Review Article

Cholangitis: Diagnosis, Treatment and Prognosis

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Abstract

Cholangitis is a serious life-threatening situation affecting the hepatobiliary system. This review provides an update regarding the clinical and pathological features of various forms of cholangitis. A comprehensive search was performed in the PubMed, Scopus, and Web of Knowledge databases. It was found that the etiology and pathogenesis of cholangitis are heterogeneous. Cholangitis can be categorized as primary sclerosing (PSC), secondary (acute) cholangitis, and a recently characterized form, known as IgG4-associated cholangitis (IAC). Roles of genetic and acquired factors have been noted in development of various forms of cholangitis. PSC commonly follows a chronic and progressive course that may terminate in hepatobiliary neoplasms. In particular, PSC commonly has been associated with inflammatory bowel disease. Bacterial infections are known as the most common cause for AC. On the other hand, IAC has been commonly encountered along with pancreatitis. Imaging evaluation of the hepatobiliary system has emerged as a crucial tool in the management of cholangitis. Endoscopic retrograde cholangiography, magnetic resonance cholangiopancreatography and endoscopic ultrasonography comprise three of the modalities that are frequently exploited as both diagnostic and therapeutic tools. Biliary drainage procedures using these methods is necessary for controlling the progression of cholangitis. Promising results have been reported for the role of antibiotic treatment in management of AC and PSC; however, immunosuppressive drugs have also rendered clinical responses in IAC. With respect to the high rate of complications, surgical interventions in patients with cholangitis are generally restricted to those patients in whom other therapeutic approaches have failed.

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Abbreviations: AC, acute cholangitis; ALP, alkaline phosphatase; ALT, alanine aminotransferase; CBD, common bile duct; CIP, chronically ill patients; ERCP, endoscopic retrograde cholangiography; EUS, endoscopic ultrasonography; EUS-BD, EUS-guided biliary drainage; EUS-CDS, EUS-guided choledo-choduodenostomy; EUS-GBD, EUS-guided gallbladder drainage; EUS-HGS, EUS-guided hepaticogastrostomy; IAC, IgG4-associated cholangitis; IBD, inflammatory bowel disease; IDUS, intraductal ultrasonography; MDR, multidrug resistance; MRCP, magnetic resonance cholangiopancreatography; PSC, primary sclerosing cholangitis; PTBD, percutaneous transhepatic biliary drainage; SC-AIP, cholangitis-associated autoimmune pancreatitis; UC, ulcerative colitis.

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Definition of cholangitis

Cholangitis syndromes are complex end-stage hepatobiliary disorders.[1] Given this broad concept, a wide range of abnormalities fall into the diagnostic criteria for cholangitis. These are generally associated with severe inflammation and fibrosis of the hepatobiliary system that is characterized by eventual narrowing and obstruction of the bile ducts.[2] Therapeutic interventions for obviating the obstructive lesions in biliary-hepatic ducts is the primary approach for management of cholangitis. Nevertheless, the only established curative therapy for cholangitis is liver transplantation, especially in patients with progressed disease.[3] New hopes are emerging, however, as improvements have been reported with therapies involving antibiotics and antifibrotic drugs.

Various type of cholangitis

The etiology and pathogenesis of various forms of cholangitis are heterogeneous. Cholangitis may be triggered by both genetic and acquired mediators.[4] Cholangitis may also present as a primary immune condition.[5] In a broad classification system, cholangitis cases can be divided into three main categories, including primary sclerosing cholangitis (PSC), secondary cholangitis, and immune cholangitis.[6]

PSC is a serious disorder with yet unknown etiology; however, a role has been proposed for immune dysregulation in the progression of PSC.[4] Bacterial infections secondary to bile fluid stasis may also complicate PSC.[7] On the other hand, the most common form of secondary cholangitis is acute cholangitis (AC; also known as recurrent pyogenic cholangitis, supportive cholangitis and ascending cholangitis). AC is characterized by infections involving the biliary system and leading to inflammation and obstruction of the biliary ducts.[8,9] Furthermore, the insidious role of the immune system has been highlighted in IgG4-associated cholangitis (IAC). Autoantibodies of IgA class that are reactive against biliary epithelial cell have been recently identified in IAC.[10] Nevertheless, the immune system may not be the sole contributor in IAC, as bile stones or bile duct abnormalities also have been related to occurrence of this condition.[11]

PSC

PSC is a heterogeneous disease regarding histopathological features, clinical presentation and treatment response, as well as malignant transformation rate.[12] PSC commonly follows a chronic and progressive course that may terminate in hepatobiliary neoplasms.[13] PSC has shown higher rates of incidence in recent years, with reports of 1/10000 in the population of Northern Europe.[14,15] The majority of PSC-affected

patients are men of European origin.[15,16] However, PSC affects all age groups worldwide, with higher prevalence in the 3rd and 7th decades of life.[17] Despite the suspected autoimmune nature of PSC, this condition is not responsive to immunosuppressive therapies.[18]

It has been noted that 90% of PSC cases are related to acquired environmental factors.[13] PSC is commonly associated with inflammatory bowel disease (IBD).[19] In fact, IBD-PSC has been proposed as a distinct clinical entity from isolated PSC, suggesting a strong association between the two disorders.[20] A range of 34–75% of the patients with PSC suffer from IBD, with the majority presenting with ulcerative colitis (UC).[2,21,22] There has been reported that this association highlights the role of gut microorganisms in PSC-IBS syndrome.[23] Reduced number of T-regulatory cells in inflamed hepato-biliary tissues of patients with PSC suggests a role for immune hyperactivity in pathogenesis of this condition.[24] In line with this, PSC may also develop in the context of other immune-mediated conditions, such as immune hepatitis, type 1 diabetes, sarcoidosis and immune thyroiditis.[25]

The role of demographic features in PSC remains controversial. In a cohort study by Fraga *et al.*[26] demographic parameters including male sex, pancolitis, non-smoking and previous appendectomy were significant risk factors for PSC. Smoking seems to be a protective factor against cholangitis.[20] The role of genetic predisposition in PSC has been noted. To date, 23 identified genetic loci have been related to PSC susceptibility.[13] The DRB01*03 haplotype of human leukocyte antigen loci is one of the loci with strong relation to PSC development.[16]

IAC

Cholangitis presentation may be observed in the context of a broader autoimmune disorder characterized with high levels of IgG4 in serum along with proliferation of lymphocytic populations positive for IgG4 (known as IgG4-related cholangitis).[11,27] Accordingly, IAC is characterized with infiltration of the biliary system with IgG4-positive lymphocytes.[28] Involvement of the bile ducts and pancreatitis are common features described in AIC. IAC is predominantly encountered in older individuals, and is mainly a feature of male subjects.[27,29,30] However, IAC has also been reported in children and adolescents;[31] the pathogenesis of this form of cholangitis is under investigation.

IAC or PSC, a diagnostic dilemma

With respect to the similar clinical features of IAC and PSC, the two may be misdiagnosed for one another.[22] However, these two entities can be differentiated based on the dominance of IgM and albumin serum level in PSC, while elevated levels of IgG4 are a feature of IAC.[22] The ratio of IgG4/IgG1 has also been suggested as useful for differentiating IAC from PSC.[32] IAC may also be distinguished from PSC according to the context of its specific histological features, such as more pronounced infiltration by immune cells (plasma cells, lymphocytes, and eosinophils).[30] The infiltrating plasma cells have been shown to express IgG4 in IAC.[33] Eosinophilic infiltration of hepatic tissue in IAC may also be useful for differentiation of the two conditions.[34]

Association of IAC with pancreatitis is a useful parameter that could be exploited for discriminating IAC from PSC.[27,30] In cases of isolated IAC without autoimmune pancreatitis, some features of IAC, including stenosis on cholangiography, stromal inflammation and response to immunosuppressive drugs, may be helpful in differential diagnosis.[27] On the other hand, PSC patients show hepatic fibrous change, and segmental stricture as pathological findings.[33] Presentation of obstructive jaundice, which is rarely seen in PSC, can assist in clinical differentiation of these two entities.[35] In addition to these, one can bring into mind that patients with PSC are generally younger that those with IAC.[33]

AC

AC (as well as suppurative cholangitis or ascending cholangitis) was first identified as a disorder associated with recurrent fever, abdominal pain and jaundice. This clinical combination has been traditionally known as Charcot's triad. AC is primarily an infectious disease characterized by the proliferation of bacteria within bile and with the secondary blockage of biliary tracts.[8] The Reynolds' pentad is defined as the occurrence of confusion and shock along with Charcot's triad.[36]

The initial version of the Tokyo Guidelines for the Management of AC and Cholecystitis (TG07) was introduced for the first time as a standard for diagnosis and management of AC; however, the TG07 suffered from lack of specificity and sensitivity, as well as having limited application in clinical practice.[37,38] These flaws were obviated to a large extent by the revised guidelines that were published in 2013 (version TG13). The TG13 statements achieved both high sensitivity and specificity (87.6% and 77.7% respectively). This approach uses three domains, including clinical, laboratory and imaging findings, with 2, 4 and 1 items (Table 1).[38] A severity score was also incorporated into the TG13. Based on this, AC can be classified into the following three grades: Grade III, severe form associated with organ failure; Grade II, moderate form requiring biliary drainage therapy; and Grade I, mild form including otherwise.[37,39]

Bile stone and obstruction of the bile duct are considered the main causes for acute bacterial cholangitis.[36] In addition, bile duct obstruction in AC may also be triggered by other

Table 1. Diagnostic criteria for acute cholangitis, Tokyo Guidelines

Parameter	Items
Clinical features	1. Previous biliary disorder
	2. Fever and/or chills
	3. Jaundice
	4. Abdominal pain
Laboratory features	5. Presence of inflammation indicators (elevated leukocyte count, positivity for C-reactive protein)
	6. Elevated liver enzymes
Imaging findings	7. Biliary dilatation, other abnormalities suggesting hepatobiliary disorder
Suspected diagnosis	Two or more items of clinical features
Definite diagnosis	Either Charcot's triad (2+3+4) or two items in the clinical features along with both items in the laboratory and imaging findings

etiologies. Choledocholithiasis has been described among the most common etiologies for AC; nevertheless, this phenomenon is often accompanied by secondary bacterial infections within the biliary system.[40] Other etiologies include gallstones, malignancies (source being pancreas, gallbladder, cholangiocarcinoma, or metastatic tumors) or benign obstructions (surgical, pancreatitis, or chronic cholangitis), and some parasitic disorders.[8] In a survey of 31 patients, Gossard *et al.*[41] reported cholecystectomy, stones in bile ducts, chronic pancreatitis, and abdominal trauma as the causes for AC.

Diagnostic modalities for cholangitis

Imaging evaluation of the hepatobiliary system has the primary role in diagnostic modalities for cholangitis. Imaging evaluation also has applications in staging and management of cholangitis.[42] A diagnostic imaging procedure for various forms of cholangitis should be able to reveal multiple characteristics of the biliary hepatic system, including stenosis and dilatation of bile ducts, as well as thickness of bile ducts walls, intrahepatic calculus, abnormalities of hepatic parenchymal tissue, evidences of hepatic dysplasia, and portal hypertension.[6,43] The most frequently used imaging studies are endoscopic retrograde cholangiography (ERCP), magnetic resonance cholangiopancreatography (MRCP), and endoscopic ultrasonography (EUS).[44]

Role of ERCP in cholangitis

ERCP is the gold standard for diagnosis of cholangitis.[45,46] ERCP may also be applied as a reference method for evaluating other imaging procedures, such as MRCP.[47] ERCP can be effectively exploited for diagnosis of cholangiocarcinoma in PSC, with specificity and sensitivity of 97% and 65%, respectively.[48] Furthermore, ERCP delivers a high (98.8%) success rate. Asymmetrical dilatation of bile ducts, as well as presence of calculi, is seen in ERCP. Decreased divisions of the biliary tree may be seen in ERCP with a more detailed resolution, thereby allowing for small ducts to be visualized.[49] By the use of ERCP, complete assessment of a ductal tree may be accomplished, showing the presence of obstructive lesions and stenosis.[50]

Instead of a diagnostic method, ERCP may also be performed as a therapeutic procedure for biliary drainage in cholangitis.[51] The role of biliary drainage procedures is of critical importance in the management of cholangitis. This approach provides a therapeutic alternative for patients who may not tolerate surgical drainage interventions.[51] ERCP-guided implantation of a biliary endoprosthesis or stent represents the gold standard therapeutic for biliary stricture.[52] This method is an effective therapeutic modality that can be tolerated even by elderly patients.[51] Therapeutic ERCP may be indicated when patients are in shock, show signs of nervous system involvement, or show coagulation defects.[51] Overall, other drainage procedures may be considered in cases in which ERCP is not possible, or under conditions for which ERCP is not available. Performing ERCP may not be feasible when there is pyloric or duodenal stenosis. ERCP may also fail if the catheter cannot be inserted properly or in patients with prior operations on the gastrointestinal tract.[52]

It is suggested that the biliary drainage procedure be performed with 24 hours of the cholangitis diagnosis.[53] Delay in performance of ERCP has been shown to increase the rate of recurrent cholangitis by 37%.[54] In accordance, ERCP is recommended to be performed within 24 hours of admission for patients with AC, as delaying this procedure can prolong hospital stay for these patients.[55] Nevertheless, no significant differences were reported in mortality rate or hospital stay among patients with cholangitis who had undergone ERCP during 24, 48 or 72 hours after admission for the procedure.[56] Timing of ERCP can be influenced by some factors, such as resuscitation period and hemostatic disease.[55]

ERCP is associated with higher rates of complications respective to other endoscopic procedures. These complications include pancreatitis, bleeding, trauma, and cardiopulmonary problems.[57] ERCP may lead to complications such as pancreatitis in 1.2–4% and cholangitis in 2–2.5% of cases.[58,59] Pancreatitis, perforation and bleeding, as well as cholangitis comprise the most common complications of ERCP in PSC patients. The overall rate of ERCP complications requiring hospital stay in PSC patients has been reported as 10%.[60] Other ERCP-related complications include increased common bile duct (CBD) diameter, biliary dilatation, biliary stent insertion, and cholangiocarcinoma.[61]

MRCP

MRCP, along with ERCP, is known to be one the most reliable procedures for diagnosing PSC. One major advantage of MRCP, however, is its noninvasive nature. In MRCP imaging, degree of intra- and extrahepatic bile duct, as well as gallstones and cholesterol stones, can be evaluated. In addition, low-diameter strictures are detectable by MRCP.[62] MCRP provides 80% and 90% sensitivity and specificity for diagnosis of PSC, respectively.[42] Considering the invasive nature of ERCP and its related complications, MRCP is gaining more and more pros as the first line assessment procedure in suspected PSC.[63] MRCP is also an effective method to follow up the patients, and for screening to provide timely diagnosis of complications.[63]

In comparison to clinical based-diagnostic approaches, use of MRCP resulted in a 3-fold increase in identification of PSC patients.[64] PSC can be characterized by randomly distributed annular strictures alternating with slightly dilated bile ducts, usually on both intra- and extrahepatic bile ducts in MRCP analysis.[63,65] MRCP has the ability to accurately detect stones of large size in the CBD.[44] Nevertheless, sensitivity of MRCP in identifying small stones is not satisfactory.[44] In addition; MRCP may miss bile duct dilatations in PSC.[66]

Role of EUS in cholangitis

Sonography is a relatively inexpensive and widely available method of imaging. EUS eventually may replace ERCP as a primary procedure for biliary drainage.[67] Endoscopic procedures are important in many aspects for managing patients with cholangitis, encompassing diagnostic, therapeutic and monitoring of the disease. Biliary duct dilatation, and small stones can be well diagnosed by EUS.[44] For detection of malignant transformations, EUS is a useful method and superior to ERCP.[68]

Regarding the invasiveness of ERCP and the low sensitivity of MRCP to detect cholangitis lesions in early stages of the disease, EUS has been proposed as a useful first-line diagnostic tool for cases with suspected cholangitis.[69] With respect to ERCP, EUS has the benefit of lower complication rates; and with respect to MRCP, it has significantly lower

costs.[70] EUS may become the first-line therapeutic and diagnostic method for biliary hepatic disorders in the near future.

EUS is also considered as an alternative drainage method for cases in which ERCP has failed.[67,71] The therapeutic approach of EUS in biliary hepatic diseases, designated as EUS-guided biliary drainage (EUS-BD), has been introduced as an alternative option for other drainage methods, such as percutaneous transhepatic biliary drainage (PTBD) and ERCP (Table 2). The endoscopic drainage encompasses balloon-dilatation and/or stenting of strictures, and improves the clinical picture and biliary-liver enzyme profile.[72]

EUS-BD is divided into EUS-guided choledo-choduodenostomy (EUS-CDS), EUS-guided hepaticogastrostomy (EUS-HGS) and EUS-guided gallbladder drainage (EUS-GBD) that can be used in various obstructive biliary hepatic disorders, each with a high rate of success (93%, 97% and 100%, respectively).[73] Nevertheless, regarding the low rate of complications of EUS, there has been suggestion to consider the EUS-BD as the first line therapy, even in cases without failed ERCP.[67,74] Another advantage of the EUS-BD approach is preserving bile flow, as compared to PTBD or surgical drainage methods.[75] However, stent occlusion, migration and shortening are among the difficulties faced by EUS-BD, all of which may necessitate stent replacement.[76]

Radial EUS has been applied for diagnostic goals in AC. Concentric wall thickness of bile ducts has been noted as the most reliable finding to predict correct diagnosis of AC by this method.[77] Intraductal ultrasonography (IDUS) diagnostic modalities have been noted to be useful in differentiation of PSC and IAC. Irregular inner margin, diverticulum-like outpouching and obliteration of three layers are the IDUS features specific for PSC, in comparison with IAC.[78] IDUS analysis in IAC patients shows circular-symmetric wall thickness, smooth outer margin, smooth inner margin and homogeneous internal echo in the stricture. A bile duct wall thickness greater than 0.8 mm in regions of non-stricture on the cholangiogram is a feature specific to IAC.[79]

Transabdominal US has been successfully applied for diagnosis of IAC, by observing thickness of the bile duct walls.[80] In this regard, results of IDUS can be used for characterization and identification of cholangitis-associated autoimmune pancreatitis (SC-AIP) from PSC or biliary caner, which is characterized with symmetrical wall thickness, presence of homogeneous internal foci and presence of lateral mucosal lesions continuous to the hilar.[81]

IDUS findings could also be used for estimating severity of cholangitis, namely by irregular inner surface, heterogeneous internal echo, and irregular outer contour, which correlate with severity of cholangitis.[82]

Antibiotics for cholangitis

New light has been shedding on the role of microbial components in development of various forms of cholangitis. Due to the high rate of positive microbial cultures from the bile ducts of cholangitis patients, it has been suggested to obtain a microbial profile before performing drainage methods. The most common bacterial infections in cholangitis include the *Escherichia coli*, *Klebsiella* spp., pesudomonal species, *Enterobacter* spp., *Acinetobacter* spp. of Gram-negative bacteria, and enterococcus, streptococcus, and staphylococcus Gram-positive bacteria.[84,85] Selection of antibiotics may be influenced by multiple factors, such as prior exposure of patients with hospital-acquired infections, as well as the severity of the disease.[84] For the best practice, administrated antibiotics for cholangitis should be those with broad range antimicrobial activities and which are capable of passing into the bile duct, such as third-generation cephalosporins, ureidopenicillins, carbapenems and fluoroquinolones.[86] The most effective antibiotics for cholangitis patients have been noted as imipenem-cilastatin, meropenem, amikacin, cefepime, ceftriaxone, gentamicin, piperacillin-tazobactam and levofloxacin.[87,88]

Table 2. Applications of endoscopic ultrasonography in cholangitis

Type of cholangitis	EUS approach	Number of patients	Specific diagnostic findings	Reference, year
IAC	Transabdominal ultrasonography	2	Bile duct thickening	Kobori *et al.,*[80] 2016
PSC and IAC	IDUS	15 patients with PSC and 35 patients with IAC	Irregular inner margin, diverticulum-like outpouching, disappearance of three layers are specific for PSC	Naitoh *et al.,*[78] 2015
AC	Radial EUS	28	Diffuse and/or concentric wall thickening (more than 1.5 mm), and intraductal heterogeneous echogenicity without acoustic shadowing are suggestive for AC	Alper *et al.,*[77] 2011
IAC	Transpapillary IDUS	23	Bile duct wall thickness more than 0.8 mm in regions of non-stricture is highly suggestive of IAC	Naitoh *et al.,*[79] 2009
AIDS-related sclerosing cholangitis	Simple	50	EUS findings are highly correlated with ERCP findings	Daly *et al.,*[83] 1996

Abbreviations: AC; acute cholangitis; AIDS, autoimmune deficiency syndrome; EUS, endoscopic ultrasonography; ERCP, endoscopic retrograde cholangiography; IAC, IgG4-associated cholangitis; IDUS, intraductal ultrasonography; PSC, primary sclerosing cholangitis.

Antibiotics in AC

The rates of polymicrobial-positive cultures in AC vary from 30–78%,[86,89,90] and the response rate to antibiotics in AC is satisfactory in the majority of patients.[40] The achievement of effective antibiotic therapy for AC decreased the death rate of this condition dramatically during the 1970s through 1980.[40]

An appropriate profile of antibiotic administration is vital in the early stages of acute infectious cholangitis. The majority of patients with acute bacterial cholangitis benefit from board-spectrum antibiotics.[36] It is an immediate need to administrate antibiotic therapy along with procedures performed for correcting the biliary obstruction.[90] There are no recommendations for discontinuing of antibiotic therapy, however, and it seems that cessation after relief from clinical symptoms, such as fever, and following drainage therapy has no adverse outcomes on the clinical course of the disease.[53]

In parallel, short-duration antibiotic therapy (of 3 days) appears sufficient when adequate drainage is achieved and fever is abating.[91] Regardless, it is highly recommended to preserve antibiotic therapy in the early phases of AC.[44] Furthermore, as septic shock is a potential threat in AC, it is a necessity to administrate broad-spectrum antibiotic therapies as early as possible (within 1–4 hours) following signs of septic shock development.[92] Either oral or intravenous administration of antibiotics seemed to be of equal efficiency in eradiation of bacteria in AC patients.[93]

Resistance to various antibiotics, including quinolone, carbapenems, vancomycin and ampicillin, has been observed in cultures isolated form AC patients.[90] In a study of a German population, 29% multidrug resistant (MDR) isolates were recovered from bile cultures of patients with AC. Risk factors for MDR in that study included male sex, previous antibiotic therapy and biliary stenting, with the recent factor being an independent risk factor.[90] Also, stent therapy was reported as a significant risk factor for acquiring MDR infections in AC patients.[94]

Antibiotics in PSC

The beneficial role of antibiotics in PSC is controversial.[95] A high rate of positive cultures has been reported for PSC patients.[86,89] The idea that antibiotic therapy may be useful in slowing down the progression of PSC originates from studies that described a role for bacterial species residing in the human gastrointestinal tract in the pathogenesis of PSC.[96] However, antibiotic therapy for 12 weeks with rifaximin resulted in no significant effects on the clinical course of PSC.[97]

In contrast, using vancomycin in conjunction with routine ursodeoxycholic acid therapy resulted in decreased liver enzyme levels in PSC patients, and in a relief of some clinical symptoms such as fatigue, pruritus, diarrhea and anorexia.[98] Significant reduction of alkaline phosphatase (ALP) enzyme was also observed in PSC patients treated with a combination of ursodeoxycholic acid and metronidazole, in comparison with ursodeoxycholic acid and placebo.[99] Vancomycin administration also improved alanine aminotransferase (ALT), gamma-glutamyl transpeptidase, and erythrocyte sedimentation rate in children with PSC.[100]

Both vancomycin and metronidazol therapy were found effective during a 3-month treatment period resulting in reduced ALT and bilirubin levels, and in the Mayo PSC risk score.[101] Vancomycin administration in patients with PSC-IBD resulted in an elevation in T-regulatory CD4+, CD25+ lymphocytes, which can modulate immune system activity. This was further reported to be associated with normalization of ALT and leukocyte counts in PSC.[43]

Role of surgery in cholangitis

Surgical intervention in cholangitis provides either a selective or emergency option. Although invasive, surgical intervention generally results in more persistent regression of the cholangitis.[102] Choosing a surgical intervention is dependent upon multiple factors, including patient characteristics (fulfilling requirement for general anesthesia, tolerability of surgical procedure, history of treatment failure) and pathological features of the hepatobiliary lesions and obstructions (Table 3).[103] Surgical therapy has been indicated for PSC patients with major obstructive lesions which failed removal by endoscopic drainage methods.[104] Accordingly, the surgical approach has been described as an effective treatment in AC that can be associated with significant improvement of clinical symptoms with the least post-surgical complications (3–6%).[105] It's noteworthy that caution must be taken to avoid unnecessary surgical intervention for IAC cases who may be misdiagnosed as bile duct carcinoma.[106,107]

Liver transplantation is the definitive surgical treatment for PSC.[108] Surgical treatment may also be indicated as a drainage procedure.[103] In such cases, surgery is the method of choice when other drainage methods such as ERCP and EUS-BD are not possible.[108] The drainage interventions along with surgery is indicated in cases with duct strictures, dilation or obstructive stones. Most commonly, hepaticojejunostomy is the method of choice for surgical biliary drainage.[103] Patients who underwent surgical drainage showed a higher mortality rate and longer hospital stay than those treated with endoscopic drainage.[111] Surgery may also be performed as partial hepatectomy in patients with cholangitis.[112] Generally, liver resection approaches are considered in cases with tissue hypertrophy or in cases with suspected cancer.[103] Interestingly, curative success of partial liver resection has been noted in three patents with PSC, but large cohort studies are needed for confirmation.[112]

Outcome and prognosis of cholangitis

Regardless of etiology, cholangitis is a serious life-threatening biliary-hepatic condition. A scoring system based on four parameters, including fever, hyper bilirubinemia, bile duct dilatation and presence of bile duct stones, has been proposed to predict severity of cholangitis.[113]

Prognostic features of AC

In a comparison between PSC and secondary SC patients, those with secondary diseases showed poorer prognosis and shorter life expectancy.[41] Using a delta neutrophil index which reflects the number of circulating immature granulocytes in blood has been noted as a significant prognostic factor in AC. In this regard, higher index corresponded with higher rate of early mortality in AC patients.[114]

Severe obstructions of bile ducts can cause extreme infected bile reflux and appearance of bacteria in blood, rendering a dire situation. In addition, low level of serum albumin along with prothrombin time (international normalized ratio) of >1.5 were associated with poorer prognosis and

Table 3. Surgical interventions in cholangitis

Cholangitis type	Number of patients, period and country of origin, sex, median age	Surgical procedures	Complications	Ref
Recurrent pyogenic cholangitis	94, 2007–2016 India, 66 women and 28 men, median age 40 years	Drainage procedure (HJ) (53%), left hepatectomy (19%), left lateral segmentectomy (14%), right hepatectomy (4%), right posterior sectorectomy (1%), left hepatectomy + HJ 5%, left lateral segmentectomy + HJ (2%), Right hepatectomy + HJ (1%)	Surgery-related complications in 32/94 patents, mild wound infection (9), severe wound infection (10), postoperative bile leak (6), postoperative hemorrhage requiring blood transfusion (1), chest infection (2), acute cholangitis (2), acute renal failure (1), sepsis (1)	102
Recurrent pyogenic cholangitis	80, 2001–2010 Hong Kong, 45 women and 35 men, median age 60 years	Hepaticocutaneousjejunostomy (100%), left lateral sectionectomy (19/80), left hepatectomy (11/80), right hepatectomy (5/80), right posterior hepatectomy (2/80), segment VIII resection (1/80)	23/80 (28.8%) residual stones, 31.3% recurrent stones, wound infection (9), postoperative ileus (1), intra-abdominal collection requiring drainage (1), bile leak (1), incisional hernia (2)	109
Recurrent pyogenic cholangitis	85, 1995–2008 China, 50 women and 35 men, median age 61 years	Hepatectomy (65.9%), left hepatectomy (15.3%), left lateral sectionectomy (47.1%), right hepatectomy (2.4%), right posterior sectionectomy (1.2%), hepatectomy + drainage procedure (9.4%), left hepatectomy + HJ (2.4%), left lateral sectionectomy + HJ (4.7%), left lateral sectionectomy + sphincteroplasty (1.2%), right hepatectomy + HJ (1.2%), drainage procedure (14.1%), hepaticojejunostomy (7.1), transduodenal sphincteroplasty (1.2%), T-tube drainage (5.9%), percutaneous choledochoscopy (10.6%)	Wound infection (50%), intra-abdominal collection (21.7%), pleural effusion (6.5%), bile leak (4.3%), atrial fibrillation (4.3%), wound dehiscence (2.2%), incisional hernia (2.2%), others (8.7%)	103
Recurrent pyogenic cholangitis	27, 1986–2005 USA, 15 women and 12 men, median age 54.3 years	Liver resection+ choledochojejunostomy with Hutson access loop (11/27), liver resection only (6/27), common bile duct exploration (10/27)	Wound infection (3), deep venous thrombosis (1), perihepatic hematoma (1), perihepatic abscess (3), hepatic insufficiency (1)	110

Abbreviation: HJ, hepaticojejunostomy.

refractory disease in AC.[115] In another study, the five adverse predictive factors of AC included hyperbilirubinemia, high fever, leukocytosis, advance age and hypoalbuminemia.[36] Likewise, parameters such as higher age, low blood pressure, leukocytosis, high C-reactive protein, and long period of antibiotic therapy were associated with poor prognosis in AC.[116] Likewise, severe leukocytosis (>20.000/μL) and total bilirubin >10 mg/dL have been associated with adverse outcome in AC.[117]

Prognostic features in PSC

Generally, PSC is a progressive disorder associated with the least response to routine therapeutics. There is still no established drug with true known positive effect on PSC. Despite the proposed role for the immune system in the development of PSC, effectiveness of immunosuppressive drugs involves slowing down the progression of the disease, but the mechanism is not clear. Liver transplantation is currently the only established treatment. Antibiotic and anti-fibrotic agents have shown beneficial effects in PSC,[2] but the overall results are controversial.

Hepatic involvement in PSC is characterized by a progressive fibrotic condition. Eventual deterioration of the bile duct in PSC may ultimately result in liver cirrhosis. Furthermore, development of extra- and intrahepatic ducts may accelerate neoplastic transformation.[16] The patients are at risk of cholangiocarcinoma, hepatic cancer, biliary cancer, and colon cancer.[2,4,118] The estimated rate of cholangiocarcinoma is as high as 10–12% in PSC patients.[118,119] To this rate, one should incorporate a 2–4% risk of hepatocellular carcinoma in end-stage liver disease.[118] The overall risk of neoplastic diseases in PSC is estimated to be 13–14%.[42] In another crude estimate, PSC patients are considered likely to die

from cancer in 40–58% of cases.[42] Overall, life expectancy of >10 years has reached 80% for PSC patients who undergo liver transplantation.[42] Patients with PSC may survive 12–15 years following diagnosis of PSC if not treated with liver transplantation.[2,23]

The main determinants of prognosis of PSC patients are timely diagnosis, appropriate timing of liver transplantation, and well management of the complications.[42] Other reported prognostic factors with poor outcome include higher ages,[120,121] higher levels of serum bilirubin,[120–122] albumin, alkaline phosphatase, presence of hepatomegaly, and/or splenomegaly.[121,122] Complications of PSC with bacterial infection is a further adverse feature of PSC that can result in recurrent acute cholangitis.[7] Risk of death, requirement of liver transplant, and malignancy were significantly higher in PSC patients with concurrent IBD.[123] Lower age onset of PSC seems to be a better prognostic factor respective to adulthood disease; however, in one-third of pediatric cases, the disease may be progressive.[21] Septic shock in PSC is a serious adverse outcome, with a high rate of mortality and a median survival rate of 1.1 years.[124] ALP level has been suggested as a prognostic factor that is capable of predicting such outcomes as need for liver transplantation and PSC-associated death.[125]

Prognostic factors in IAC

Generally, IAC patients seem to have more favorable prognosis than PSC patients.[22] IAC patients respond to steroid therapy,[28] but involvement of several organs in IAC has been associated with adverse outcome and failure of steroid treatment in IAC.[126]

Conflict of interest

The author has no conflict of interest related to this publication.

Author contributions

Conception and design, collection and assembly of data, data analysis and interpretation, manuscript writing, final approval of manuscript (AHMA).

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