Non-Viral Infections of the Liver

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Abstract. The function and anatomy of the liver renders this organ peculiarly susceptible to bacterial and parasitic infections; fungal infections are increasingly recognised in the immunocompromised. As biochemical abnormalities of liver function can be non-specific, a high index of suspicion of liver or biliary infection is required. A need for prompt investigation is emphasised by the potentially rapid progression and poor prognosis of some bacterial and fungal infections, and the public health implications of parasitic diseases. This review encompasses the major infections of the liver and biliary tree other than viral hepatitis and includes aspects of pathogenicity, epidemiology, clinical presentation, diagnosis and management.
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Primary non-viral infections of the liver parenchyma itself are uncommon, presumably the phagocytic kupffer cells play a key role in preventing the infection. The liver's dual blood supply (Fig 1) renders it uniquely susceptible to infection: receives blood from the intestinal tract via the hepatic portal system, and is sustained by systemic circulation via the hepatic artery. Because of this unique perfusion, the liver is frequently exposed to systemic or intestinal infections or the mediators of toxemia. The biliary tree provides a further conduit for gut bacteria or parasites to access the liver parenchyma.

Infections of the liver with a wide range of organisms present variously from asymptomatic biochemical abnormalities to symptomatic hepatitis, or space occupying lesions e.g. abscesses or granulomatas producing biochemical changes of cholestasis but rarely significant jaundice. Some of these infections have a high mortality if not treated promptly. We describe non-viral infectious diseases affecting the liver caused by bacteria, mycobacteria, spirochetes, rickettsia, fungi and parasites.

BACTERIAL, SPIROCHAETAL AND RICKETTSIAL INFECTIONS

Bacterial Sepsis

Bacterial sepsis precipitating jaundice is a well recognised phenomenon particularly in the newborn and young infants.[1] The exact pathogenesis of hepatic insult is not known, but may be multifactorial, including direct invasion of liver parenchyma by blood-borne pathogens, and non-specific injury due to hypoxia, or endotoxin-mediated paralysis of biliary canaliculi inducing cholestasis. Implicated bacteria include 'coliforms', pseudomonads, *Salmonella* spp, anaerobes, *Haemophilus influenzae*, streptococci and *Staphylococcus aureus*. In patients with jaundice, serum bilirubin is usually between 5 and 10 mg/dl. Hepatomegaly is found in 50% of cases and liver enzymes usually mildly elevated. Clinical evaluation and microbiological investigation may identify the source of sepsis and antimicrobial therapy usually results in complete resolution.

Liver Abscess

Pyogenic liver abscess (PLA) in infancy and childhood is uncommon, with incidence ranging from 3 to 25 per 100,000, but carries a high mortality.[2,3,4] The aetiology of PLA is variable. Though PLA in healthy children is a rare entity, upto 40-50% has occurred among immunocompromised children.[2] Pyogenic bacteria can reach the liver through various routes: i) portal: secondary to gut pathologies such as appendicitis, inflammatory bowel disease or diverticulitis, sometimes complicated by portal pyelophlebitis and portal vein system thrombosis; ii) biliary: caused by extrahepatic biliary tract disease such as stricture, calculus, or malignancy; iii) blood-borne from an infected focus anywhere in the body *via* hepatic artery; iv) contiguous extension from gallbladder or perinephric abscess; v) following penetrating wounds of liver; vi) cryptogenic.[2]

PLA may present as single large lesion or multiple abscesses, the latter often secondary to biliary tract infection. The importance of the portal venous route has fallen with better diagnosis and management of appendicitis. In most reviews , more than 60% abscesses are in the right lobe, 20-25% bilateral, and less than 15% in the left lobe.[4] Predisposing factors include immunosuppression, quantitative or qualitative

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granulocyte abormalities like chronic granulomatous disease, trauma, umbilical vein catheterisation, omphalitis, sickle cell disease, biliary tract surgery, hepatic artery thrombosis (post-liver transplantation), liver biopsy percutaneous or endoscopic biliary drainage, diabetes, worm infestation and protein energy malnutrition especially in developing countries.[4,5]

Multiple abscesses complicate biliary diseases such as bacterial cholangitis, sclerosing cholangitis, congenital biliary anamolies (Carolie's disease) and gallstones with higher mortality. *Staphylococcus aureus* is the most common isolate in children but gram negative aerobes, anaerobes and microaerophilic streptococci are also common.[2,4] Less frequent causes include *Pseudomonas* spp., *Clostridium* spp., *Salmonella typhi, Yersinia enterocolitica* and *Pasteurella multocida*. The classic presentation is pyrexia, chills, right upper (RUQ) tenderness, abdominal pain, hepatomegaly and leucocytosis but may be non-specific. The diagnosis must be entertained in any pyrexia of unknown origin (PUO). Unusual presentations include an abdominal mass or acute abdomen secondary to rupture in to the peritoneal cavity or portal hypertension secondary to portal pyemia and portal vein thrombosis. Liver function tests may be unhelpful with non-specific changes. Ultrasonography (US), computerised tomography (CT) and magnetic resonance imaging (MRI) are all sensitive but can not always differentiate abscesses from other lesions such as cysts, tumours or hâemorrhage. US or CT-guided drainage of as much pus as possible (from as many abscesses as possible) confirms diagnosis, and is central to the management. Initial treatment is conservative with broad-spectrum antibiotics (e.g. ampicillin, gentamicin plus metronidazole or clindamycin) and should be adjusted when culture results are available.[6] Duration of treatment is usually 3-6 weeks. Patients with multiple abscesses has to be on conservative treatment after a diagnostic tap, and up to 3 to 4 months of antibiotic therapy has been recommended to prevent relapses.[7] Prognosis is worse in multiple abscesses. Most reports emphasize the good outcome after percutaneous drainage, which should be US or CT guided.

Contraindications to drainage include ascites and inaccesible lesions. Complications of aspiration include haemmorrhage, hepatic laceration, fistula formation, peritonitis and additional abscess formation. Indications for open drainage procedure are biliary obstruction, loculated or highly viscous abscesses, persistence of fever for more than two weeks despite percutaneous catheter drainage and appropriate antimicrobial therapy. Predisposing immunodeficiency conditions should be managed with appropriate expert opnion from immunologists or infectious diseases experts.

Cholangitis

The normal biliary tract is sterile and, in children, acute cholangitis rarely occurs in the absence of congenital abnormalities or interventions in the biliary tract.[8] The children at highest risk include those with portoenterostomy or choledochal cyst, and those who have non-operative biliary manipulations such as transhepatic cholangiography or endoscopic retrograde cholangiography with stent placement. Risk of cholangitis in children after Kasai operation has been reported to be 40% to 50%.[8] Partial biliary obstruction encourages bacterial growth, with increased intraductal pressure and reflux of bacteria into blood vessels and perihepatic lymphatics leading to bacteraemia. Infection may ascend from the duodenum or an infected gallbladder, or *via* lymphatics or bloodstream.[9] Cholangitis is a clinical diagnosis based on fever, abdominal pain, jaundice, pale stools or hepatic tenderness. However, the spectrum encompasses mild disease to severe sepsis, or shock, with bacteraemia.[8]

Although *Escherichia coli, Klebsiella* spp., *Enterobacter* spp. and *Pseudomonas* spp. are usually implicated, infection may be polymicrobial and include anaerobes.[8] Leucocytosis is common, but changes in liver function tests are non-specific; the serum bilirubin may be normal. In recurrent cholangitis liver biopsy may be indicated for confirmation and microbiological examination. Treatment requires supportive care and an urgent USS or CT will help establish whether obstruction requires drainage. Broad-spectrum antibiotics should be administered – such as an acylureidopenicillin (piperacillin, mezlocillin, or piperacillin-tazobactam) or late generation cephalosporin (e.g. ceftazidime), plus an aminoglycoside.[10] Single agents, such as piperacillin, piperacillin-tazobactam, ciprofloxacin and imipenem or meropenem, appear safe and effective if an aminoglycosides is contraindicated. Duration of treatment is generally 3 weeks for acute cholangitis but prolonged therapy may be necessary for recurrent cholangitis and multiply resistant bacteria.[11] Three months of intravenous antibiotics through central line has been helpful in treating recurrent cholangitis in biliary atresia children with portoenterostomy.

Tuberculosis (TB)

TB of the liver is almost invariably a complication of miliary disease, and occurs in 50% and 75% of patients with pulmonary or extrapulmonary TB, respectively. The site of primary focus usually dictates presentation. Rarely the liver appears to be the sole site of infection such as in congenital TB acquired *via* the ductus venosus.[12,13] Congenital TB may present in first few weeks of life with failure to thrive, hepatosplenomegaly and jaundice. In older children hepatic TB presents with PUO, weight loss, abdominal discomfort and hepatomegaly.[12,13] In areas of low incidence a positive tuberculin skin test is diagnostically useful. However, confirmation requires liver biopsy, histology and culture confirmation. Caeseating granulomata on liver biopsy are highly suggestive of TB, but may be absent; a granulomatous hepatitis can complicate Bacille Calmette-Guerin (BCG)

administration. The diagnosis of TB should be sought by specific staining and culture of material from other sites, including bronchoalveolar lavage; lymph node or pleural biopsy; marrow aspirate; lumbar puncture or early morning gastric aspirates, as clinically indicated. Polymerase chain reaction (PCR)-based tests may be helpful but require further evaluation. Standard anti-tuberculous therapy is effective, but expert advice should be sought in areas with a high incidence of drug resistant TB or in compromised patients, including those with concurrent HIV infection.

Brucellosis

It is a multisystem infection caused by *Brucella melitensis, B. suis, B.abortus* and *B. canis; B. melitensis* causes more severe disease with a higher risk of chronicity. In endemic areas transmission is often by ingestion of unpasteurised dairy products or raw meat. Granulomatous hepatitis may occur in acute or chronic disease and manifests as non-specific changes in liver function tests.[14] Diagnosis requires clinical suspicion; blood and bone marrow cultures; serology and histopathological examination. PCR-based tests for brucellosis are available. The recommended treatment for children under nine years of age with uncomplicated brucellosis is trimethoprim – sulphamethoxazole. For teatment of serious infection the addition of gentamicin or streptomycin is recommended for the first 1-2 weeks. Older children should receive doxycycline (6 weeks) plus rifampicin or streptomycin (2 weeks).

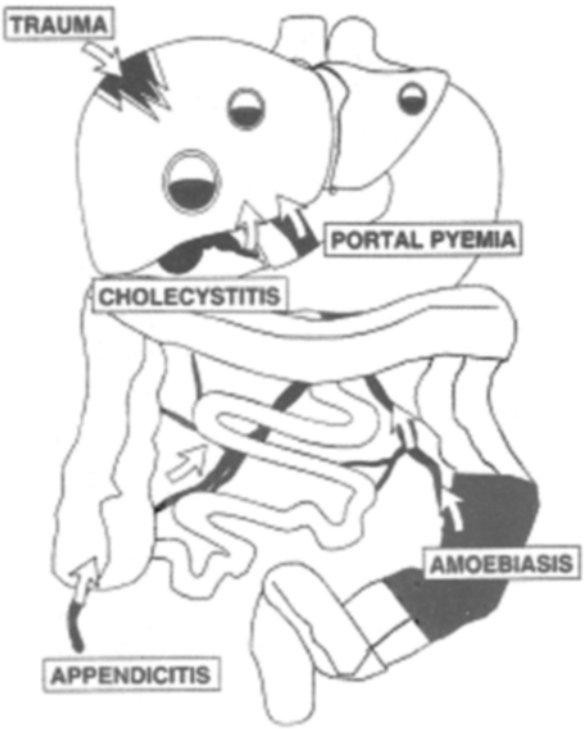

Fig. 1.

Listeriosis

Listeria monocytogenes may cause liver disease as part of systemic intrauterine infection of the foetus - granulomatosis infantiseptica at birth or later in the neonatal period and in older immunocompromised children after ingestion of contaminated food or water. The major hepatic manifestation is granuloma; jaundice is rare. Diagnosis is achieved by recovering the bacterium from blood culture, cerebrospinal fluid or liver aspirates. Treatment is with high dose ampicillin, with or without gentamicin.

Tularaemia

Francisella tularensis has been isolated from many wild mammals, domestic animals and birds. Human infection usually follows bites from parasites of these animals or direct contact with animals. In some cases a hepatitis-like picture follows with raised aminotransferases. Hepatomegaly is rare and biopsy may show necrosis. Diagnosis is usually serological as the bacterium is difficult to recover in culture. Treatment with streptomycin or gentamicin is effective; the fluoroquinolones appear promising but require further evaluation.

Leptospirosis

Human infection follows exposure to leptospires excreted in the urine of chronically infected animals – including rats, cattle and dogs - or water contaminated with urine. Children are usually infected when swimming in contaminated rivers, ponds or lakes, or by canine exposure.[15] Leptospires gain entry *via* skin abrasions, conjunctivae or mucosae and an initial leptospiraemia presages a multisystem infection. The incubation period is 5 -15 days and in 90% of patients there is a self-limiting anicteric disease but 5-10% develop jaundice (Weil's Disease).[16] Classically the anicteric leptospirosis runs a biphasic course, with a leptospiraemic phase lasting for 3-7 days and a second phase associated with leptospiruria and rising antibody titres lasting for 4-30 days. Predominant manifestations are fever, headache, myalgia, abdominal pain, nausea, vomiting, meningism, conjuctival suffusion, maculopapular rash, impaired renal function, lymphadenopathy and hepatosplenomegaly. Weil's Disease is characterised by hepatic, renal and vascular dysfunction with persistent fever, profound jaundice, abdominal pain, renal failure, confusion, epistaxis, hematuria, gastrointestinal bleeding and other haemorrhagic phenomenon. Death may follow cardiovascular collapse, renal failure and gastrointestinal or pulmonary haemorrhage, though with supportive therapy mortality should be less than 10%. Liver histology reveals swollen perivenular hepatocytes with increased mitoses indicative of regeneration and disorganised liver cell plates. Leptospires may be recovered from blood, urine or CSF during the first week of illness, and from

urine thereafter, and may be seen by dark ground microscopy of blood in the early stage of disease and in urine thereafter. Diagnosis, however, is usually serological using complement fixation tests (CFTs), enzyme linked immunosorbent assay (ELISA) or a microagglutination test. PCR can detect leptospiral DNA in blood, serum, CSF, urine or aqueous humor. Penicillin or doxycycline are recommended and most beneficial if started early in the disease: the benefits of commencing antimicrobials later in Weil's Disease are less clear.

Borreliosis

Borrelia burgdorferi, is a tick–borne spirochaete which causes systemic infection in humans (Lyme disease) following exposure to these vectors in forest or parkland. Predominant manifestations of acute disease are fever, malaise, extending erythematous rash, meningism, arthralgia, hepatitis and lymphadenopathy. Abnormal liver function tests occur in up to 20 % of patients and, rarely, hepatomegaly and RUQ tenderness.[17] Diagnosis requires clinical suspicion, positive serology and histopathology. Spirochetes may be seen in liver biopsy with a mixed inflammatory infiltrates in sinusoids, mitotic activity and ballooning degeneration of hepatocytes with hyperplastic Kupffer cells. Ampicillin or amoxicillin is administered for three weeks in early disease in children less than nine years of age; tetracycline for older children. In late disease intravenous cefotaxime or ceftriaxone for 2-4 weeks is recommended followed by oral ampicillin plus probenicid for a further 4-8 weeks.

Syphilis

Treponema pallidum may infect the foetus at any stage of maternal syphilis, causing disseminated infection. Congenital syphilis may result in mucocutaneous lesions, a diffuse rash, pneumonitis, myocarditis, hepatosplenomegaly, jaundice, lymphadenopathy, haemolytic anaemia, thrombocytopoenia, perichondritis and osteochondritis; the infant is usually small for age. Late stigmata include arthropathy with bilateral knee effusions, notched upper incisors, frontal bossing of the skull and poorly developed maxillae. Neonatal death usually results from liver failure, severe pneumonia or pulmonary haemorrhage. Diagnosis requires detection of spirochaetes by dark-field examination (skin rash, nasal secretions) or serology, including detection of specific IgM antibodies; long bone radiography at 1-3 months of age may contribute to diagnosis. Benzylpenicillin (10-14 days) remains the drug of choice.

Q Fever

Q fever is a systemic infection caused by the rickettsia *Coxiella burnetii* following exposure to infectious dust or aerosols from farm or domestic animals, or consumption of raw milk. Illness is usually a self-limiting 'flu-like illness with an incubation period of 1-2 weeks. However acute Q fever can present with atypical pneumonia and hepatitis with jaundice, hepatomegaly and abnormal liver function tests.[18] The characteristic histopathological findings is granulomata with dense fibrin rings around central lipid vacuoles. Diagnosis is by detecting IgG and IgM to phase II antigens of *C burnetii*, usually by indirect fluorescent antibody test or ELISA. Seroconversion occurs at 7-15 days after onset of symptoms with 90% patients having detectable antibodies by the third week. Titres of antibodies to phase I antigens exceed those to phase II antigens in chronic disease. Treatment is recommended for all cases to prevent chronicity. tetracycline or chloramphenicol are effective.

Fungal Infections

Fungal infections of the liver are usually seen in the immunocompromised - including those with acute liver failure. Although *Candida albicans* predominates, other *Candida* spp. and *Aspergillus* spp. infections are increasingly reported. Rarer fungal causes of hepatic infection include actinomycosis, mucormycosis and cryptococcosis.

Candidiasis

Severely immunocompromised patients are prone to disseminated candida infections with the liver (and often spleen) affected in 50-70%. Typically hepatosplenic candidiasis presents in haemato-oncology patients rendered neutropoenic at the time of recovery of the neutrophil count. The hallmark is multiple small lesions in the liver and spleen on USS or CT scan with raised alkaline phosphatase. Yeasts may be visible on fine needle aspiration or liver biopsy and cultures may be positive; blood cultures are usually negative. Hepatic or hepatosplenic candidiasis is treated with fluconazole or amphotericin B. Although prolonged therapy may be required, the immune status of the patient is the key determinant of outcome.

Aspergillosis

Disseminated aspergillosis is an increasingly recognised problem in the severely immunocompromised. Increased incidence is seen in hospital with building constructions. Hepatic aspergillosis may manifest as an aspergilloma or granulomata formation, with hepatomegaly, elevated bilirubin, alkaline phosphatase and amino-transferases. Confident diagnosis requires both histopathological demonstration of invading hyphae and isolation of *Aspergillus spp.* (usually *A. fumigatus*) from liver biopsy. To date serology has been unhelpful, but detection of circulating cell wall galactomannan by ELISA and PCR-based tests show promise. Treatment with amphotericin B should be commenced immediately - on clinical suspicion alone - in immunocopromised patients. Itraconazole is an alternative if amphotericin B is contraindicated or not tolerated; voriconazole and caspofungin require further evaluation.

Other fungal infections of the liver include

cryptococcosis, mucormycosis, histoplasmosis, blastomycosis, coccidioidomycocsis and paracoccidioidomycocsis.

PARASITIC INFECTIONS

Amoebiasis

Entamoeba histolytica is most commonly encountered in the tropics and subtropics. Hepatic abscess is a major complication of invasive amoebiasis and seen in 3-9% of adult cases but is less common in children.[19] Amoebic trophozoites reach the liver *via* the portal vein, induce hepatocyte apoptosis and a leukocyte response resulting in abscesses containing viscous brown pus. Hepatic abscesses can be demonstrated by US or CT scanning, are usually single, and most frequent in the right lobe. Multiple abscesses may be associated with more severe disease. A typical presentation is with pyrexia (75%) and RUQ pain radiating to the right shoulder. In left lobe disease there may be epigastric or left shoulder pain. Tenderness in the hypochondrium (85%), tender hepatomegaly (80%) and localised swelling over the liver (10%) may be elicited.[20] Less specific symptoms include nausea, vomiting, concurrent diarrhoea or dysentery (10%) and loss of weight. Jaundice is present in up to 8% of cases. The white blood cell count is usually elevated.

Demonstrating cysts in stool may contribute to diagnosis, but serum antibodies are present in more than 95% of patients. Aspiration under US guidance may yield 'anchovy sauce' pus; rarely amoebae are seen in necrotic abscess wall or adjacent parenchyma. Abscesses may rupture in to the peritoneal cavity, pleural cavity or lungs, pericardium, portal vein or biliary tract, intraperitoneal rupture being more common than intrathoracic. Extraintestinal amebiasis should be treated with metronidazole or dehydroemetine for at least 2 weeks.[21] The cure rate with both the drugs are same, but metranidazole has advantage being less toxic and being effective for both heaptic and intestinal phases of the disease.To prevent continued intraluminal infection, luminal amoebicide, such as paromomycin or diloxanide furoate should be given. Occassionally amoebic abscess do not respond to metronidazole and addition of daily chloroquine may be considered for two to three weeks. Chloroquine has an additive effect to metronidazole and better penetration of the abscess wall. Percutaneous needle aspiration is recommended for large abscesses, failure to respond, or if there is imminent risk of rupture, particularly in to the pericardium.

Schistosomiasis

Schistosomiasis affects 200 million people worldwide, the majority children aged 5-15 years.[22] Transmission occurs in endemic areas (Middle East, Brazil, West Indies, Far East, and South-East Asia) after exposure to water inhabited by infected snails. The intermediate hosts: larvae (cercariae) released from snails can penetrate intact skin and disseminate *S. japonicum*, *S. mansoni* and *S. mekongi* cause hepatosplenic disease subsequent upon portal venous system obstruction by a granulomatous response to eggs, and subsequent periportal fibrosis and portal hypertension. Granulomata consist of eosinophils, epitheloid cells, plasma cells and lymphocytes encirching an ovum. Patients present with pyrexia, urticaria, cosinophilia hepato-splenomegaly or upper gastrointestinal tract bleeding from oesophageal varicies. Dilated abdominal wall veins and ascites reflect portal venous hypertension and US may reveal thickening of the portal vein. Ova should be sought in stool and urine and may be identified in liver or rectal mucosal biopsy. Serological tests cannot distinguish past from active infection but a negative ELISA excludes the diagnosis. Praziquantel is the drug of choice; oxamniquine an alternative for *S. mansoni*.

Hydatid Disease

Echinococcus granulosus is the dog tapeworm. Typically dogs are infected by being fed offal from infected livestock - such as sheep - which contain hydatid cysts. Humans become infected by close exposure to domestic dogs and the eggs passed in their faeces. The liver is most frequent site for cyst formation, usually in the right lobe (60-80%). Presentation is with hepatic enlargement, with or without palpable mass, epigastric pain, nausea, and vomiting; secondary cyst pressure effects include portal hypertension, inferior vena cava compression or thrombosis, and biliary cirrhosis. US of the liver reveals round solitary or multiple cysts of variable size with multiple internal daughter cysts; calicification may be noted. Diagnosis requires demonstration of specific antibody by ELISA, CFT, indirect agglutination or latex agglutination tests. Closed aspiration should not be undertaken: definitive therapy requires surgical removal which may be complicated by spillage of contents, anaphylaxis, and seeding of new cysts. To avoid this, cysts can be injected with chlorhexidine or hydrogen peroxide prior to surgery. Both mebendazole and albendazole may successfully treat small uncomplicated cysts.

Ascariasis

Adult *Ascaris lumbricoides* worms cause disease by migrating into the pancreatic ducts, gallbladder, and biliary tract. Biliary ascariasis is more common in children than in adults. Children with a heavy worm burden may be malnourished. Presentation of biliary involvement includes fever, RUQ pain, vomiting and passing of worms in stool or vomitus. Mechanical obstruction by worms can cause acute cholecystitis, cholangitis and biliary colic. Adult worms in the biliary tract may be demonstrated by USS, cholangiography or endoscopic retrograde cholangiography (ERCP); eggs should be sought in the faeces.[23] Treatment is usually with mebendazole or albendazole - though endoscopic removal of adult worms

may be necessary if there are persisting biliary symptoms.

Toxocariasis

Taxocariasis is caused by infection with the dog roundworm *Toxocara canis*. Ingested eggs hatch in the small intestine and larvae penetrate the mucosa before migrating to the liver, lungs and many other tissues. Visceral larva migrans (VLM) refers to a syndrome of eosinophilia, pyrexia, leukocytosis, hepatosplenomegaly, lymphadenopathy and hperglobulinemia as the larva migrate. Occular disease may also occur. A history of exposure to puppies should be sought. Humans are a 'dead-end' host: adult worms do not develop so eggs are not passed. Serodiagnosis is with an ELISA. In massive infection liver biopsy may reveal eosinophils surrounding larvae or granulomata formation with epithelioid giant cells and lymphocytes. VLM is treated with thiabendazole. Severe disseminated disease or occular infection may warrant concomitant steroids.

Liver Fluke Infestation

Fasciola hepatica infection follows ingestion of aquatic plants - such as watercress-contaminated with eggs passed by infected sheep or cattle. After hatching, larvae penetrate the gut wall, enter the peritoneum and having breached the liver capsule pass through the parenchyma to the bile ducts. The flukes mature and lay eggs in the biliary tract, causing cholangitis and hepatomegaly. Diagnosis is made by demonstrating ova in stool and positive serology. ERCP may show filling defects due to inflammation and worms can be aspirated. Liver biopsy shows infiltration with eosinophils, histiocytes and polymorphs; granulomas may or may not be present. Treatment is with bithionol.

Clonorchis sinensis is endemic in the far East. Infection follows ingestion of cysts in uncooked freshwater fish or crabs. Metacercariae excyst in the small intestine and invade the bile ducts in which the flukes mature, producing eggs which may be demonstrated in the faeces. Infection is usually asymptomatic, but bile duct fibrosis with liver impairment, strictures and pancreatitis may ensue. Praziquantel is the treatment of choice.

Toxoplasmosis

In the immunocompetent patient acute acquired *Toxoplasma gondii* infection usually presents as self-limiting lymphadenopathy, though hepatosplenomegaly and hepatitis can occur.

The risk and severity of congenital toxoplasmosis vary according to the trimester in which maternal infection with the protozoan occurs. The likelihood of foetal infection increases through pregnancy, whilst disease severity decreases. The spectrum of disease in infected neonates includes: retinochoroiditis, meningoencephalitis, hydrocephalus, intracranial calcification, pneumonitis, myocarditis, purpura, hepatitis, hepatosplenomegaly and hydrops fetalis. Congenital toxoplasmosis must be differentiated from the other major causes of congenital infection: rubella virus, cytomegalovirus, herpes simplex virus, *T. pallidum* and *L. monocytogenes*. Diagnosis of congenital infection requires full clinical evaluation and exclusion of other infections, with recovery of *T. gondii*, histology or serological investigation. Reference laboratory tests include culture (blood, body fluids, placenta), the dye test (for serum and CSF) and ELISAs for IgG, IgM, IgA and IgE detection in both neonate and mother. *T. gondii* DNA may be detected in body fluids (blood, urine and CSF) by PCR. Treatment is with pyrimethamine plus sulphadiazine, though expert advice should be sought. Toxoplasmosis in the immunocompromised may follow reactivation or new acquisition and usually presents as central nervous system disease though other organs, including the liver, may be affected. *T. gondii* may be transmitted in the graft at liver transplantation and cause liver and severe systemic disease thereafter.

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