Tropical liver disease

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Abstract

The liver is frequently involved in infections that are prevalent in different regions of the tropics, and chronic liver disease, sometimes with multiple aetiological explanations, is an important cause of early morbidity and mortality. This article describes some hepatic and biliary problems that are seen in the tropics or can be imported from resource-poor settings. The epidemiology of hepatitis A is changing in some areas, and hepatitis E is now recognized in an increasing range of tropical and non-tropical settings. Vaccines have been developed against hepatitis E. Hepatitis B and C continue to cause chronic liver disease, cirrhosis and hepatocellular carcinoma, but these can be eclipsed in epidemiological importance by the sequelae of the emerging epidemic of non-alcoholic fatty liver disease in many parts of the tropics. The pathophysiology of acute and chronic liver disease caused by aflatoxins is better understood, as is the relationship of veno-occlusive disease of the liver to pyrrolizidine alkaloids. Self-poisoning with hepatotoxins is common in many countries. The diagnosis and management of cystic hydatid disease of the liver has been rationalized, based on a systematic approach to the classification of imaging findings.

Keywords Aflatoxins; biliary parasites; hepatitis; hepatobiliary tumours; jaundice; MRCP; tropical liver disease

Key points

- The differential diagnosis of liver disease in people arriving from the tropics includes many conditions that are rare in developed countries
- Food-borne toxins are common in resource-poor settings, causing both acute and chronic liver disease
- Traditional medicines can cause liver disease
- Chronic viral hepatitis (B, C, D) is common in individuals who were born in resource-poor settings, is typically acquired in childhood and is often iatrogenic
- Mass lesions or cysts in the liver can be of parasitic origin
- Expert advice should be sought when dealing with unusual imported hepatic conditions

Introduction

Some hepatic and biliary problems are specifically seen in or can be imported from the tropics (summarized in Table 1).

Jaundice and/or hepatitis (see also *Medicine* 2018; 46(1): 20–23)

Several prehepatic, intrahepatic and post-hepatic conditions are specific to resource-poor settings. Haemolysis, resulting from haemoglobinopathies and other inherited blood disorders, is common; it is sometimes associated with secondary gallstones, and can be provoked by acute infections, particularly pneumococcal disease and malaria. Many infections, including malaria, cause hepatitis, with varying degrees of jaundice and hepatosplenomegaly (see also *Medicine* 2018; **46(1):** 52–58). Some, such as viral hepatitis, are widespread, whereas others, such as yellow fever, are found only in specific geographical regions.

Hepatitis A used to be a universal childhood infection in most of the tropics, inducing life-long immunity; therefore a jaundiced adult in the tropics was unlikely to have acute hepatitis A unless they were an unvaccinated visitor from a resource-rich setting. However, childhood infection is becoming less common in countries where sanitation is improving, such as Singapore and the Middle East, and in Sri Lanka <70% of adults have had childhood exposure; therefore adults and adolescents are now being seen with acute hepatitis A. Hepatitis E is present throughout the tropics, has caused several recent epidemics in Sub-Saharan Africa, and is endemic in Central America and the Indian subcontinent. Hepatitis E is now the most common cause of acute viral hepatitis in travellers returning to the UK (see Hepatitis E, A and other hepatotropic viruses, pages 740–745 of this issue).

Asymptomatic infections with the glandular fever group of viruses (e.g. Epstein–Barr virus, cytomegalovirus) are also common in childhood in the tropics, and are quite common causes of acute hepatitis in young adults returning to the UK after travelling overseas.

The history and geographical setting usually limit the number of likely diagnoses in patients with abnormal liver function tests (LFTs) with or without jaundice. For example, in Sri Lanka, the most likely causes of increased LFT values with or without jaundice and fever include cholangitis/cholelithiasis, dengue and leptospirosis.

In tropical communities with high carriage rates of hepatitis B, an outbreak of jaundice with high mortality could suggest an epidemic of 'superinfection' of chronic hepatitis B carriers with hepatitis D (formerly delta hepatitis), known as 'Santa Marta' or 'La Brea fever' in parts of South America. In most tropical

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Tropical liver disease by presentation and/or aetiology

Jaundice/hepatitis/hepatosplenomegaly
Acute viral hepatitis A, B, C, D and E
Biliary flukes
Brucellosis
Dengue
Enteric fever
Hepatobiliary ascariasis
HIV related (e.g. cryptococcosis)
Inherited haemolytic disorders
Leptospirosis
Malaria
Oriental cholangiohepatitis
Rickettsial infection
Secondary syphilis
Sepsis
Tuberculosis
Viral haemorrhagic fevers
Yellow fever
Toxins and drugs
Ackee poisoning
Aflatoxins
Amanita phalloides (death cap mushroom)
Bantu siderosis (iron)
Bush teas
Illicit alcohol (methanol)
Industrial toxins
Indian childhood cirrhosis (copper)
Paraquat
Traditional herbal remedies (pyrrolizidine alkaloids)
Cirrhosis and/or fibrosis
Alcohol
Chronic hepatitis B, D and C
Non-alcoholic fatty liver disease
Schistosomiasis (fibrosis)
Hepatomegaly
Alveolar hydatid
Amoebic liver abscess
Cholangiocarcinoma
Cystic hydatid
Hepatocellular carcinoma
Liver fluke *Fasciola hepatica*
Pyogenic liver abscess
Massive hepatosplenomegaly
Hyperreactive malarial splenomegaly
Late-stage schistosomiasis
Tropical splenic lymphoma
Visceral leishmaniasis

Table 1

communities experiencing a sudden outbreak of jaundice, the more likely diagnoses are water-borne or food-borne problems, including:

- hepatitis E — especially affects young adults, and can cause deaths of pregnant women and fetal loss
- leptospirosis — often associated with heavy rains/floods
- food toxins (e.g. aflatoxin) — acute poisoning reported in India and Kenya.

Dengue

Dengue fever, a febrile illness transmitted by mosquitoes, can be complicated by potentially lethal hypovolaemia because of intravascular fluid leakage and/or bleeding (severe dengue). The global incidence of dengue has increased, and around half of the world population living in urban and semi-urban areas is at risk of infection. Hepatic dysfunction is a well-recognized complication of dengue, occurring more often in adults than children.[1] Aminotransferase elevation is observed in almost all patients, the degree of elevation correlating with the severity of the illness. Typically, serum bilirubin is normal or only minimally raised, and aspartate aminotransferase (AST) concentration exceeds alanine aminotransferase concentration, compared with the reverse pattern for viral hepatitis. Jaundice and acute liver failure develop in a small proportion of patients.

The pathogenesis of liver illness in dengue is not well established, but direct viral involvement, immunologically mediated mechanisms and ischaemia may all contribute. In some patients, rapid elevation of aminotransferases to very high levels follows hepatic ischaemia, and AST >1000 U/litre is one indicator of severe dengue. This is more common in critically ill patients who are in cardiovascular shock, and can rapidly lead to acute liver failure. One factor that can influence the pattern of disease seen in adults is the potential for underlying chronic liver disease, especially non-alcoholic fatty liver disease (NAFLD) or chronic viral hepatitis, to compound the effects of severe dengue.

Early detection of the leaking phase and appropriate fluid replacement are key to preventing ischaemic organ dysfunction. Patients with dengue who are at high risk of severe liver damage should be monitored frequently so that significant liver damage can be detected early. Patients with impending liver failure or who develop liver failure need intensive care management under a liver intensivist.

Leptospirosis

Leptospirosis is suggested by exposure to water, subconjunctival haemorrhages, raised serum creatine kinase, mild elevation of aminotransferases relative to bilirubin, and renal or cardiac involvement. These are initial clues pending the availability of specific serology.

Tuberculosis

Tuberculosis affects the liver in several ways. Caseating granulomatous hepatitis ranges from mild to severe and results rarely in hepatic failure, usually in the context of advanced disseminated infection. Obstructive jaundice, although rare, can result from lymphadenopathy obstructing the porta hepatis, and tuberculosis therapy can be complicated by drug-induced hepatitis. Patients with HIV can have invasive non-tuberculous mycobacterial or cryptococcal hepatitis.

Biliary parasites

The roundworm *Ascaris lumbricoides* infects billions of people. Its major acute morbidity is associated bowel obstruction in children. However, adult worms occasionally migrate up the

biliary tree to cause cholangitis, which can be relieved by endoscopic removal. Hepatopancreatic ascariasis (Figure 1) is more common in women and can account for one-quarter of cases of pancreatitis in India. The worms occasionally migrate further up the biliary tree and can form a nidus for infection and subcapsular hepatic abscesses. Biliary fluke (*Clonorchis/Opisthorchis*) infections in South-East Asia cause cholangitis with blood eosinophilia and can be recognized by the presence of fluke eggs in the faeces. They respond to treatment with praziquantel. Chronic fluke infection is associated with cholangiocarcinoma, particularly in male patients.

Toxins

Environmental contamination can lead to acute or chronic poisoning; for example, individuals who work in the polyvinyl chloride industry are at increased risk of cholangiocarcinoma. Illicitly brewed alcohol, sometimes contaminated with methanol, is associated with epidemics of acute and often fatal liver disease every year. Natural contaminants of grain, especially aflatoxins, are important as co-factors in the induction of hepatocellular carcinoma (HCC), especially in association with chronic hepatitis B; these contaminants are also responsible for outbreaks of severe acute liver disease in parts of Africa and India.[2]

In addition to the hazards of prescribed drugs, especially antibiotics, traditional herbal remedies (frequently used by patients before seeking allopathic medical advice) can be hepatotoxic. These can easily be overlooked when seeking the explanation for jaundice in immigrants to Western countries unless the history is taken carefully. 'Bush teas' in Africa and the West Indies predispose to Budd–Chiari syndrome. Outbreaks of veno-occlusive disease of the liver continue to be reported in Afghanistan, with high mortality. Known locally as camel belly, this is caused by contamination of flour with pyrrolizidine alkaloids from heliotrope weeds known locally as charmak, another local synonym for the disease.

Finally, there is less control over access to hepatotoxic chemicals in many parts of the tropics and these may be used in suicide attempts – paracetamol poisoning has decreased in the UK as a result of controls of sales and packaging, but such controls are absent in many countries. Self-poisoning with the weedkiller paraquat is still common in a large number of countries and can lead to acute liver failure.

Chronic liver disease

Chronic liver disease caused by hepatitis B is widespread in the tropics and is usually caused by transmission perinatally or in early childhood. Healthcare-associated transmission of hepatitis B and C and HIV is a major problem in resource-poor areas of the world, with reuse of needles and infusion kits because of ignorance or deliberate recycling of hospital waste. The largest known iatrogenic epidemic of a blood-borne infection occurred in the 1960–1980s, when a significant proportion of the Egyptian population was infected with hepatitis C during mass campaigns to treat schistosomiasis with intravenous tartar emetic. The increasing incidence of hepatitis C in many resource-poor regions remains a major concern.

The natural history of chronic hepatitis B and C can be accelerated by alcohol, aflatoxins and NAFLD. Co-infection with HIV is a particular problem, with complex immunological and therapeutic interactions that may impact on the future roll-out of antiretroviral drugs in the tropics. Schistosomiasis causes periportal fibrosis rather than cirrhosis, with massive splenomegaly common particularly where *Schistosoma mansoni* is prevalent (Africa, South America). Progression of portal hypertension and splenomegaly is faster when combined with cirrhosis caused by chronic viral hepatitis.

Miscellaneous local genetic conditions are becoming less common. Indian childhood cirrhosis is a non-Wilsonian copper overload disease in infants and children of Indian origin, and sporadic cases of Indian childhood cirrhosis or similar diseases have also been recognized in other countries. Bantu siderosis (African iron overload), seen in South Africa, was caused by a combination of inherited defects in hepatic iron handling and excess iron intake from traditional cooking and brewing vessels.

In many parts of the tropics, there is an accelerating trend towards urbanization and development of diseases associated with lifestyles common in developed countries. One of these is NAFLD, traditionally encountered in individuals with obesity and/or diabetes mellitus as well as hyperlipidaemia, and recognized as the hepatic aspect of the metabolic syndrome. Currently considered to be the most common cause of chronic liver disease in the developed world, NAFLD is increasingly recognized in both adults and children in the Asia–Pacific region. In Sri Lanka, it is present in 66% of urban adults aged 42–72, based on recognized ultrasonographic screening criteria. Alcoholic and

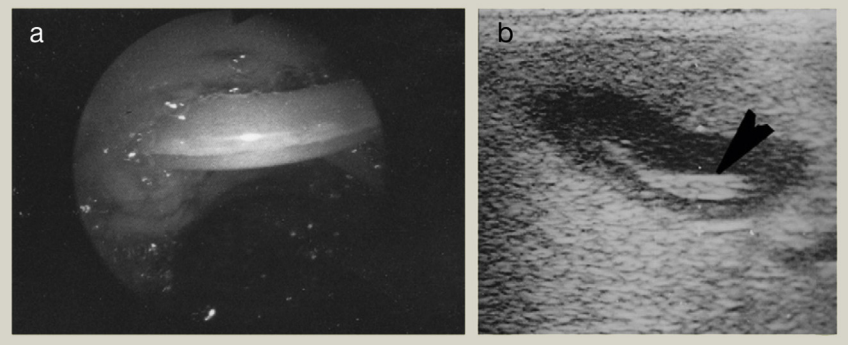

Figure 1 Spectrum of hepatobiliary ascariasis. (**a**) Endoscopic duodenoscopy shows the roundworm in the papilla of Vater. (**b**) Ultrasonography shows a long, linear echogenic filling defect (black arrow) in the gallbladder lumen. The defect is caused by the presence of the roundworm. Source: Courtesy of Professor Shoukat Ali Zargar, Sher-e-Kashmir Institute of Medical Sciences, Srinagar, India.

non-alcoholic fatty liver disease has become the most common cause of cirrhosis in patients referred for liver transplantation in India, overtaking chronic viral hepatitis.

Liver abscesses/masses

See also Medicine 2018; 46(1): 16–19. The main differential diagnosis of a tender, enlarged liver in the tropics includes acute pyogenic or amoebic liver abscess, primary or secondary tumours, and hydatid cysts. In areas where liver flukes are found (e.g. temperate parts of the world, Middle East), invasive fascioliasis is suggested by tender hepatomegaly, peripheral blood eosinophilia and ultrasound or computed tomography appearances of transient tracks or 'lakes' in the liver, reminiscent of peliosis hepatis. Eggs of the flukes may be found in faeces and are an indication for treatment with triclabendazole or nitazoxanide (neither of which is licensed in the UK).

Amoebic liver abscesses, caused by *Entamoeba histolytica*, usually have an acute onset, with point tenderness of the liver even if it is not enlarged, right shoulder-tip pain, signs at the base of the right lung, neutrophilia and positive amoebic serology. Neither a history of dysentery nor the presence or absence of amoebae in faeces or rectal scrapings has any positive or negative predictive value in distinguishing amoebic liver abscesses from pyogenic abscesses. Pyogenic liver abscesses are more likely to be multiple and are usually associated with generalized or intra-abdominal sepsis. Blood cultures are essential, and diagnostic aspiration can be helpful, especially as infections acquired outside the UK often have resistance to many antimicrobial agents. Therapeutic aspiration is indicated particularly for large, left-sided hepatic abscesses, which can rupture into the pericardium with serious consequences.

Tropical infections, such as melioidosis (*Burkholderia pseudomallei*), can present with a liver syndrome; this infection is common in South-East Asia and Northern Australia, and particularly affects people with diabetes mellitus, chronic alcoholic liver disease and conditions leading to iron overload.

Hepatobiliary tumours

HCC is depressingly common in the tropics, although it is disappearing in children and young adults in countries such as Taiwan as a result of long-standing hepatitis B immunization programmes. Hepatitis B, with or without alcohol and aflatoxin as co-factors, is the most important infectious cause of HCC in most parts of the tropics, while hepatitis C predominates in some areas. Several other infections contribute to a high prevalence of biliary tumours in the tropics.[3] Patients with cholelithiasis are more likely to become typhoid carriers, and both gallstones and the chronic typhoid carrier state are epidemiologically linked with gallbladder cancer. Chronic infection with *Clonorchis/Opisthorchis* flukes is linked to cholelithiasis, biliary cirrhosis and cholangiocarcinoma, the incidence of which decreases in communities with active control programmes for these infections.

Hydatid disease

Hydatid disease of the liver is still prevalent in many countries, with two distinct epidemiological and clinical patterns. The most common is cystic hydatid disease caused by the dog tapeworm, *Echinococcus granulosus*. Man is an incidental intermediate host for tissue cysts that localize in the liver in about 75% of cases and can exceed 10 cm in diameter. Cysts can also be present in lung, other intra-abdominal sites or elsewhere. The cysts are well demarcated from otherwise normal hepatic tissue by a thick pericyst wall. Cysts are often asymptomatic and may be found incidentally as a curvilinear or solid calcified shadow on plain X-ray. Hepatic cysts can present with chronic pain caused by expansion within liver tissue but occasionally behave like an acute abscess if bacterial infection occurs. Spontaneous rupture of cyst contents into the biliary tree causes obstructive jaundice and cholangitis, resembling gallstone disease (Figure 2). In this situation, the cyst can sometimes be removed endoscopically.

The diagnosis of hydatid disease relies on ultrasonography (Figure 3), which is often superior to other imaging modalities, especially as it can be repeated on many occasions to monitor progress with treatment. The appearances of multiple daughter cysts within a well-defined circular cyst are typical of early, viable cysts. Ultrasound appearances correlate well with parasitological viability of the cyst on follow-up, and form the basis of a staging classification scheme to determine the most appropriate management approach.[4] Degenerate cysts typically have an amorphous central content and can be sufficiently calcified for the wall to be visible on plain X-ray. Such cysts are more likely to be parasitologically sterile. A variety of rather crude serological tests can be employed, with varying sensitivity and specificity. The Casoni skin test is obsolete, and peripheral eosinophilia is rarely present unless there has been leakage of cyst contents (e.g. from inadvertent puncture). A suspected hydatid cyst should not

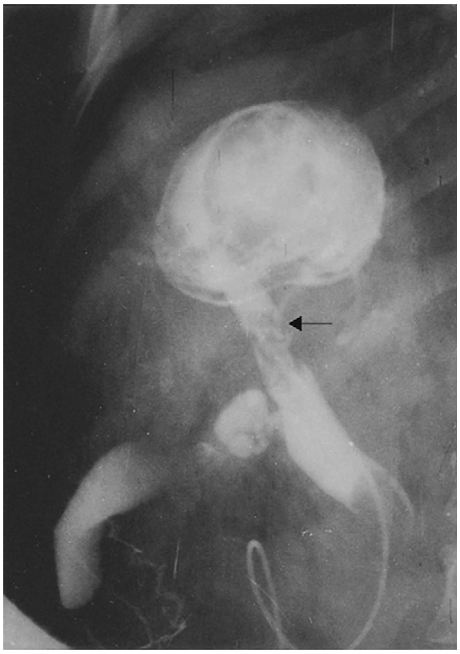

Figure 2 Endoscopic cholangiogram showing the right hepatic duct communicating with a large hydatid cyst. The common bile duct has an oval filling defect at the lower end, and the common hepatic duct shows ill-defined filling defects (arrow). Defects in both these locations represent daughter cysts lying loose in the biliary duct after rupture of the main cyst. Source: Courtesy of Professor Shoukat Ali Zargar, Sher-e-Kashmir Institute of Medical Sciences, Srinagar, India.

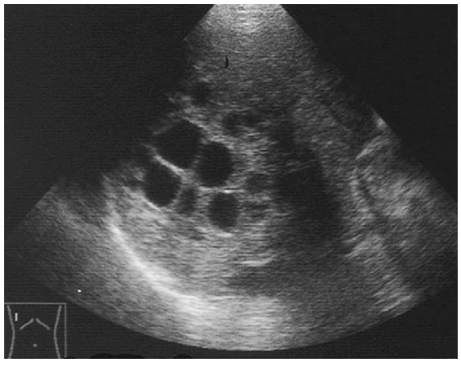

Figure 3 Hepatic cystic hydatid appearance on ultrasonography, with multiple daughter cysts visible near the surface and a posterior calcified pericyst membrane.

be aspirated for diagnostic purposes as leakage of the proteinaceous contents can cause anaphylactic shock or be followed by disseminated abdominal hydatid disease if the cyst contains viable protoscolices.

Initial treatment for all cysts is high-dose albendazole (approximately 10 mg/kg/day, unlicensed) for several weeks to months, which sterilizes most cysts and can be sufficient to cure small ones. Albendazole is more completely absorbed when taken with a fatty meal. It can cause significant disturbance of aminotransferases, which should be monitored during therapy, and the drug should be avoided in pregnancy unless it is essential. After this treatment, larger cysts are often amenable to surgical resection, whereas simple thin-walled cysts in the liver can be managed by percutaneous aspiration, instillation of hypertonic sodium chloride or alcohol, and re-aspiration ('PAIR'). This gives results comparable to surgery in expert hands and is now the preferred approach. Praziquantel (unlicensed) is used to treat the adult hydatid worm in dogs and can have a role in the treatment of cystic hydatid in humans, but there is little hard evidence to guide best practice; an expert should be consulted for current advice on all aspects of management of hydatid disease.

In contrast to cystic hydatid, alveolar hydatid disease caused by *Echinococcus multilocularis* localizes in the liver in 99% of patients and has a poor prognosis. The germinal layer is on the outside of the gelatinous cyst, which spreads like a poorly defined tumour throughout the liver and can metastasize to the lungs and elsewhere. Patients present as if they have liver cancer with weight loss, fever, painful and irregular hepatomegaly and an irregular mass on ultrasonography. Treatment is by palliation with long-term albendazole. Radical surgical resection or even liver transplantation may be necessary. Traditionally limited to South America, foci of this infection are spreading in China, Central Europe and elsewhere.

Massive splenomegaly

Although massive splenomegaly can be caused by portal hypertension, schistosomiasis or cirrhosis, other causes can predominate. Visceral leishmaniasis, particularly in parts of India and the Sudan, results in massive splenomegaly with variable hepatomegaly. In other areas of the world where malaria is endemic, a very large spleen can be caused by hyperreactive malarial splenomegaly or tropical splenic lymphoma.[5] ◆

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FURTHER READING

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USEFUL WEBSITES

Viral Hepatitis Prevention Board: www.vhpb.org/ – a useful site for statistics related to viral hepatitis in different geographical areas, as well as numerous slide presentations and lectures.

World Health Organization: www.who.int/hepatitis/en – an excellent collection of resources on viral hepatitis around the world.

TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 36-year-old man presented with a 5-day history of nausea and jaundice. He was a UK resident and had returned 2 weeks previously after visiting relatives in the Sudan for 4 weeks.
On clinical examination his temperature was 37.2°C and he was jaundiced. There were no clinical features of hepatic encephalopathy or chronic liver disease.

Investigations

- Haemoglobin 126 g/litre (130–180)
- Total white cell count 5.7 × 10^9/litre (4–11)
- Eosinophils 0.3 × 10^9/litre (0.04–0.40)
- Platelets 160 × 10^9/litre (150–400)
- Serum total bilirubin 260 micromol/litre (1–22)
- Serum alanine aminotransferase 2940 U/litre (5–35)
- Serum alkaline phosphatase 456 U/litre (45–105)
- Serum γ-glutamyltransferase 127 U/litre (<50)

What additional aspect of the history would be most useful in identifying the likely diagnosis?

A. Alcohol intake
B. Country of birth
C. Immersion in fresh water while overseas
D. Use of illicit drugs
E. Use of malaria chemoprophylaxis

Question 2

A 56-year-old man presented with a 10-day history of fever, rigors and right hypochondrial pain. He had lived in the UK all his life and had returned 4 weeks previously from an uneventful 3-week holiday in rural South America.
On clinical examination he looked unwell, with temperature 39.6°C, heart rate 102 beats/minute, blood pressure 125/85 mmHg, respiratory rate 18 breaths/minute. He had tenderness in his right hypochondrium. He did not have jaundice, rash or signs of chronic liver disease.

Investigations

- Haemoglobin 115 g/litre (130–180)
- Total white cell count 17.6 × 10^9/litre (4–11)
- Eosinophils 0.2 × 10^9/litre (0.04–0.40)
- Platelets 467 × 10^9/litre (150–400)
- Serum total bilirubin 30 micromol/litre (1–22)
- Serum alanine aminotransferase 165 U/litre (5–35)
- Serum alkaline phosphatase 320 U/litre (45–105)
- Serum γ-glutamyltransferase 78 U/litre (<50)
- CT scan of liver showed a large cystic lesion in left lobe of liver 16 x 13 cm in diameter, with irregular edges and poorly defined internal shadows.

What is the most important next intervention?

A. Aspiration of lesion
B. Oral albendazole
C. Oral metronidazole
D. Oral paromomycin
E. Oral praziquantel