morbidity.[34] Hui et al demonstrated that patients with acute cholangitis having tachycardia (heart rate > 100 beats/min), albumin less than 30 g/L, prolonged prothrombin time of more than 14 seconds and total bilirubin of more than 85 μmol/L are significantly more likely to fail initial medical treatment thus requiring an emergent ERCP.[35] Similarly, Pang and Chun found that a prolonged prothrombin, older age and dilated common bile duct predicted an urgent ERCP.[34] Based on their multivariate analysis, Gigot et al found that there seven statistically significant risk factors in predicting mortality (old age, female gender, acute renal failure, liver abscesses or liver cirrhosis and acute cholangitis secondary to malignant biliary strictures or post percutaneous transhepatic cholangiography).[20]

Treatment

The treatment of acute cholangitis is aimed at the two main aetiological components of the disease process; biliary infection which requires systemic antibiotics and initial medical treatment, and biliary obstruction which necessitates decompression and drainage. Broad spectrum intravenous antibiotics should be started as early as possible whenever the diagnosis

of acute cholangitis is suspected.[36] Biliary drainage can be achieved with ERCP, EUS, percutaneous transhepatic cholangiography (PTC) or open surgical drainage.

Antibiotics

Blood cultures should ideally be taken upon presentation before intravenous antibiotics are started. The role of antibiotic is to control inflammation, sepsis and not to sterilise bile. The choice of the broad spectrum antibiotics depends on the most likely bacterial organisms causing bile infection, severity of the disease, comorbidities of patients such as allergies, renal failure, liver failure and previous antibiotic history used by patients. Most common organisms causing acute cholangitis are Escherichia Coli, Enterococcus species, Klebsiella species and Pseudomonas aeruginosa. A penicillin/² -lactamase inhibitor such as piperacillin/tazobactam is usually used as the initial antibiotic. When the results of the blood cultures are available in a few days, the broad spectrum antibiotic should be changed to a narrow spectrum antibiotic. Intravenous piperacillin/tazobactam is usually enough for mild cases of acute cholangitis. For moderate and severe acute cholangitis, the addition of a third or fourth generation cephalosporin antibiotic should be considered. If the first choice antibiotic is not effective, fluoroquinolone or carbapenem are considered good alternatives. [37] The duration of intravenous antibiotics is usually 7 to 10 days depending on the response to treatment and biliary drainage.[36,38,39] The prolonged use of intravenous antibiotics is associated with lengthy hospital stay, increased risk of nosocomial infections, antibiotic resistance and high costs. Consequently, changing intravenous antibiotics to oral antibiotics as early as possible is sensible. Van Lent et al found that short term intravenous antibiotic of three days duration was adequate when satisfactory biliary drainage was performed and fever was resolving.[39] Park et al did not find any statistically significant differences in terms of

clinical symptoms, laboratory findings, recurrence of acute cholangitis and 30 day mortality between a group of patients with acute cholangitis who had a successful biliary decompression drainage who was on intravenous antibiotic for six days and then changed to oral antibiotic for eight days compared to another group of biliary decompressed acute cholangitis patients who was on intravenous antibiotic for 10 days and then switched to oral antibiotic for four days.[40] Solomkin and Mazuski suggested that intravenous antibiotic should be changed to oral antibiotic when there is no more fever or leucocytosis and when patients can tolerate oral intake. [41] Kogure et al performed a prospective study involving 18 patients with acute cholangitis who had successful endoscopic biliary drainage and suggested to stop all antibiotics when body temperature was less than 37^{o}C for 24 hours.[42] Out of those 18 patients, none had recurrent cholangitis within three days of stopping antibiotics.

Biliary decompression and drainage

ERCP is the procedure of choice for biliary decompression and drainage. However, ERCP itself can cause acute cholangitis. The incidence of acute cholangitis post ERCP varies between 0.5% and 5.8%.[43,44] When clinically assessing a patient, acute cholangitis should be categorised into severe and non-severe acute cholangitis. Severe (grade 3) acute cholangitis requires urgent ERCP. Initially, it is not often possible to differentiate between mild (grade 1) and moderate (grade 2) acute cholangitis as patients need to be given time to see if they "response to initial medical treatment" which is the criteria that separates mild and moderate acute cholangitis. According to the Tokyo guidelines for the treatment of acute cholangitis, mild (grade 1) acute cholangitis needs observation with initial medical treatment, moderate (grade 2) acute cholangitis requires early biliary drainage and severe (grade 3) acute cholangitis warrants urgent biliary drainage.[45] Biliary drainage by ERCP includes stent

placement or nasobiliary drain placement with or without sphincterotomy. Sharma et al found no statistically significant difference in effectiveness between biliary stents and nasobiliary drain.[46] However, there is more patient discomfort with nasobiliary drain.[47] Biliary drainage and stent placement can be successfully done without sphincterotomy as the latter is associated with acute pancreatitis, bleeding and retroduodenal perforation.[48] There are two types of biliary stents; plastic and metallic stents. The choice of the stent being used depends on the availability of the stents, cost and preference of the ERCP operator. Plastic stents are easier to insert and to remove and are more cost effective than metallic stents.[49] Plastic stents are also less likely to have tumour ingrowth or overgrowth which can cause stent obstruction but are more likely to be occluded with biofilm and sludge compared to metallic stents.[49] The two commonly used biliary stent sizes are 7 French and 10 French. Sharma et al found no significant difference in the safety, effectiveness, occlusion of stent or stent migration and time required for clinical symptoms and laboratory results to improve between two groups of patients with acute cholangitis with size 7 French and size 10 French straight flap biliary stents. [50] PTC is the second line procedure of choice for biliary drainage in acute cholangitis if ERCP is not available or fails. This is because PTC carries more serious complications such as biliary peritonitis and intraperitoneal bleeding, longer hospital stay and more significant patient discomfort resulting from the percutaneous catheter.[51-52] EUS guided biliary drainage can be done in tertiary institutions with appropriate expertise and equipment and can be an alternative to PTC. However, there is a lack of studies in the current literature comparing EUS to ERCP or PTC. Open surgical drainage is only considered when ERCP, PTC or EUS are not successful or are contraindicated.

Conclusion

Acute cholangitis is a serious condition caused by bile infection and biliary tree obstruction which can lead to sepsis and death. The introduction of the internationally accepted Tokyo Guidelines for the diagnosis of acute cholangitis, which is based on patient's clinical presentations, laboratory results and diagnostic imaging, provides an international platform for its early diagnosis and helps to improve morbidity and mortality. Blood cultures should be taken as early as possible and early intravenous antibiotics and fluids are fundamental in the initial management of acute cholangitis. Biliary decompression and drainage or treatment of the underlying aetiology should then be performed. Depending on the availability of resources, ERCP, PTC, EUS or open surgical drainage should be considered.

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List of Supporting Information

1. Table S1 (Positive rate of blood test results in acute cholangitis as reported in the literature)
2. Table S2 (Diagnostic criteria for acute cholangitis)
3. Table S3 (Severity assessment of acute cholangitis)