Biliary Parasites

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Biliary parasites are a group of unrelated parasites which invade, involve or live in the biliary tract and produce a spectrum of clinical manifestations. Table 1 shows the classification of biliary parasites.

Biliary Parasites un Immunocompetent Host

Hepatobiliary & Pancreatic Ascariasis (HPA). Ascariasis is a helminthic infection of humans caused by the nematode *Ascaris lumbricoides*. Ascariasis has a global distribution. It has been estimated that more than 1.4 billion throughout the world are infected with A. lumbricoides. Hepatobiliary and pancreatic ascariasis (HPA) is one of the most common and well-described entities caused by *Ascaris lumbricoides*. Ascarides in the duodenum enter the ampullary orifice and can block it; they can advance further to the bile ducts, gall bladder, hepatic ducts and pancreatic duct. The magnitude of the problem of HPA in an endemic area was often underestimated in the past as worms move actively in and out of the bile duct from the duodenum and usually are not present in the ducts at the time of imaging or surgery. In prospective studies and with the use of ultrasonography and endoscopic retrograde cholangiopancreatography (ERCP) early in the disease, HPA is as common as gallstones as the cause of biliary and pancreatic disease in endemic areas (1, 2).

HPA is more common in women than men (female-to-male ratio of 3:1) with a mean age of occurrence being 35.0 years (range 4 to 70 years). HPA can cause five distinct clinical presentations. 1. Biliary colic. Biliary colic presents as sudden right hypochondrial pain associated with nausea and vomiting usually lasting just a few days. The pain may be recurrent in nature or severely prolonged demanding large doses of narcotic analgesics. 2. Acalculous cholecystitis. The patients present with pain the right hypochondrium, referred across to the back and lower angle of the scapula and to the right should and associated with vomiting and low-grade fever (37.2 to 37.8°C). Most of the patients have tenderness and guarding in the right

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Table 1. Classification of Biliary Parasites

Host immunity	Parasite	Disease	Mechanism of biliary involvement	Biliary Disease	Management
Immunocompetent	*Ascaris lumbricoides*	Ascariasis	Ascarides enter ducts through ampullary orifice	Biliary colic, cholangitis, cholecystitis, pancreatitis, hepatic abscess	Symptomatic, antihelmintic, endo-therapy in selected cases.
	Echinococcus granulosus	Cystic hydatid disease	Cyst rupture, compression, sclerosing cholangitis due to scolecoidal agent	Cholestasis, cholangitis	Surgery or Endo-Therapy, Albendazole as an adjuvant therapy, percutaneous drainage contra-indicated
	Echinococcus alveolaris	Alveolar hydatid disease	Grows and invades bile ducts	stricture	Long term albendazole, resection and endo-therapy
	Echinococcus vogeli	Polycystic hydatid disease	compression	cholestasis	Long term albendazole, resection and endo-therapy
	Fasciola hepatica	Fascioliasis	Fluke resides in bile ducts	Biliary colic, Cholestasis, cholangitis, stones	Bithionol, endo-therapy
	Clonorchis sinensis	Clonorchiasis	Flukes reside in bile ducts	Biliary colic, cholestasis, stones, cholangiocarcinoma	Praziquantel, endo-therapy
	Opisthorchis viverrini	Opisthorchiasis	Flukes reside in bile ducts	Biliary colic, cholestasis, stones, cholangiocarcinoma	Praziquantel, endo-therapy
	Opisthorchis felineus	Opisthorchiasis	Flukes reside in bile ducts	Biliary colic, cholestasis, stones, cholangiocarcinoma	Praziquantel, endo-therapy
Immunocompromised	*Cryptosporidium parvum*	Cryptosporidiosis	Invades papilla and biliary tree	Papillary stenosis, sclerosing cholangitis (HIV cholangiopathy)	Paromomycin with azithromycin (poor response), Endo-therapy
	Microsporidia	Microsporidiosis	Invades papilla and biliary tree	Acalculous cholecystitis in AIDS patients	Albendazole, endo-therapy
	Cyclospora cayetanensis	Cyclospora infection	Invades papilla and biliary tree	Acalculous cholecystitis in AIDS patients	Trimethoprim/sulfa methoxazole, endo-therapy
	Isospora belli.	Isosporiasis	Invades papilla and biliary tree	Papillary stenosis, sclerosing cholangitis (HIV cholangiopathy)	Trimethoprim/sulfa methoxazole, endo-therapy

hypochondrium, and a mass is palpable in the right hypochondrium. 3. Acute cholangitis. The patients present with hypochondrial pain and high-grade fever (38.3 to 40°C); jaundice; a tender enlarged liver; pronounced leukocytosis, and raised serum bilirubin, serum alkaline phosphatase, and serum alanine aminotransferase. In patients with pyogenic cholangitis, pus is seen exuding out of the papilla at duodenoscopic examination or recovered on bile aspiration at ERCP. These patients are critically ill with hypotension and metabolic acidosis (endotoxic shock). 4. Acute pancreatitis. The

patients present with epigastric pain referred to the back, vomiting, and raised serum amylase and alkaline phosphatase. Ninety percent of patients had mild pancreatitis, and 10% had severe pancreatitis. 5. Hepatic abscess. The patients present with right upper quadrant pain, high fever, and tender enlarged liver with intercostal tenderness, and edema of the right chest wall. Ultrasonography reveals an echo-poor lesion in the right lobe or left lobe (or both), and ultrasound-guided aspiration reveals pus, which yields ova or A. lumbricoides (3, 4).

Diagnosis of HPA can be made by ultrasonography and ERCP. The characteristic sonographic findings of worms in the ducts have been well described. The bile ducts are dilated and contain a thick, long, linear or curved, non-shadowing echogenic strip containing a central, longitudinal anechoic tube, probably representing the alimentary canal of the worm. These structures show characteristic writhing movement within the ducts. Ultrasonography is a highly sensitive and specific method for detection of worms in the biliary tree. ERCP has an advantage as a diagnostic tool in that it permits identification of the worms in the duodenum and those across the papilla. On cholangiogram, the worms in the ducts appear as smooth, linear filling defects. ERCP, in addition, has therapeutic potential, allowing removal of worms form the ducts or the duodenum (5).

The rational treatment for biliary ascariasis is to treat cholangitis by conservative means and affect the paralysis of worms in the intestines by oral administration of anthelmintic agents, from where they are expelled by effective peristaltic activity of the intestines. The administration of an anthelmintic agent into the biliary tree at cholangiography cannot be advocated as treatment for biliary ascariasis because it impedes the migration of live worms out of ducts into the duodenum. Endoscopic intervention is performed when patients do not respond to energetic symptomatic treatment within the first few days of hospitalization or when worms have not moved out of the ducts into the duodenum at 3 weeks. Worm extraction is successful in all patients from the ampullary orifice and in more than 90% of patients from the bile or pancreatic duct. After worm extraction, patients with biliary disease or acute pancreatitis have rapid relief of symptoms. Few (6%) patients developed complications related to endoscopy, including cholangitis and hypotension (6).

Biliary Hydatid Disease. Biliary disease can be caused by any of the agents causing hydatid disease. Hydatid disease, also known as echinococcosis or hydatidosis, is a zoonotic infection caused by larval forms (metacestodes) of the tapeworms of the genus *Echinococcus* and is characterized by development of expanding cysts in the liver and other body organs. Within the genus Echinococcus, four species are recognized. *E. granulosus* causes cystic hydatid disease, *E. alveolaris* causes alveolar hydatid disease, *E. vogeli* and *E. oligarthrus* cause polycystic hydatid disease (7).

Cystic hydatid disease can cause biliary disease through a number of ways. Rupture is the most common complication of complication in cystic hydatid

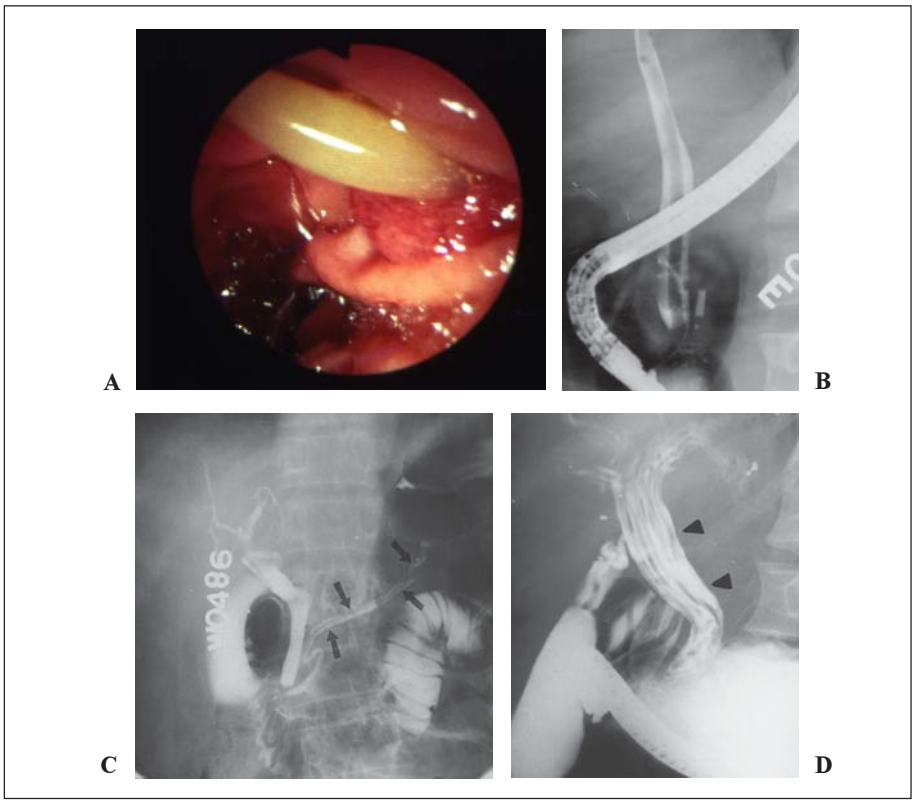

Fig 1. Hepatobiliary & Pancreatic Ascariasis. A. Duodenoscopic view of the ampulla of Vater with an ascarid in the ampullary orifice, B. Cholangiogram obtained at ERCP showing a long smooth filling defect of an ascarid in the bile duct, C. ERCP showing a long linear filling defect of an ascarid in the pancreatic duct (arrows), D. Cholangiogram obtained at ERCP with multiple linear filling defects of ascarides in bile ducts (arrows), note filling smooth curved filling defects of ascarides in the duodenum.

disease and occurs in around one third of patients. Cyst rupture could be of 3 types namely contained, communicating and direct. Contained rupture causes disruption of the laminated membrane, however, the ectocyst is intact and there is no communication with the biliary tree. Patients present with urticaria and skin rashes due to allergic reaction to the hydatid fluid. Communicating rupture causes break of the laminated membrane and ectocyst and communication with the biliary tree. Cyst rupture into the biliary tree causes obstruction of the ducts by daughter cysts and laminated membranes and presents as biliary colic, cholangitis and progressive cholestasis. Cyst contents may block the ampullary orifice causing acute pancreatitis. Cyst may get infected simulating pyogenic liver abscess. Direct rupture into the

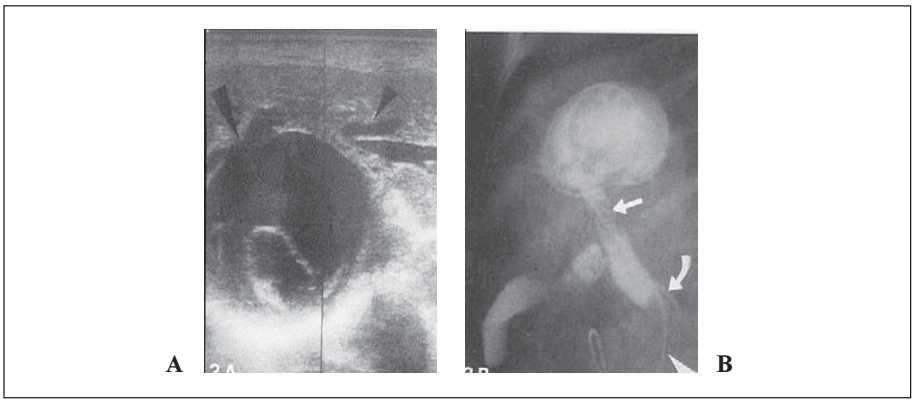

Fig 2. Biliary Hydatid Disease. Cystic hydatid disease with rupture and biliary communication. A. Ultrasound of the liver showing a large hydatid cyst, note floating laminated membrane, tear in the cyst wall (long arrow) and dilated bile ducts (short arrow), B. Cholangiogram obtained at ERCP showing dilated bile ducts with filling defects caused by laminated membranes and daughter cysts (arrows) and filling of the cyst cavity.

peritoneum causes immediate life threatening anaphylaxis and if the person survives, the scoleces implant on the peritoneal surface resulting in extensive peritoneal hydatidosis.[27, 28] Cyst can rupture into the pleural cavity or lung and can establish cysto-bronchial fistula.[23] Biliary peritonitis and biliary fistula may occur if the rupture occurs into biliary tree as well. A large cyst in the hilar region can compress the common hepatic duct causing cholestasis. Management of cysts in the porta hepatis may lead to inadvertent damage to bile ducts and cause biliary strictures. Use of scolecoidal agents to treat cysts with biliary communication can lead to severe progressive chemical sclerosing cholangitis. Alveolar hydatid disease causes formation of solid masses in the liver and commonly invades biliary tree causing strictures. Polycystic hydatid disease may compress and invade biliary tree causing biliary strictures (8-13).

Diagnosis of biliary hydatidosis requires high index of suspicion. Diagnosis should be suspected in a patient with biliary disease from endemic area, patient with previously known cyst or mass lesion in the liver or patient previously treated for hydatid disease either in liver or other sites. Diagnosis can be obtained by joint application of sonography and endoscopic cholangiography (14). Rupture of liver cysts into the bile ducts can be suspected on ultrasound. Ultrasound appearances include dilated bile ducts, non-shadowing echogenic structures within the ducts and loss of continuity of the cyst wall adjacent to the bile duct representing site of communication. However, ERCP is the recommended tool and reveals filling defects of varying shape and size in the dilated bile ducts and leakage of contrast medium into the cyst cavity.[26] Some-

times daughter cysts or laminated membranes in the bile ducts may be seen projecting into the duodenum through ampulla of Vater. Computed tomography is an alternative tool to visualize the cyst and has advantage for better documentation of site, size and structure of cyst. Magnetic resonance imaging may show a characteristic intense rim.

Treatment options for uncomplicated cystic hydatid disease are surgery, drug therapy and percutaneous drainage (15). However, percutaneous drainage is contraindicated if intrabiliary rupture is suspected. Inadvertent installation of sclerosing agent in to a cyst with biliary communication can cause sclerosing cholangitis (13). Treatment options in presence of intrabiliary communication include surgery or endoscopic treatment (16). Drug therapy is useful to effectively kill scolices and avoid progressive biliary or systemic hydatidosis. Surgery has the potential to remove cysts, clear the bile ducts of the hydatid material and lead to complete cure. Surgery is contraindicated in patients at extremes of age, pregnant women, and patients with co-morbid diseases and in those with multiple cysts and cysts, which are difficult to access. Operative mortality varies from 0.5-4.0 percent in centers with adequate medical and surgical facilities. Cyst fluid spillage can occur during surgery resulting in anaphylaxis and/ or secondary echinococcosis (2-25 percent of cases). Endoscopic therapy has been used in a small number of patients with hepatic cysts, which have ruptured into bile ducts. At ERCP, endoscopic sphincterotomy is performed; laminated membranes and daughter cysts are extracted and a nasobiliary drain is placed in the bile duct. The cyst regresses and disappears over the next 4 to 6 weeks.

Fascioliasis. Fascioliasis is caused by the sheep liver fluke *Fasciola hepatica*. Mature flukes reside in the biliary tree and cause chronic obstructive biliary symptoms. Fascioliasis is endemic in parts of Europe and Latin America, North Africa, Asia, the Western Pacific, and some parts of the United States (17).

Three clinical syndromes are recognized: acute or invasive, chronic latent and chronic obstructive. The acute phase corresponds to migration of young flukes through the liver and is marked by fever, pain right upper quadrant, urticaria, hepatomegaly and eosinophilia. Liver tests reveal mild abnormalities. The latent phase corresponds to the settling of the flukes into the bile ducts and can last for months to years. Affected patients may experience vague gastrointestinal symptoms. Eosinophilia persists and fever can continue. The chronic obstructive phase is a consequence of intrahepatic and extrahepatic bile duct inflammation and hyperplasia evoked by the flukes. Recurrent biliary colic, cholangitis, cholelithiasis, and cholestasis may result. Liver tests reveal features of biliary obstruction. Long-term infection can lead to biliary cirrhosis and secondary sclerosing cholangitis.

Diagnosis of acute infection is done by detection of antibodies by counter immuno-electrophoresis or enzyme immuno-electrophoresis

(ELISA). Chronic infection can be diagnosed by detection of eggs in feces, duodenal aspirate or bile. Hepatic imaging by ultrasonography or CECT is useful to define biliary dilatation and secondary hepatic changes due to cholestasis. ERCP will demonstrate adult flukes in the biliary tree and can be used to extract the parasites from the ducts.

Bithionol is the drug of choice and is administered in a dose of 50 mg/kg/day for 10 days. Bacterial cholangitis needs aggressive treatment with intravenous antibiotics and bile duct strictures need appropriate management.

Clonorchiasis & Opisthorchiasis. *Clonorchis sinensis, Opisthorchis viverrini*, and *Opisthorchis felineus* are trematodes of the family Opisthorchiidae. *C. sinensis* and *O. viverrini* are widespread in East and South-east Asia and linked to lower socioeconomic status. *O. felineus* infects humans and domestic animals in Eastern Europe (18, 19).

Clinical manifestations are cause by the presence of adult flukes in the bile duct, which release eggs that cause severe inflammation and fibrosis. Fever, pain right hypochondrium, tender hepatomegaly and eosinophilia are initial symptoms. Later features of chronic biliary obstruction occur. Patients develop cholelithiasis, cholecystitis, and recurrent pyogenic cholangitis. Liver tests reveal elevated serum bilirubin and alkaline phosphatase. Long-term infection leads to exuberant inflammation, marked biliary epithelial hyperplasia and dysplasia, and a substantially increased risk of cholangiocarcinoma.

Diagnosis is made by detection of characteristic fluke eggs in the stool except late in the disease. Cholangiography, at ERCP or PTC, reveals slender, uniform filling defects within intrahepatic ducts. Bile ducts reveal strictures, dilation and sacculation mimicking sclerosing cholangitis.

Praziquantel is the drug of choice and is administered in a dose of 75 mg/kg in three divided doses over one day. The response to therapy is suboptimal and recurrences are common. Dead flukes from the bile ducts need endoscopic or surgical therapy.

Biliary Parasites in Immunocompromised Host

HIV Cholangiopathy. A number of parasites can involve the biliary tree in patients with HIV infection and lead to a spectrum of clinical manifestations including HIV cholangiopathy and acute cholecystitis (20). Among these are included *Cryptosporidium parvum*, *Microsporidia*, *Cyclospora cayetanensis*, and *Isospora belli*. Most patients with cholangiopathy have severe immunosuppression, with $CD4^+$ counts of less than $200/mm^3$. Apart from the above named parasites HIV cholangiopathy can also be caused by cytomegalovirus (CMV), Mycobacterium avium intracellulare complex infection and candida albicans infection.

Typical clinical symptoms are right upper quadrant pain, fever, and elevated serum alkaline phosphatase level. Jaundice is uncommon. Diarrhea is common because many of the pathogens infect the small bowel as well. On physical examination right upper quadrant or epigastric tenderness is characteristic. Endoscopic retrograde cholangiopancreatography shows intrahepatic or extrahepatic changes of sclerosing cholangitis. Papillary stenosis is common as well.

Diagnosis is established by modified acid fast stain of the stool which can visualize the oocysts of the parasites. ELISA or direct fluorescence of the stool is also useful to detect the antigens of the parasites. Intestinal biopsy taken at endoscopic examination reveals numerous basophilic organisms stud the surface of the enterocysts.

Treatment includes use of antimicrobial and antiparasitic drugs and endoscopic management of biliary disease. Endoscopic sphincterotomy is adequate in patients with papillary stenosis, while bile duct strictures may need dilatation or stenting.

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