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Acute Biliary tract infections, Diagnostic criteria and Treatment

[1] Murtaza Mustafa,[2]Jayaram Menon[3],MDS. Rahman[4,] MTH. Parash,[5]SC.Shimmi

[1,3,4,5,] *Faculty of Medicine and Health Sciences, University Malaysia Sabah,KotaKinabalu.Sabah,Malaysia.*
[2.]*Department of Gastroenterology, Hospital Queen Elizabeth,Kota Kinabalu,Sabah,Malaysia.*

ABSTRACT:*Biliary tract infections, bile duct obstruction include biliary colic,choleocystitis cholangitis,and choleolithiasis are the common health problem worldwide.Twenty-five million adults have gallstones in the United States and 120,000 choleocystomies are performed in U.S. each year. Frequent risk factors include advance age, female sex,pregnancy using estrogen,diabetes,obesity,impacted gallstones, tumors of biliary tree, and bacterial and parasite infection. Women have twice to three times risk of developing gallstones than men, and whites have twice the prevalence of blacks,and Latina women showed higher prevalence than whites Intestinal flora are the frequent cause of acute cholecystitis and acute cholangitis.Severity of acute choleocystitis is classified into mild,grade I,moderate ,gradeII,and severe gradeIII.Diagnosis include clinical presentation,ultrasonography,CTscan,MRIscholangiography,endoscopic retrograde cholangiopancreatography- ERCP and, hepato-iminiodiacetic acid- HIDA test.Tokyo guidelines for the management of acute cholangitis are heplful.Drugs of choice are the broad spectrum antibiotics such as cefazolin,ceftriaxone,and pipercillin/tazobactam, mainly to cover enteric and anaerobic organisms.Early diagnosis of acute cholecystitis can prevent morbidity and mortality.*

KEYWORDS:*Cholecystitis, Cholangitis,Diagnostic criteria,and Treatment.*

I. INTRODUCTION

Infections of the biliary tract, including the common bile duct and gallbladder, are most often associated with obstruction to the flow of bile. In the United States and many developed countries, gallstones are very common and most often asymptomatic. In the United States, for example, it is estimated that 25 million adults have gallstones [1].In a small percentage of cases; gallstones may obstruct the cystic or common bile ducts, resulting in inflammation. Approximately 120,000 choleocystomies are performed every year in the United States for acute choleocystitis,most commonly secondary to impacted gallstones(cholelithiasis)[2] Other causes of biliary obstruction include tumors of the biliary tree or adjacent structures, strictures secondary to surgery or other injury(including prior infection),and in may geographic areas, infection by parasites including *Ascaris* and *Clonorchitis*.Stasis of bile, inflammation, and loss of mechanical barriers can lead to bacterial infection of the bile, which can result in severe morbidity and death[3]Women have two to three times the prevalence of gallstones compared with men, and whites have twice the prevalence of blacks. Latina women showed a higher prevalence than whites, blacks or Asians. Black women did not have a significantly higher prevalence than the white sample, other factors that appear related to the incidence of gallstones include,obesity,parity,using estrogens and diabetes mellitus[4].Mustafa I,*et al*. reported 12 cases of acute acalculous choleocystitis(AAC) in children[5].The severity of acute choleocystitis is classified into three grades mild(grade I),moderate (grade II),and severe(gradeIII),Grade III(severe acute choleocystitis) is defined as acute cholecystitis with organ failure[6].Enteric organisms are the frequent cause of acute choleocystitis and acute cholangitis, with monomicrobial(76%) and polymicobial(24%),with anaerobes included[7].Diagnostics tests include plain roentgenograms,ultrasonography,sonographic deigns,CTscan,MRIscholangiography(endoscopic retrograde cholangiopancreatography-ERCP),HIDA(hepato-iminodiacetic acid) a functional scan test, whereas ultrasonography is an anatomic test[8,9].Empiric antibiotic regimens are aimed primarily at gram-negative bacteria.Cefazolin,ceftriaxone, and pipercillin/tazobactam are equally effective. In elderly or critically ill patient and the patient with prior common duct or complex biliary procedures, a therapeutic regimen that includes anaerobic activity is reasonable [7].Cholecystectomy remains the treatment of choice for acute choleocystitis [8].The paper reviews the diagnostic criteria, and management of acute biliary infections.

II. PATHOPHYSIOLOGY

In choleocystitis only 20% of patients with gallstones experience biliary colic typified by right upper quadrant pain after a fatty meal when the contracting of gallbladder is prevented from emptying by obstructing stone. Biliary colic must be distinguished from the more serious acute choleocystitis which occurs in 1% to 3% of persons with symptomatic gallstones. In this disease, biliary obstruction is accompanied by an intense

inflammatory reaction. Obstruction is thought to lead to increased intraluminal pressure, may lead to compromised blood supply and lymphatic drainage; and in the setting of supersaturated bile, leads to acute inflammation.This process is mediated, at least in part, by prostaglandins, particularly postglandins,I_2 and E_2[10].Infection is not thought to precipitate acute choleocystitis, but it may complicate 20% to 50% of cases. In a microbiologic study of biliary tract processes,24(46%) of 52 patients presenting with acute choleocystitis had positive bile cultures, compared with 0 of 42 of normal controls and 49(22%) of 221 patients with symptomatic gallstones but no evidence of acute choleocystitis[11].Untreated choleocystitis may abate spontaneously, but serious complications also occur at a high rate. Once infection is established complications include gangrenous choleocystis emphysematous cholecystitis,gallbladder empyema, pyogenic liver abscess, and bacteremia.In acalculous choleocystitis 2% to 15% of cases,choleocystitis occurs in the absence of gallstones, although usually in the presence of other predisposing conditions. These include critical illnesses such as truma,burns and sepsis,as well as human immunodeficiency virus (HIV)infection, immunosuppression,diabetes,nonbiliary surgery, and childbirth[12].Some of these conditions predispose to ischemia in the gallbladder wall or stasis of bile(or both),resulting in concentration of bile salts and leading to inflammation and necrosis of the gallbladder[3].

Cholangitis refers to inflammation or infection of the common bile duct. The normally sterile bile may become infected because of loss of protective factors, including the flow of bile. Obstruction of the common bile duct leafs to stasis, which favors the growth of bacteria; increased pressure predisposes to bacteremia [3].Other factors may involve the antibacterial activity of bile on the proximal small intestine, allowing the greater growth of bacteria. Bacteria may then ascend to biliary tract(hence the terms *ascending and suppurative* cholangitis).Other routes of infection have been proposed, including via the portal system or the lymphatics.Primary sclerosing cholangitis is a disease of immunologic origin. AIDS related cholangiopathy, which has many features of acute cholangitis [3].

III. INFECTING MICROFLORA

Bacterial cultures from the bile and surgical sites of patients' acute chleocystitis and acute chlolangitis typically yield constituents of the normal intestinal flora [13].These include gram-negative bacilli such as *E.coli,Klebsiella*spp.,Enterobacter spp.Anaerobes,most frequently *Bacterioides* spp.*Fusobacterium* spp.,and clostridia are recovered less frequently but are isolated more often from patients with prior biliary tract surgical procedures and those with biliary-intestinal anastomoses. Finally, enterococci are not commonly found in infected bile, usually in association with other organisms[14].Parasites that infect the biliary tree include *clonorchis sinensis,0pisthrochis felineus,0pisthrochis viverrini,*and *Fasicola hepatica*[15].These organisms are prevalent in the regions of Asia and can cause acute and relapsing cholangitis with associated stricture and stone formation. *Clonorchis* and *0pisthrochis* infection can lead to the development of carcinoma of the biliary tract. *Ascaris lumbricoides*,a more common cosmopolitan parasite, occasionally obstructs the biliary tree, resulting in acute cholangitis[16].Echinococcal disease can cause biliary obstruction due to mass effect. Parasites that complicate HIV disease may also invade biliary tree [3].

AIDS cholangiopathy

Biliary tract disease is a complication of advanced HIV infection. In the era of potent antiretroviral therapy, AIDS cholangiopathy is now a rare entity [17,18].Although it is possible this condition is caused by infection of the biliary tract with HIV per se,more likely results from opportunistic infection of the biliary system. The pathologic findings of AIDS cholangiopathy include stenosis of the distal common duct and irregularities of the intrahepatic and extrahepatic bile ducts[19].The most common pathogen associated with cholangitis in HIV is *Cryptosporidium* .After an outbreak of cryptosporidiosis in Milwaukee in 1995,29% of patients with HIV infection and intestinal cryptosporidiosis developed cholangiopathy as well[20]. Cytomegalovirus is also a major cause of AIDS cholangiopathy include *Enterocytozoon bieneusi,Isospora belli,*and *Mycobacterium aviumintracellulare*.The clinical manifestations of biliary tract disease do not differ markedly from those non-HIV-infected individuals and include right upper quadrant pain fever. Diagnosis is usually made by characteristic finding on ultrasound, with dilatation of the common bile duct observed in approximately two thirds of cases. Endoscopic retrograde cholangiopancreatography (ERCP) demonstrates dilation and irregularities of the ducts and has become the gold standard for diagnosis [21].It is also useful in treatment: Sphincterotomy provides symptomatic benefits for many patients [3].

IV. CLINICAL MANIFESTAION

Patients with biliary tract disease most often present with pain in the right upper quadrant of the abdomen, although occasionally localizing findings are absent. The pain may radiate to the infrascapular region.Chleocystitis and cholangitis are distinguished from simple biliary colic by the continuous nature of the

pain [3].The finding of tenderness in the right upper quadrant on physical examination and the presence of Murphy's sign (inhibition of inspiration by pain when the area of the gallbladder fossa is palpated), with or without a mass, are highly suggestive of biliary tract disease. Fever and tachycardia are frequent findings [3]. Complications of acute choleocystitis, which occur in 10% to 15% of cases, include hepatic or intra-abdominal abscess, necrosis or gangrene of gallbladder, and perforation, which in turn leads to sepsis and peritonitis [3].
Acalculous choleocystitis,paerticularly in critical ill patient who is unresponsive, may produce very subtle findings, such as unexplained fever or vague abdominal pain. A high index of suspicion is required, because serious complications such as gangrenous gallbladder and perforation frequently occur [22].
Acute or ascending cholangitis is suggested by Charcot's triad of right upper quadrant or epigastric abdominal pain, fever or chills (or both), and jaundice, reported in 50% to 70% of patients [23].The additional less frequent signs of hypotension and altered mental status, in combination with Charcot's triad, constitute Reynold's pentad, which is reportedly seen in fewer than 14% of patients with ascending cholangitis. Symptoms and signs of an inflammatory response usually are present and are reflected in the presence of fever, leukocytosis, and other markers [24].

V. DIAGNOSTIC WORKUP

All patients require CBC,an elevated leukocytosis a left shift is the most frequent laboratory abnormality in acute cholepcystitis.Alkaline phosphatase and bilirubin are not usually elevated unless the common bile duct in involved. However, in one study of 217 patients with acute cholepcystitis,25% of patients without obstruction of common bile duct had elevated bilirubin[22].The role of bile and blood cultures in the diagnosis of cholecystitis is not well established. Recently developed practice guidelines(the "Tokyo Guidelines")advocate culturing blood(although Infectious Disease Society of America[IDSA} guidelines state that blood culture are not often useful)and when obtained,bile,since positive cultures may be predictive of progression to severe choleocystitis[25].Conversely guidelines of the IDSA recommend against collecting blood cultures from patients with community-acquired intra-abdominal infections[26].Tokyo Guidelines for the management of acute cholangitis and choleocystitis were published in 2007 (TG07).The severity of cholecystitis is classified into three grades. Grade 1(mild acute choleocystitis) is defined as acute choleocystitis in a patient with no organ dysfunction and limited disease in the gallbladder, making cholecystectomy a low- risk procedure. Grade 11(moderate acute cholecystitis) is associated with no organ dysfunction but there is extensive disease in the gallbladder, resulting in difficulty in safety in performing a cholecystectomy. Grade 11 disease is usually characterized by an elevated white cell count; disease duration of more than 72h; and imaging studies indicating significant inflammatory changes in the gallbladder. Grade 111(severe acute choelocystitis) is defined as acute choleocystitis with organ dysfunction [6].Acute cholangitis results in presentation with the clinical findings mentioned above. Abnormalities suggestive of sepsis syndrome, including leukocytosis, are frequently observed. Additional laboratory abnormalities include cholestatic liver function tests with elevation in alkaline phosphatase and bilirubin, particularly conjugated bilirubinElevation in ɣ-glutamyl transpeptidase is often seen as well. Abnormal amylase may suggest an associated pancreatitis and elevation in transaminases may indicate associated inflammation in liver parenchyma (or both).As in acute choleocystitis,the Tokyo guidelines recommend obtaining aerobic and anaerobic cultures of bile aspirates and blood in cases of cholangitis/Bile cultures are positive in 50% to 95% of patients, and blood cultures are positive in 30% to 40%[27].

Tokyo Guidelines (TG07) has been widely cited in the world literature. Because of new information that has been published since 2007.Tokyo Guidelines revision committee conducted and analyzed a multicenter analysis to develop the updated Tokyo Guidelines (TG13)[28].The major changes in diagnostic criteria of TG07 were re-arrangement of the diagnostic items and exclusion of abnormal pain from the diagnostic list. The sensitivity improved from 82.8%(TG07) to 91.8%(TG13).While the specificity was similar to TG07,the false positive rate in cases of acute choleocystitis was reduced from 15,5% to 5.9%.The sensitivity of Charcot's triad was only 26.4% but the specificity was 95.6%.However, the false positive rate in cases of acute choleocystitis was 11.9% and not negligible. As for severity grading 11(moderate) acute cholangitis is defined as being associated with any two of the significant prognostic factors which were derived from evidence presented recently in the literature. The factor chosen allow severity assessment to be performed soon after diagnosis of acute cholangitis.TG13 present a new standard for diagnosis, severity grading, and management of acute cholangitis[28].

Ultrasonography findings

Ultrasonography can frequently establish the diagnosis of choleocystitis and is usually the first study obtained. A sonographic Murphy's sign (i.e,,pain when the ultrasound transducer probes the gall bladder)is a useful diagnostic clue. In addition, the testing may be done at the bedside of critically ill patients, is relatively inexpensive and can directly visualize stones, particularly in the gallbladder. Abnormalities such as gallbladder wall thickening of greater than 4 mm,pericholecystic fluid, and intramural gas or ductal dilation are suggestive

of choleocystitis.[2].The combination of stones and either wall thickening or a sonographic Murphy's sign in the appropriate clinical picture were shown to have positive and negative predictive values exceeding 90%[29].
Radionuclide cholescintigraphy(hepato-iminodiacetic acid [HIDA} scanning) may be used if ultrasound fails to ascertain a diagnosis. A technetium 99m(^{99m}Tc)-labeled derivative of acetanilide iminodiacetic acid is injected intravenously and excreted into the bile. It is taken up by the gallbladder, which can then be visualized. Failure of the gallbladder to accumulate the marker is highly suggestive of choleocystitis due to obstruction of the cystic duct. Normally, visualization of the common bile duct and small bowel occurs, within 30 to 60 minutes; failure to visualize these structures indicates obstruction within the common bile duct or at ampula.In one study of cholescintigraphy in the diagnosis of acalculous choleocystitis in 62 critically ill patients, ultrasonography had sensitivity of only 30% whereas HIDA scanning had sensitivity of 100% and specificity 88%[30].
CT is not commonly used for the clinical evaluation of choleocystitis and its sensitivity and specificity for detection of this condition are not known. CT finding associated with acute choleocystitis include gallstones, particularly within the cystic duct, gallbladder distention and mural thickening, and enhancement of the liver adjacent to the gallbladder, which is CT equivalent of the scintigraphic"rim sign"[31].Magnetic resonance(MR)cholangiography is noninvasive technique that has been used to visualize the bile ducts. In one study of 35 patients comparing ultrasonography with MR cholangiography, the later modality showed 100 sensitivity for the presence of stones but was less sensitive than ultrasound in the detection of gallbladder wall thickening (69% vs.96%)[32].In a meta- analysis of 67 studies of MR cholangiography, the technique was highly sensitive-99%- for the detection of biliary obstruction and 92% sensitive for the detection of stones[33].

VI. TREATMENT

The biliary disease results most commonly from obstruction of the bile ducts, definitive treatment involves removal of the obstruction or the infected material. This can be accomplished surgically, percutaneously or endoscopically(i.e.,by ERCP).Antibiotics and other supporting measures must be considered temporizing[2].The role of antibiotics in acute choleocystitis has not been well established. Studies of patients with uncomplicated choleocystitis have failed to demonstrate a reduction in complications such as percholic abscess or perforation with antibiotic administration [34].Indeed; many cases of acute choleocystitis remit spontaneously. Antibiotics are clearly indicated for patients with complications of choleocystitis such as emphysematous or gangrenous cholecystitis or perforation.Antibiotics directed against enteric flora, should be given to patients who are debilitated, severelyill,elderly, immunocompromised or jaundiced. A β-lactam-β-lactamase inhibitor combination such as ampicillin/sulbactam or piperacillin/tazobactam is reasonable empirical therapy for community acquired choleocystitis,depending on local susceptibility pattern[34].Alternatively, a third- or fourth generation cephalosporin's may be used despite the lack of activity against enterococci [26].In one study, a cephalosporins (cefpime) was as effective as a combinations that covered enterococci(mezocillin and gentamicin),despite the presence of enterococci in bile cultures of 6 of 56 cefepime-treated patients[14].This finding may be the result of the low pathogenic potential of enterococci in this setting, elimination of other pathogens effectively treats the infection even in setting of persistent enterococcal contamination. As enterococci resistance to many antibiotics increases, the difficulty in directing therapy to these pathogens makes attempts at empirical coverage more difficult [26].

Acute cholangitis remains a disease with substantial mortality, and therapy should include antibiotics and supportive measures along with decompression/drainage of the biliary system for cases that do not respond promptly to conservative therapy. A variety of antibiotic regimens have been used in the management of acute cholangitis[24].Empirical coverage should be directed against enteric gram-negative bacilli. A β-lactam/β-lactamaseInhibitor such as ampicillin/sulbactam,ticarcillin/calvunate or piperacillin/tazobactam is appropriate initial empirical therapy[27].Cephalosprins,carbapenems,and fluroquinolones have also proved efficacious[27]. Selection of empirical antibiotic therapy in cases of health care- associated disease be influenced by local nosocomial resistance patterns as well as the patient's prior antibiotic exposures and known microbial colonization in acute cholangitis, the addition of metronidazole to the non β lactamβ-lactamase inhibitor combination and noncarbapenem regimens is advisable[27].Drainage of the biliary tract may be accomplished surgically, endoscopically,or percutaneously.ERCP has, to a large extent supplanted open surgical procedures in the management of acute cholangitis and is successful in more than 90% of cases[35].Paradoxically,ERCP is not infrequently the cause of acute cholangitis when it is used in an attempt to decompress and obstructed but not frankly infected bile duct[36]ERCP is generally thought to have a lower morbidity rate than open surgery, and it is more likely to offer definitive treatment(e.g.,by removal of an impacted gallstone) than percutaneous biliary drainage[3].

VII. CONCLUSION

Delay in diagnosis of acute choleocystitis increases morbidity and mortality.ERCP has supplanted open surgical procedures. Tokyo guidelines (TG13) present a new standard for the diagnosis, severity grading, and management of cholangitis.

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